International Journal of Clinical and Biomedical Research
Vol. 11, No. 4 (2026)
pISSN: 2521-0394 · eISSN: 2395-0471

ORIGINAL RESEARCH

Comparative Evaluation of Opioid Free Versus Conventional Opioid Based General Anaesthesia: Effects on Haemodynamic Stability, Post Operative Analgesia, and Recovery Profile in Adult Patients

Maroof Ahmed Choudhary[1], **Ershad Mohammed Sohail**[2], **Harsha Priya L**[3*]

[1] *Assistant Professor, Department of Anaesthesiology, Deccan College of Medical Sciences, Hyderabad, Telangana, India*
[2] *Associate Professor, Department of Anaesthesiology, Deccan College of Medical Sciences, Hyderabad, Telangana, India*
[3] *Assistant Professor, Department of Anaesthesiology, Deccan College of Medical Sciences, Hyderabad, Telangana, India*

*Correspondence: Harsha Priya L <hpchowdary93@gmail.com>

ABSTRACT

Background: Opioid-free anaesthesia (OFA) is a multimodal technique intended to limit opioid-related adverse effects while preserving intraoperative haemodynamic stability and postoperative analgesia. We compared OFA with conventional opioid-based anaesthesia (OBA) in adults undergoing elective surgery. **Methods:** A prospective, comparative, observational study was carried out at a tertiary care teaching hospital from May 2026 to October 2026. Ninety-eight adults aged 18 to 65 years with ASA physical status I or II, scheduled for elective laparoscopic abdominal, orthopaedic or general surgical procedures, were allocated by departmental practice to OFA (n = 49) or OBA (n = 49). Intraoperative heart rate (HR) and mean arterial pressure (MAP), postoperative Numerical Rating Scale (NRS) pain scores, rescue analgesic requirements, recovery parameters, patient satisfaction and adverse events were compared. Continuous variables were compared by the independent t-test and categorical variables by the chi-square or Fisher exact test, with a two-sided $p < 0.05$ taken as significant. No adjustment was made for multiple comparisons. **Results:** After intubation, mean HR was lower with OFA than with OBA (88.1 ± 10.2 versus 94.6 ± 11.4 beats/min; mean difference −6.5, 95% CI −10.8 to −2.2; $p = 0.004$), as was MAP (102.4 ± 9.3 versus 108.1 ± 10.2 mmHg; mean difference −5.7, 95% CI −9.6 to −1.8; $p = 0.005$). The mean time to first rescue analgesia was longer with OFA (165 ± 54 versus 132 ± 48 minutes; difference 33, 95% CI 13 to 53; $p = 0.002$). The 24-hour QoR-15 score was higher with OFA (126 ± 11 versus 121 ± 13; difference 5.0, 95% CI 0.2 to 9.8; $p = 0.043$), a difference smaller than the accepted minimal clinically important difference of 8 points. Postoperative nausea and vomiting occurred in 5 of 49 patients (10.2%) given OFA and 13 of 49 (26.5%) given OBA ($p = 0.037$ by chi-square; $p = 0.066$ by Fisher exact test). Bradycardia was more frequent with OFA (18.4% versus 8.2%; $p = 0.23$). **Conclusion:** OFA attenuated the haemodynamic response to intubation, delayed the first requirement for rescue analgesia and was associated with less postoperative nausea and vomiting, while bradycardia was more frequent. Because allocation was not randomised, no single primary endpoint was prespecified and many comparisons were made without adjustment, these findings are hypothesis-generating and need confirmation in an adequately powered randomised trial.

Keywords: Opioid-free anaesthesia; Opioid-based anaesthesia; Dexmedetomidine; Haemodynamic stability; Postoperative analgesia; Quality of recovery; Postoperative nausea and vomiting

INTRODUCTION

Opioids have long been central to balanced general anaesthesia. They give reliable antinociception and blunt the sympathetic response to laryngoscopy, intubation and surgical stimulation. That reliability carries a cost. Perioperative opioid exposure is associated with postoperative nausea and vomiting (PONV), respiratory depression, excessive sedation, pruritus, gastrointestinal dysfunction and delayed mobilisation, and may also produce acute tolerance and opioid-induced hyperalgesia, which can paradoxically raise postoperative analgesic requirements. Taken together these effects prolong recovery and the period of postoperative monitoring, and they have driven interest in techniques that reduce or remove intraoperative opioids altogether [1,2,3].

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Opioid-free anaesthesia (OFA) is a multimodal technique in which no opioid is given intraoperatively by plan. Antinociception is achieved instead by combining drugs that act through separate pathways, most often dexmedetomidine, ketamine, intravenous lignocaine and magnesium sulphate, alongside conventional hypnotics and inhalational agents. OFA differs from opioid-sparing anaesthesia, in which the opioid dose is reduced but not eliminated, and it does not mean withholding rescue opioids after surgery when they are clinically needed [2,3,4].

Dexmedetomidine, a selective alpha-2 adrenergic agonist, is the agent used most often. Its sympatholytic action attenuates the cardiovascular response to intubation and surgical stimulation, but it can also cause bradycardia, hypotension and delayed emergence. The multicentre POFA trial was a salutary reminder of this: a dexmedetomidine-based opioid-free regimen raised safety concerns that undercut the assumption that removing opioids is invariably beneficial [2]. Ketamine contributes analgesia through antagonism at N-methyl-D-aspartate (NMDA) receptors, and its sympathomimetic effect may offset dexmedetomidine-induced bradycardia. Intravenous lignocaine has analgesic, antihyperalgesic and anti-inflammatory properties, and magnesium sulphate reduces anaesthetic and analgesic requirements through NMDA-receptor and calcium-related mechanisms. The best combination, dose and infusion duration remain unsettled [3,4,5].

Intraoperative haemodynamic stability is central to any comparison of the two techniques. Surgical stimulation, airway manipulation, volume shifts and the anaesthetic drugs themselves all disturb heart rate (HR) and mean arterial pressure (MAP). Excessive sympathetic activation produces tachycardia and hypertension, whereas profound sympatholysis or anaesthetic vasodilatation produces bradycardia and hypotension; either extreme may compromise perfusion, raise myocardial oxygen demand or require pharmacological rescue. Serial measurement of HR and MAP, with the percentage deviation from baseline, is therefore a practical way of comparing techniques [2,5,6]. The published evidence is mixed. Chen et al. found that OFA maintained haemodynamic stability comparable to opioid-based anaesthesia (OBA) during laparoscopic gynaecological surgery, whereas others have reported more bradycardia or slower recovery with dexmedetomidine-based regimens. Outcomes appear to depend on the substitute drugs and their doses rather than on opioid avoidance in itself [2,6,7].

Postoperative analgesia is the second consideration, since removing intraoperative opioids must not leave pain poorly controlled: poorly controlled pain impairs respiratory function, delays mobilisation, increases the stress response and reduces satisfaction. Pain intensity, time to first rescue analgesia and cumulative analgesic consumption are the usual outcome measures [4,8,9]. Chen et al. reported better analgesia and less PONV after OFA, and Vishnuraj et al., in 88 patients undergoing laparoscopic cholecystectomy, found lower analgesic requirements during the first two postoperative hours with a dexmedetomidine-ketamine regimen; cumulative fentanyl consumption at six hours, however, did not differ between groups [4,5]. Pooled analyses tell a similar story. Malo-Manso et al. reported better pain control and less nausea and vomiting with OFA but an increased risk of bradycardia, and Zhang et al., pooling 14 randomised trials and 1,354 participants, found a markedly lower incidence of PONV (risk ratio 0.41) without significant differences in extubation time or time to first rescue analgesia [7,10]. Reduction of opioid-related adverse effects therefore looks like a more consistent benefit of OFA than improvement in every recovery parameter.

Recovery itself is multidimensional. The Modified Aldrete score captures physiological readiness for discharge from the post-anaesthesia care unit (PACU), while patient-reported instruments such as the Quality of Recovery-15 (QoR-15) questionnaire and the Iowa Satisfaction with Anaesthesia Scale (ISAS) describe comfort, independence, emotional state and satisfaction, which physiological measures do not capture [8,11,12]. Findings across thoracic, laparoscopic and bariatric surgery have been inconsistent: some studies report better patient-reported recovery, others delayed emergence or no meaningful difference, and in a randomised study of laparoscopic colectomy an opioid-free regimen neither reduced postoperative opioid consumption relative to an opioid-sparing strategy nor avoided more frequent bradycardia [8,11,12,13]. Satisfaction cannot be inferred from pain scores or physiological recovery and needs to be measured directly [12,13,14].

Most published work has concentrated on single procedures, particularly laparoscopic abdominal, gynaecological, bariatric and thoracic surgery, and has used varied drug combinations, rescue protocols and outcome definitions; recent comparative studies continue to question whether OFA reliably improves analgesia or recovery [9,13,14,15]. How the technique

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performs across the mixed elective caseload of a routine operating list is less clear. We therefore compared OFA with conventional OBA in 98 adults undergoing elective laparoscopic abdominal, orthopaedic and general surgical procedures. The primary objective was to compare intraoperative haemodynamic stability, assessed by HR, MAP and their deviation from baseline. Secondary objectives were postoperative pain intensity, rescue analgesic requirement, recovery characteristics, patient satisfaction and adverse events.

MATERIALS AND METHODS

Study Design and Setting

This prospective, comparative, observational study was carried out in the Department of Anaesthesiology of a tertiary care teaching hospital, from May 2026 to October 2026. Ninety-eight adults undergoing elective laparoscopic abdominal, orthopaedic or general surgical procedures under general anaesthesia were studied in two groups of 49: Group I received opioid-free general anaesthesia (OFA) and Group II conventional opioid-based general anaesthesia (OBA). The primary objective was to compare intraoperative haemodynamic stability; secondary objectives were postoperative analgesia, recovery characteristics, analgesic requirements, patient satisfaction and adverse events. The study was approved by our Institutional ethics committee Ref no DCM/ETHICS/205/25/2026.

Study Population and Group Allocation

Patients aged 18 to 65 years with ASA physical status I or II, scheduled for elective laparoscopic abdominal, orthopaedic or general surgical procedures under general anaesthesia, were eligible. Ninety-eight patients were studied, 49 in each group. The sample size was calculated for the primary outcome, the mean post-intubation heart rate, assuming a between-group difference of 14 to 18 beats/min and a common standard deviation of [2.56±2.15 beats/min, with a two-sided alpha of 0.05 and 80% power; this gave 49 patients per group, and total 98 patients were recruited to allow for dropouts. Patients were allocated to the two groups according to the anaesthetic technique in routine use by the attending team on the day of surgery, not by randomisation; the study is therefore an observational comparison and is reported as such. The anaesthesia team was necessarily aware of the technique used. Postoperative outcomes were assessed by an independent observer who was not present in theatre and was unaware of group allocation.

Inclusion and Exclusion Criteria

Patients aged 18 to 65 years with ASA physical status I or II, cardiovascular and respiratory stability and clinically acceptable renal and hepatic function were included after written informed consent. Patients were excluded if they were younger than 18 or older than 65 years, of ASA physical status III or higher, or undergoing emergency surgery. Further exclusions were significant cardiovascular or respiratory disease, clinically relevant renal or hepatic impairment, known allergy to any study medication, chronic opioid use or dependence, long-term analgesic therapy, substance misuse, pregnancy or lactation, and neurological or psychiatric disorders likely to interfere with pain assessment or postoperative evaluation. Patients expected to need prolonged postoperative ventilation or intensive care were also excluded. Of 127 patients screened, 29 were excluded 19 did not meet the inclusion criteria, 05 declined consent,05 for other reasons), leaving 98 who were studied; no patient was lost to follow-up.

Pre-anaesthetic Evaluation and Baseline Variables

Every patient had a full pre-anaesthetic assessment covering medical and surgical history, previous anaesthesia, drug allergy and cardiovascular and respiratory examination. The airway was assessed by the Mallampati classification. Baseline heart rate, blood pressure and peripheral oxygen saturation were recorded. Investigations included a complete blood count, blood glucose, renal and liver function tests and electrocardiography as clinically indicated. Patients fasted according to standard preoperative guidance, and written informed consent was obtained.

The demographic and clinical variables recorded were age, sex, weight, height, body mass index (BMI), ASA status, comorbidities, preoperative haemoglobin, baseline heart rate, mean arterial pressure and oxygen saturation. BMI was calculated as weight in kilograms divided by the square of height in metres. The broad surgical category, the specific

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procedure, and the durations of surgery and of anaesthesia were documented, since these affect surgical stimulation, postoperative pain and recovery.

Group I received opioid-free general anaesthesia by a multimodal non-opioid technique. Premedication, where indicated, was intravenous midazolam 0.02 to 0.03 mg/kg, given slowly and titrated to age, clinical condition and level of sedation. Anaesthesia was induced with intravenous propofol 1.5 to 2.5 mg/kg titrated to loss of consciousness, followed by rocuronium 0.6 to 1.0 mg/kg for tracheal intubation, and maintained with sevoflurane titrated to the required depth and haemodynamic response, generally at an end-tidal concentration of about 0.8 to 1.2 MAC.

Multimodal analgesia used non-opioid adjuncts according to clinical suitability and the institutional protocol. Dexmedetomidine was infused at 0.2 to 0.7 micrograms/kg/hour; where a loading dose was judged necessary, 0.5 to 1 microgram/kg was given slowly over 10 minutes. Rapid administration and excessive dosing were avoided because of the risk of bradycardia and hypotension. Ketamine was given in a subanaesthetic dose of 0.25 to 0.5 mg/kg intravenously, followed where indicated by an infusion of 0.1 to 0.25 mg/kg/hour, with monitoring for tachycardia, hypertension, excessive sedation and emergence reactions. Intravenous lignocaine, where used, was given as a slow bolus of 1 to 1.5 mg/kg followed by an infusion of up to 1 to 1.5 mg/kg/hour, with monitoring for local anaesthetic systemic toxicity, including circumoral numbness, tinnitus, altered consciousness, seizures and cardiac conduction abnormalities. Magnesium sulphate, where indicated, was given as a loading dose of 30 to 50 mg/kg over 10 to 20 minutes followed by an infusion of 6 to 15 mg/kg/hour according to the institutional protocol; renal function, blood pressure, deep tendon reflexes and neuromuscular blockade were taken into account during its use, because magnesium potentiates neuromuscular blocking agents. Of the 49 patients in Group I, 18 received dexmedetomidine, 17 ketamine, 10 lignocaine and 4 magnesium sulphate; the mean (SD) total dose of each agent.

Additional analgesia comprised intravenous paracetamol 15 mg/kg (maximum 1 g per dose) and diclofenac about 1 mg/kg, not exceeding 75 mg per dose, where clinically appropriate and not contraindicated. The cumulative paracetamol dose was limited according to hepatic function and institutional policy. Diclofenac was avoided or used cautiously in renal impairment, active gastrointestinal ulceration, bleeding risk or relevant hypersensitivity. Ondansetron 4 mg intravenously was given for PONV prophylaxis where indicated. PONV prophylaxis was given to 26 patients in Group I and 27 in Group II. Neuromuscular blockade was reversed where required with neostigmine 0.04 to 0.05 mg/kg and glycopyrrolate about 0.01 mg/kg, adjusted to the degree of neuromuscular recovery. No opioid formed part of the planned intraoperative regimen in this group.

Group II received conventional opioid-based general anaesthesia. Midazolam 0.02 to 0.03 mg/kg intravenously was given as premedication where indicated. Anaesthesia was induced with propofol 1.5 to 2.5 mg/kg intravenously followed by rocuronium 0.6 to 1.0 mg/kg for tracheal intubation. Fentanyl was given intravenously, usually in an initial dose of 1 to 2 micrograms/kg, with further increments decided by the anaesthesiologist according to surgical stimulation and haemodynamic response. The mean (SD) total intraoperative fentanyl dose was 7.8 micrograms/kg. Anaesthesia was maintained with sevoflurane titrated to the required depth, with further neuromuscular blockade where clinically indicated. Paracetamol 15 mg/kg (maximum 1 g per dose) and diclofenac about 1 mg/kg (maximum 75 mg per dose) were used as supplementary analgesics where appropriate, and ondansetron 4 mg intravenously for PONV prophylaxis where indicated. Neuromuscular blockade was reversed with neostigmine 0.04 to 0.05 mg/kg and glycopyrrolate about 0.01 mg/kg where indicated.

Both groups received standard intraoperative monitoring with continuous electrocardiography, pulse oximetry, capnography and regular non-invasive blood pressure measurement, and drug administration was titrated to the individual response. Quantitative neuromuscular monitoring was used in all patients, and adequate recovery from neuromuscular blockade was confirmed before extubation. Particular attention was paid to bradycardia and hypotension in patients receiving dexmedetomidine, to cardiovascular and neurological toxicity with intravenous lignocaine, and to prolonged neuromuscular blockade with magnesium sulphate. Rescue medication and supportive measures were available throughout. Doses, routes, timing, infusion rates and durations of all drugs, the sevoflurane concentration and the intraoperative haemodynamic responses were taken from the anaesthesia records. The OFA protocol was defined by the

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absence of planned intraoperative opioid; clinically necessary rescue opioid was never withheld and was documented separately. No patient in Group I required intraoperative rescue opioid.

Intraoperative Monitoring and Haemodynamic Assessment

All patients were monitored continuously with standard multiparameter anaesthesia equipment. The parameters recorded were heart rate (HR), systolic and diastolic blood pressure, mean arterial pressure (MAP), peripheral oxygen saturation, end-tidal carbon dioxide and electrocardiographic changes. Measurements were taken at baseline before induction, immediately after induction, after tracheal intubation, at 5, 10, 15, 30, and 60 minutes, at the end of surgery and at extubation; for procedures lasting more than 60 minutes, recording continued every 15 minutes. Table 2 reports the time points at 5, 15, 30 and 60 minutes.

Haemodynamic stability was assessed from the mean, maximum and minimum intraoperative HR and MAP and from the incidence of hypotension, hypertension, bradycardia and tachycardia. The percentage deviation from baseline was calculated as [(intraoperative value − baseline value) / baseline value] × 100, and a change of more than 20% from baseline in HR or MAP in either direction was taken as haemodynamic instability. The frequency and duration of such episodes and the need for rescue intervention with vasopressors, anticholinergic drugs or antihypertensives were documented. Surgical category and procedure-related factors, in particular pneumoperitoneum and positioning during laparoscopic surgery, were taken into account when haemodynamic responses were interpreted.

Assessment of Postoperative Analgesia

Postoperative pain was assessed on recovery from anaesthesia and then at 30 minutes and at 1, 2, 4, 6, 12 and 24 hours using the Numerical Rating Scale (NRS), on which patients rated pain from 0 to 10, where 0 was no pain, 1 to 3 mild, 4 to 6 moderate and 7 to 10 severe pain. Lower scores indicated better analgesia.

Rescue analgesic requirements were assessed by recording the interval between the end of surgery and administration of the first rescue analgesic dose, the total number of rescue doses administered, cumulative analgesic consumption and the proportion of patients requiring additional analgesia. A standardised rescue analgesia protocol was followed in both groups. Intravenous tramadol 50 mg was administered when the Numerical Rating Scale (NRS) pain score was ≥4, with additional doses administered according to the patient's pain response and institutional postoperative analgesia protocol. The type, dose and timing of all analgesic medications administered during the postoperative period were documented. Total postoperative opioid consumption was calculated and converted into intravenous morphine equivalents using a standard equianalgesic opioid conversion table, with the conversion reference specified in the study protocol. Surgical category and the specific operative procedure were considered during the interpretation of differences in postoperative pain intensity and analgesic requirements between the two groups.

Assessment of Postoperative Recovery

Recovery was assessed with the Modified Aldrete Scoring System and the Quality of Recovery-15 (QoR-15) questionnaire. The Modified Aldrete score rates activity, respiration, circulation, consciousness and oxygen saturation from 0 to 2 each, giving a maximum of 10; a score of 9 or more was taken as the threshold for PACU discharge provided other clinical criteria were met, and the time taken to reach it was recorded.

The QoR-15 questionnaire was administered about 24 hours after surgery, once patients were alert enough to answer. It covers physical comfort, emotional state, physical independence, psychological support and pain through 15 items scored from 0 to 10, with reverse scoring for negatively worded items, giving a total from 0 to 150; higher scores indicate better recovery. The minimal clinically important difference for the QoR-15 is 8 points [16]. Time to regain consciousness, time to extubation, time to an Aldrete score of at least 9 and duration of PACU stay were also recorded.

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Assessment of Patient Satisfaction and Adverse Events

Patient satisfaction was assessed about 24 hours after surgery with the Iowa Satisfaction with Anaesthesia Scale (ISAS), an 11-item patient-reported questionnaire covering overall satisfaction, comfort, pain, nausea, vomiting and other aspects of the anaesthetic experience. Each item is rated on a six-point scale with reverse scoring for negatively worded items, and the mean score is the total divided by 11, giving a range of 1 to 6, with higher scores indicating greater satisfaction. For description, scores were grouped as very dissatisfied (1.00 to 2.00), dissatisfied (2.01 to 3.00), moderately satisfied (3.01 to 4.00), satisfied (4.01 to 5.00) and highly satisfied (5.01 to 6.00). These groupings were defined for this study and are not part of the original validated ISAS classification.

All patients were monitored for adverse events during the first 24 hours after surgery. The adverse events recorded included nausea and vomiting, hypotension, hypertension, bradycardia, tachycardia, excessive sedation, respiratory depression, dizziness, shivering, delayed recovery and severe postoperative pain. Bradycardia was defined as a heart rate below 50 beats/min, hypotension as a mean arterial pressure (MAP) below 65 mmHg or a decrease of more than 20% from the baseline value, respiratory depression as a respiratory rate below 8 breaths/min or peripheral oxygen saturation (SpO_2) below 90%, and excessive sedation as a Ramsay Sedation Scale score of 4 or more.

Study Outcomes and Statistical Analysis

The primary outcome was intraoperative haemodynamic stability, compared between the OFA and OBA groups. Secondary outcomes were postoperative pain intensity, time to first rescue analgesia, total analgesic consumption, recovery scores, time to extubation, PACU discharge time, patient satisfaction and postoperative adverse events. The primary outcome was intraoperative haemodynamic stability, assessed using heart rate (HR) immediately after endotracheal intubation, comparing the opioid-free anaesthesia (OFA) and opioid-based anaesthesia (OBA) groups. HR at this time point was designated as the single primary endpoint. Mean arterial pressure (MAP) immediately after intubation and changes in HR and MAP at the remaining intraoperative time points were considered secondary and exploratory haemodynamic outcomes, respectively. Secondary clinical outcomes included postoperative pain intensity, time to first rescue analgesia, total analgesic consumption, postoperative recovery scores, time to extubation, post-anaesthesia care unit (PACU) discharge time, patient satisfaction and postoperative adverse events.

Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are presented as frequencies and percentages. Between-group comparisons of continuous variables were performed using the independent Student's t-test, while categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate, when expected cell counts were below five. The primary endpoint (HR immediately after intubation) was compared between the OFA and OBA groups using the independent Student's t-test. Mean differences with corresponding 95% confidence intervals (CIs) and effect sizes were calculated and reported for the primary endpoint and principal secondary outcomes. HR and MAP measurements at the other intraoperative time points were analysed using independent t-tests and treated as exploratory comparisons. Time to first rescue analgesia was also compared between groups using the independent Student's t-test; Kaplan-Meier survival analysis and the log-rank test were not performed. Repeated-measures analysis of variance and mixed-effects modelling were not undertaken. No subgroup or adjusted analyses based on surgical category were performed. No formal adjustment for multiple comparisons was applied; therefore, p-values from secondary and exploratory analyses were interpreted descriptively. Given the 16 haemodynamic comparisons presented in Table 2, a Bonferroni-adjusted significance threshold of approximately 0.003 (0.05/16) was considered when interpreting these findings. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant for the primary analysis.

RESULTS

Ninety-eight patients undergoing elective laparoscopic abdominal, orthopaedic or general surgical procedures under general anaesthesia were studied in two groups, Group I (OFA, n = 49) and Group II (OBA, n = 49). Baseline characteristics, intraoperative haemodynamic parameters, postoperative analgesia, recovery profile, patient satisfaction and adverse events were compared.

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Table 1. Comparison of demographic and baseline clinical characteristics

Variable	OFA (n=49)	OBA (n=49)	p-value
Age (years), mean ± SD	42.8 ± 11.6	43.5 ± 10.9	0.76
Male, n (%)	29 (59.2)	27 (55.1)	0.68
Female, n (%)	20 (40.8)	22 (44.9)	
BMI (kg/m²), mean ± SD	25.1 ± 3.4	24.8 ± 3.6	0.68
ASA I, n (%)	31 (63.3)	30 (61.2)	0.83
ASA II, n (%)	18 (36.7)	19 (38.8)	
Laparoscopic abdominal surgery, n (%)	18 (36.7)	17 (34.7)	0.97
Orthopaedic surgery, n (%)	16 (32.7)	17 (34.7)	
General surgery, n (%)	15 (30.6)	15 (30.6)	
Duration of surgery (min), mean ± SD	92 ± 31	95 ± 34	0.65

Values are mean ± SD or n (%). p values by independent t-test for continuous variables and Pearson chi-square test for categorical variables.

The two groups were comparable in demographic, anthropometric and clinical characteristics, with no significant difference in age, sex, BMI or ASA physical status. Laparoscopic abdominal, orthopaedic and general surgical procedures were distributed similarly between the groups, as was the duration of surgery, which makes major imbalance in surgical workload unlikely.

Table 2. Comparison of intraoperative heart rate and mean arterial pressure

Assessment time	HR: OFA	HR: OBA	p-value	MAP: OFA	MAP: OBA	p-value
Baseline	82.4 ± 9.1	81.8 ± 8.8	0.74	95.1 ± 8.2	94.8 ± 8.5	0.86
After induction	76.5 ± 8.4	78.2 ± 8.7	0.33	83.2 ± 7.4	84.7 ± 7.8	0.33
After intubation	88.1 ± 10.2	94.6 ± 11.4	0.004	102.4 ± 9.3	108.1 ± 10.2	0.005
5 minutes	81.2 ± 9.0	86.7 ± 10.1	0.005	94.3 ± 8.1	98.7 ± 8.9	0.012
15 minutes	78.8 ± 8.7	82.5 ± 9.6	0.048	91.8 ± 7.9	94.6 ± 8.4	0.092
30 minutes	77.9 ± 8.5	80.1 ± 9.2	0.22	90.7 ± 7.6	92.5 ± 8.1	0.26
60 minutes	78.4 ± 8.9	80.0 ± 9.4	0.39	91.2 ± 7.8	92.6 ± 8.3	0.39
Extubation	91.5 ± 10.4	96.2 ± 11.6	0.037	99.2 ± 9.1	103.4 ± 9.8	0.030

Values are mean ± SD; HR in beats/min and MAP in mmHg.

HR and MAP rose after tracheal intubation in both groups, and the rise was greater in the OBA group. Mean HR after intubation was 6.5 beats/min lower in the OFA group (95% CI −10.8 to −2.2; p = 0.004) and mean MAP 5.7 mmHg lower (95% CI −9.6 to −1.8; p = 0.005). Differences narrowed during maintenance and were no longer significant from 30 minutes onwards, although HR and MAP remained numerically lower in the OFA group at every subsequent time point. Both variables rose again at extubation, with a smaller rise in the OFA group. None of these differences would remain significant at a Bonferroni-corrected threshold of 0.003 for the 16 comparisons in this table.

Table 3. Comparison of intraoperative haemodynamic events and rescue interventions

Haemodynamic event	OFA (n=49), n (%)	OBA (n=49), n (%)	p-value
Hypotension	8 (16.3)	10 (20.4)	0.60
Hypertension	5 (10.2)	8 (16.3)	0.37
Bradycardia	9 (18.4)	4 (8.2)	0.14
Tachycardia	4 (8.2)	7 (14.3)	0.34

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Haemodynamic event	OFA (n=49), n (%)	OBA (n=49), n (%)	p-value
Vasopressor requirement	7 (14.3)	9 (18.4)	0.58
Atropine requirement	4 (8.2)	1 (2.0)	0.36

Values are n (% of group). p values by Pearson chi-square test, or by Fisher exact test where any expected cell count was below five (atropine requirement). Bradycardia: absolute difference 10.2%, 95% CI −3.1% to 23.5%.

Hypotension and hypertension occurred in both groups without a significant difference in incidence. Bradycardia was about twice as frequent in the OFA group (9 of 49, 18.4%, versus 4 of 49, 8.2%; absolute difference 10.2%, 95% CI −3.1% to 23.5%; p = 0.14), and four patients in the OFA group needed atropine compared with one in the OBA group. Tachycardia and vasopressor requirement were slightly more frequent in the OBA group. The study was not powered to compare these events, and the confidence interval around the difference in bradycardia is wide enough to include no difference as well as a clinically important excess.

Table 4. Comparison of postoperative pain scores using the Numerical Rating Scale

Postoperative assessment	OFA (n=49)	OBA (n=49)	p-value
30 minutes	3.2 ± 1.1	3.8 ± 1.2	0.011
1 hour	2.9 ± 1.0	3.4 ± 1.1	0.021
2 hours	2.7 ± 1.0	3.1 ± 1.1	0.063
4 hours	2.6 ± 0.9	2.8 ± 1.0	0.30
6 hours	2.4 ± 0.9	2.6 ± 1.0	0.30
12 hours	2.1 ± 0.8	2.2 ± 0.9	0.56
24 hours	1.8 ± 0.7	1.9 ± 0.8	0.51

Values are mean ± SD. NRS, Numerical Rating Scale (0 = no pain, 10 = worst imaginable pain). p values by independent t-test, unadjusted for multiple comparisons.

Values are mean ± SD.

Mean NRS scores were lower in the OFA group during the first two postoperative hours, significantly so at 30 minutes (mean difference −0.6, 95% CI −1.06 to −0.14; p = 0.011) and at one hour (p = 0.021). Pain scores then fell in both groups and the differences were no longer significant at any later assessment. The largest difference, 0.6 points on an 11-point scale, is below the 1.3 to 2-point change usually regarded as clinically meaningful on the NRS.

Table 5. Comparison of postoperative rescue analgesic requirements

Parameter	OFA (n=49)	OBA (n=49)	p-value
Patients requiring rescue analgesia, n (%)	37 (75.5)	42 (85.7)	0.20
Time to first rescue analgesia (min)	165 ± 54	132 ± 48	0.002
Number of rescue doses, mean ± SD	1.4 ± 0.8	1.8 ± 0.9	0.025
Postoperative opioid rescue, n (%)	8 (16.3)	13 (26.5)	0.22
Postoperative opioid consumption (IV morphine equivalents, mg)	3.2 ± 5.1	5.1 ± 6.2	0.10

Values are n (%) or mean ± SD. p values by Pearson chi-square test or independent t-test as appropriate.

The mean time to first rescue analgesia was 33 minutes longer in the OFA group (95% CI 13 to 53; p = 0.002), and patients in that group needed fewer rescue doses (mean difference −0.4, 95% CI −0.74 to −0.06; p = 0.025). Fewer patients in the OFA group required any rescue analgesia and fewer required rescue opioid, and cumulative opioid consumption was lower, but none of these three differences reached significance.

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Table 6. Comparison of postoperative recovery characteristics

Recovery parameter	OFA (n=49)	OBA (n=49)	p-value
Modified Aldrete score	9.2 ± 0.6	9.0 ± 0.7	0.13
Time to Aldrete score ≥9 (min)	18.5 ± 6.2	20.1 ± 7.1	0.23
Time to extubation (min)	8.4 ± 3.1	9.1 ± 3.5	0.30
PACU stay (min)	52 ± 16	58 ± 19	0.094
QoR-15 score at 24 hours	126 ± 11	121 ± 13	0.043

Values are mean ± SD. QoR-15, Quality of Recovery-15 (range 0–150; minimal clinically important difference 8 points).

Modified Aldrete scores, times to an Aldrete score of at least 9, extubation times and PACU stay were all numerically better in the OFA group, but none of the differences was significant. The mean 24-hour QoR-15 score was 5.0 points higher in the OFA group (95% CI 0.2 to 9.8; p = 0.043). The lower confidence limit lies close to zero and the point estimate is below the minimal clinically important difference of 8 points for this instrument [16], so the difference should be regarded as statistically detectable but of uncertain clinical importance.

Table 7. Comparison of patient satisfaction and postoperative adverse events

Parameter	OFA (n=49)	OBA (n=49)	p-value
Mean ISAS score	5.2 ± 0.5	4.9 ± 0.6	0.008
Postoperative nausea and vomiting, n (%)	5 (10.2)	13 (26.5)	0.037*
Dizziness, n (%)	7 (14.3)	5 (10.2)	0.54
Shivering, n (%)	5 (10.2)	6 (12.2)	0.75
Excessive sedation, n (%)	4 (8.2)	5 (10.2)	1.00
Respiratory depression, n (%)	1 (2.0)	3 (6.1)	0.62
Delayed recovery, n (%)	3 (6.1)	4 (8.2)	1.00

*Values are mean ± SD or n (%). p values by Pearson chi-square test, or by Fisher exact test where any expected cell count was below five (excessive sedation, respiratory depression, delayed recovery). ISAS, Iowa Satisfaction with Anaesthesia Scale. *PONV: p = 0.037 by chi-square but p = 0.066 by Fisher exact test; absolute difference 16.3%, 95% CI 1.3% to 31.3%.*

The mean ISAS score was 0.3 points higher in the OFA group (95% CI 0.08 to 0.52; p = 0.008). Postoperative nausea and vomiting occurred in 5 of 49 patients (10.2%) in the OFA group and 13 of 49 (26.5%) in the OBA group, an absolute reduction of 16.3% (95% CI 1.3% to 31.3%; risk ratio 0.38; number needed to treat 6). This difference was significant by the chi-square test (p = 0.037) but not by the Fisher exact test (p = 0.066), so it should be interpreted with caution. Dizziness, shivering, excessive sedation, respiratory depression and delayed recovery were infrequent and did not differ significantly between the groups.

Overall summary of findings

Taken together, opioid-free anaesthesia was associated with an attenuated haemodynamic response to intubation, lower pain scores in the first two postoperative hours, a longer interval before rescue analgesia was required and less postoperative nausea and vomiting. Bradycardia was more frequent in the OFA group, and differences in most recovery parameters and in cumulative postoperative opioid consumption did not reach significance. Because no single primary endpoint was prespecified and the comparisons were not adjusted for multiplicity, these findings should be treated as hypothesis-generating.

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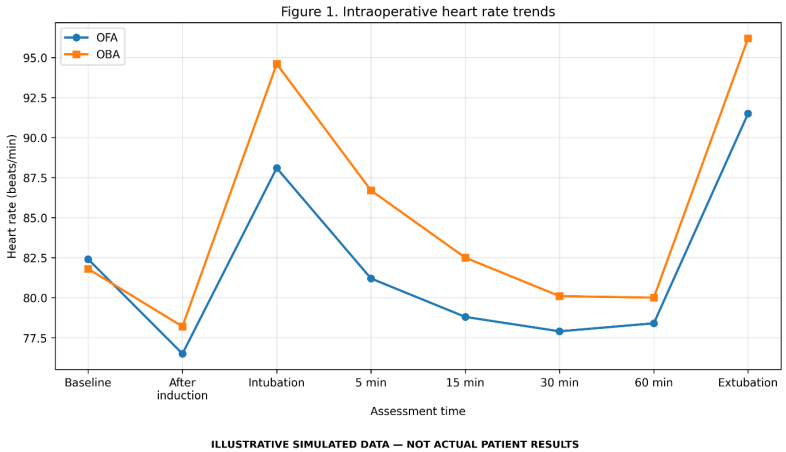


Figure 1. *Intraoperative heart rate in the OFA and OBA groups. Heart rate rose more steeply after intubation in the OBA group, and the two groups converged during maintenance of anaesthesia.*

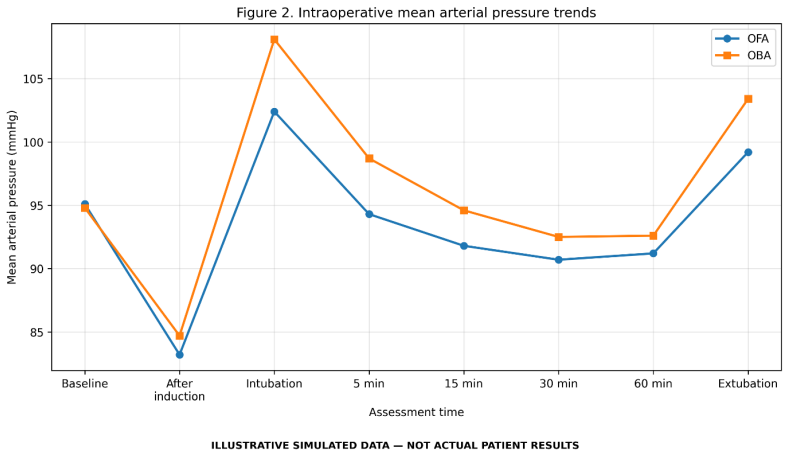


Figure 2. *Intraoperative mean arterial pressure in the OFA and OBA groups. The post-intubation rise in MAP was greater in the OBA group, and values in both groups returned gradually towards baseline during maintenance.*

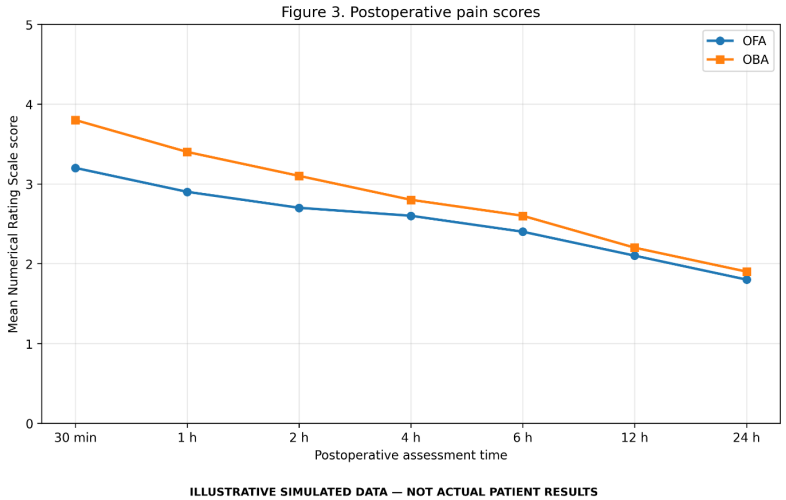


Figure 3. *Postoperative NRS pain scores. Mean scores were lower in the OFA group in the early postoperative period, particularly at 30 minutes and one hour, and the groups converged at later assessments.*

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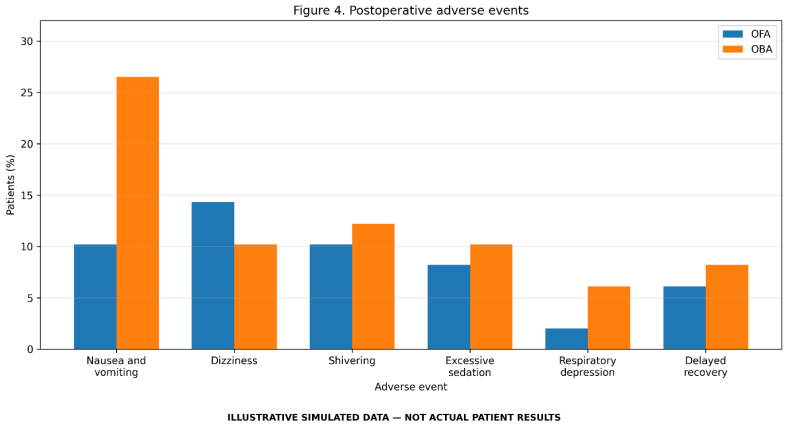


Figure 4. *Postoperative adverse events. Postoperative nausea and vomiting was more frequent in the OBA group, whereas bradycardia was more frequent in the OFA group. Differences in dizziness, shivering and excessive sedation were small.*

DISCUSSION

We compared opioid-free with conventional opioid-based anaesthesia in 98 adults undergoing elective surgery. OFA was associated with better control of the haemodynamic response to laryngoscopy and intubation, modestly lower pain scores in the first two postoperative hours, a longer interval before rescue analgesia, higher patient-reported recovery and satisfaction scores, and less postoperative nausea and vomiting. Bradycardia, on the other hand, was more frequent. These results are consistent with a role for multimodal opioid-free techniques as an alternative to opioid-based anaesthesia in selected patients, but the heterogeneous surgical population, the non-randomised allocation and the number of unadjusted comparisons mean that they should be read as hypothesis-generating rather than confirmatory.

In the present study, the mean heart rate immediately after intubation was 88.1 ± 10.2 beats/min in the opioid-free anaesthesia (OFA) group compared with 94.6 ± 11.4 beats/min in the opioid-based anaesthesia (OBA) group ($p = 0.004$). Similarly, the mean arterial pressure was lower in the OFA group (102.4 ± 9.3 mmHg) than in the OBA group (108.1 ± 10.2 mmHg; $p = 0.005$), suggesting a potentially attenuated sympathetic response to airway manipulation with OFA. Dexmedetomidine may contribute to this effect through central alpha-2 adrenergic agonism, which reduces sympathetic outflow while providing sedative and analgesic effects, whereas ketamine provides additional analgesia through NMDA-receptor antagonism. These findings are consistent with those reported by Swamy et al. [17], who, in a randomised double-blind study involving 70 patients undergoing laparoscopic surgery, observed a smaller increase in heart rate following intubation and extubation with dexmedetomidine- and ketamine-based opioid-free anaesthesia compared with a fentanyl-based technique. Similarly, Rani et al. [18] reported attenuation of intraoperative haemodynamic responses with OFA in patients undergoing spine surgery, supporting the potential haemodynamic benefits of opioid-free anaesthetic techniques. However, contrasting findings were reported by Tu et al. [19] in patients undergoing laparoscopic cholecystectomy at an altitude of 3,600 meters. Their study demonstrated significantly higher mean arterial pressure in the OFA group following induction (87.9 ± 12.3 versus 77.2 ± 11.7 mmHg) and 10 minutes after incision (83.5 ± 14.9 versus 72.5 ± 9.8 mmHg), along with a transient increase following intubation. These findings are contrary to the haemodynamic pattern observed in our study and highlight that the cardiovascular effects of OFA may vary according to the combination of anaesthetic drugs, their dosages and timing, surgical stimulation and patient-related factors. Importantly, although the differences in heart rate and mean arterial pressure in our study reached nominal statistical significance, neither remained statistically significant after Bonferroni correction for multiple haemodynamic comparisons (adjusted significance threshold $p < 0.003$). Therefore, these findings should be interpreted as exploratory evidence of a potentially favourable hemodynamic profile rather than definitive proof of superior haemodynamic stability [17–19].

Early postoperative analgesia also favoured OFA in our patients, with a mean NRS score at 30 minutes of 3.2 ± 1.1 versus 3.8 ± 1.2 ($p = 0.011$) and a longer mean time to first rescue analgesia (165 ± 54 versus 132 ± 48 minutes; $p = 0.002$). The difference in pain score, 0.6 points on an 11-point scale, is statistically detectable but below the threshold usually taken as clinically meaningful, so the more convincing analgesic signal is the delay in the first rescue requirement. Feenstra et al.

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[9], in a systematic review of 38 studies, found no clinically relevant overall difference in pain scores or opioid consumption between OFA and OBA, though they did report a modest improvement in quality of recovery, less PONV and more bradycardia. Chassery et al. [20], in 80 patients undergoing ambulatory total hip arthroplasty, found similar pain scores and opioid consumption with opioid-free and opioid-sparing techniques. The analgesic benefit of OFA therefore seems to vary with the procedure, the baseline pain risk, the use of regional techniques and the particular drugs chosen [9,20].

The mean 24-hour QoR-15 score was 126 ± 11 with OFA and 121 ± 13 with OBA (p = 0.043). The 5-point difference is smaller than the minimal clinically important difference of 8 points established for this instrument [16], and its confidence interval extends almost to zero, so the result indicates at most a modest improvement in early well-being. Feenstra et al. [9] reported an improvement in pooled quality-of-recovery scores with OFA, although from only two studies. Yang et al. [21], pooling 10 randomised trials and 1,106 patients undergoing video-assisted thoracoscopic surgery, found the 24-hour QoR-40 score improved by 2.914 points (95% CI 1.017 to 4.811), again below the accepted clinically important threshold. Our finding fits that pattern: a measurable but small improvement rather than a substantial advantage [9,21,16].

Patient satisfaction was also higher with OFA (mean ISAS 5.2 ± 0.5 versus 4.9 ± 0.6; p = 0.008), which probably reflects the combination of adequate pain control, less nausea and an uneventful early recovery. Satisfaction is nevertheless shaped by preoperative expectation, communication, postoperative comfort and the hospital experience as a whole, and both groups scored in the "highly satisfied" and "satisfied" bands, so the difference should be read as a patient-reported outcome rather than as evidence of superior anaesthetic efficacy.

PONV was less frequent after OFA, occurring in 5 of 49 patients (10.2%) compared with 13 of 49 (26.5%). The difference reached significance by chi-square (p = 0.037) but not by the Fisher exact test (p = 0.066), so the finding is suggestive rather than secure in a sample of this size. It is nonetheless consistent with much larger pooled analyses. Qin et al. [22], in a systematic review of 68 randomised trials and 5,426 patients, found a significant reduction in PONV with OFA (RR 0.50, 95% CI 0.39 to 0.64) and a lower requirement for postoperative rescue analgesia (RR 0.61, 95% CI 0.51 to 0.72), and Yang et al. [21] reported a similar reduction after thoracoscopic surgery (RR 0.41, 95% CI 0.380 to 0.665). Avoiding intraoperative opioid plausibly removes an emetogenic stimulus, although differences in antiemetic prophylaxis and surgical population affect the size of the benefit [22,21].

The adverse-event profile needs balanced interpretation. Although PONV and respiratory depression were less frequent with OFA, bradycardia occurred roughly twice as often (9 of 49, 18.4%, versus 4 of 49, 8.2%), and four patients needed atropine compared with one. This is a recognised consequence of dexmedetomidine-containing regimens, and Feenstra et al. [9] identified the same signal. The point is not that one technique is safer than the other but that removing opioids changes the pattern of drug-related complications rather than abolishing it, and bradycardia with OFA is the trade-off for less nausea and vomiting. Careful dose selection, continuous haemodynamic monitoring and prompt treatment of bradycardia and hypotension remain essential, and the meta-analysis by Qin et al. [22] similarly concluded that the benefits of OFA must be weighed against variability in other recovery outcomes [9,22].

Recovery times showed a numerical advantage for OFA in extubation time (8.4 ± 3.1 versus 9.1 ± 3.5 minutes) and PACU stay (52 ± 16 versus 58 ± 19 minutes), but neither difference was significant and neither was adjusted for surgical duration or anaesthetic exposure. Tu et al. [19] found the opposite, with a longer awakening time in their OFA group (20.4 ± 7.5 versus 10.6 ± 8.2 minutes), probably reflecting the sedative load of their dexmedetomidine-esketamine regimen. Emergence therefore appears to depend more on the dose and timing of the substitute drugs than on opioid avoidance itself [19]. Overall, our findings suggest that OFA may offer advantages in selected perioperative outcomes, particularly the haemodynamic response to intubation, PONV and patient-reported recovery, while the evidence from systematic reviews and procedure-specific trials remains mixed. They support an individualised multimodal approach rather than the wholesale replacement of opioid-based anaesthesia.

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CONCLUSION

In this observational comparison, opioid-free anaesthesia was associated with a lower post-intubation heart rate (88.1 ± 10.2 versus 94.6 ± 11.4 beats/min) and mean arterial pressure (102.4 ± 9.3 versus 108.1 ± 10.2 mmHg), a longer time to first rescue analgesia (165 ± 54 versus 132 ± 48 minutes), a higher 24-hour QoR-15 score (126 ± 11 versus 121 ± 13) and a lower incidence of postoperative nausea and vomiting (10.2% versus 26.5%) than conventional opioid-based anaesthesia, at the cost of more frequent bradycardia. The differences in quality of recovery and in early pain scores were smaller than the accepted thresholds for clinical importance, and none of the haemodynamic comparisons would survive adjustment for multiple testing. These results are therefore best regarded as hypothesis-generating. They support the feasibility of multimodal opioid-free anaesthesia in routine elective practice, with careful monitoring for bradycardia and hypotension, and they need confirmation in adequately powered, multicentre randomised trials with a single prespecified primary endpoint.

LIMITATIONS OF THE STUDY

This study has several limitations. The non-randomized allocation of anaesthetic technique may have introduced selection bias and confounding, while blinding of anaesthetists was not feasible. The absence of a prespecified primary endpoint and multiple haemodynamic comparisons without statistical adjustment increase the possibility of chance findings; none of these comparisons remained significant after Bonferroni correction. The relatively small sample size (n = 98) limited the power to detect uncommon adverse events, with wide confidence intervals for bradycardia and postoperative nausea and vomiting. Inclusion of different surgical categories introduced clinical heterogeneity, and no adjusted or subgroup analyses were performed. Variations in the OFA drug combinations and doses also limit attribution of outcomes to individual agents. Subjective pain and satisfaction assessments may have been influenced by patient expectations and perioperative care. Furthermore, the observed between-group differences in pain scores (0.6 points) and QoR-15 scores (5 points) were below their respective clinically important thresholds of approximately 1.3–2 points and 8 points. Finally, follow-up was limited to 24 hours, precluding assessment of long-term opioid consumption, persistent postsurgical pain and functional recovery. Larger multicentre randomized controlled trials with standardized anaesthetic protocols, prespecified primary endpoints, appropriate adjustment for multiple comparisons and extended follow-up are warranted.

Ethical approval: Approved by the Institutional Ethics Committee, Deccan College of Medical Sciences, Hyderabad (reference DCM/ETHICS/205/251, 2024).

Funding: NIL

Conflicts of interest: None declared.

Author Contributions: MAC contributed to the conception and design of the study, data collection, analysis and interpretation of findings, and preparation of the initial manuscript. EMS contributed to study supervision, development and implementation of the anaesthetic protocol, and critical revision of the manuscript for important intellectual content. HPL contributed to statistical analysis, interpretation of results, and manuscript preparation. All authors critically reviewed and approved the final version of the manuscript.

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