

Multiphasic Multimodal Analgesia for Postoperative Pain Management Following Abdominal Surgeries: A Randomized Controlled Clinical Trial

Haroon M. Khalil^{1,2*} , Dr. Rawand Musheer Haweizy³ 

¹Department of Nursing, Hawler Medical University, Kurdistan Region, Iraq.

²Department of Nursing, Soran Technical College, Erbil Polytechnic University, Kurdistan Region, Iraq.

³College of Medicine, Hawler Medical University, Kurdistan Region, Iraq

*Correspondence to: Haroon M. Khalil (E-mail: haroon.khalil@nur.hmu.edu.krd)

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Abstract:

Objectives: This study aims to evaluate a four-phasic MMA protocol vs the standard of care pain management in candidate patients for elective abdominal surgeries.

Methods: The study was a randomized controlled clinical trial conducted at two tertiary hospitals in Iraq. One hundred thirty-two patients undergoing elective abdominal surgery were randomized 1:1 to intervention or control (standard of care). The intervention group received preoperative education and a combination of pharmacologic and non-pharmacologic interventions during the preoperative, intraoperative, postoperative, and discharge phases. The primary outcome was the area under the curve (AUC) of the VAS pain score-time over 72 hours. Secondary outcomes included opioid consumption, recovery milestones, functional recovery (QoR-15), patient satisfaction, and adverse events.

Results: The intervention group demonstrated a significant reduction of pain AUC at 72 hours (median 162 vs 318, $P < 0.001$), opioid consumption ($P < 0.001$ at 24, 48, and 72 hours). The incidences of both constipation and nausea/vomiting were significantly lower in the intervention group. Postoperatively, both quality of recovery (QoR) and patient satisfaction demonstrated significant improvement in the intervention group compared to the controls ($P < 0.001$).

Conclusion: Our structured four-phasic MMA protocol demonstrated superior efficacy and safety compared to opioid-based postoperative pain management in patients undergoing elective abdominal surgeries.

Keywords: Multimodal analgesia, postoperative pain, abdominal surgeries, pain control

Introduction

Despite advances in surgical and anesthetic care, postoperative pain continues to pose a significant challenge in modern healthcare, with nearly 60% of patients experiencing moderate to severe pain in the first two weeks after discharge and fewer than half achieving adequate pain control.^{1,2} Moreover, the absence of standardized pain assessment protocols contributes to persistent inadequacies in pain management across clinical settings, potentially leading to delayed recovery, increased length of stay, escalated healthcare costs, and a higher risk of chronic postoperative pain.^{1,3} Effective postoperative pain control is therefore essential to improve recovery, enhance patient satisfaction, and reduce the risk of long-term complications. Optimizing postoperative analgesia has become both a clinical goal and a healthcare system requirement due to the increased focus on value-based perioperative treatment.

Postoperative pain has traditionally been managed with opioid analgesics, which remain the cornerstone of acute pain control in surgical practice.⁴ Although opioids provide potent analgesia, their use is frequently associated with adverse effects such as sedation, respiratory depression, urinary retention, nausea, vomiting, ileus, and pruritus.⁵ Additionally, opioid overdose can be fatal, and even therapeutic use may lead to dependence or substance use disorder.⁶ It was estimated that 6–10% of opioid-naïve surgical patients continue opioid use beyond the expected recovery period, raising the risks of chronic opioid dependence.⁷ Collectively, these complications not only impair recovery by delaying mobilization and gastrointestinal function but also contribute to the broader opioid epidemic.⁸ A recent meta-analysis demonstrated that, compared with opioid-based regimens, opioid-sparing analgesia

significantly reduces 24-hour morphine consumption, lowers pain scores, and decreases the incidence of postoperative nausea, vomiting, and pruritus, while improving overall patient satisfaction.⁹ Interest in opioid-sparing perioperative techniques that can enhance analgesia while reducing opioid exposure and associated risks has increased as a result of these findings.

Multimodal analgesia (MMA) addresses the limitations of opioid-centric pain management by combining multiple complementary strategies to control pain through diverse mechanisms.³ In an MMA protocol, clinicians use various pharmacologic and regional techniques, each with distinct mechanisms of action, to achieve synergistic analgesia, minimize individual drug doses, and reduce opioid requirements.^{10,11} Non-opioid agents such as NSAIDs, acetaminophen, gabapentinoids, NMDA receptor antagonists, alpha-2 adrenergic agonists, and local anesthetics are often combined with regional or neuraxial blocks. These agents act on different components of the pain pathway, including prostaglandin synthesis, calcium and sodium channel modulation, and central adrenergic signaling.^{10,11} By doing so, MMA enhances analgesic efficacy while limiting opioid-related adverse effects.^{6,8} This concept has become a core element of enhanced recovery after surgery (ERAS) protocols worldwide. Nevertheless, there is still a great deal of uncertainty about the best combination, timing, and phase-specific integration of multimodal therapies throughout the perioperative continuum, despite the general support for MMA.

Despite ongoing efforts to evaluate the efficacy of MMA in improving postoperative outcomes, no universally standardized protocol currently exists. Previous studies have differed in their selection of agents, dosages, timing, and combinations,

resulting in variable outcomes in terms of pain relief, opioid consumption, and recovery. Moreover, most investigations have primarily focused on isolated postoperative interventions rather than implementing a comprehensive perioperative strategy that integrates pre-, intra-, and postoperative components.¹²⁻¹⁴ Furthermore, only a small number of randomized trials have assessed organized multiphasic MMA regimens that integrate non-pharmacologic therapies, pharmacologic optimization, regional methods, and patient education into a single, standardized framework. This is a significant evidence gap, especially in abdominal surgery, where opioid exposure and postoperative pain burden are still high.

The present study aims to address these gaps by evaluating a standardized, four-phase MMA protocol combining preoperative education, intraoperative regional or neuraxial techniques, and postoperative pharmacologic and non-pharmacologic measures to assess its effectiveness in optimizing pain control, minimizing opioid requirements, and enhancing patient recovery and satisfaction in elective abdominal surgery. Our hypothesis was that this structured multiphasic MMA approach would improve recovery outcomes, decrease opioid intake, lessen postoperative pain, and increase patient satisfaction when compared to standard opioid-based therapy.

Methods

Study Design

This was a multicenter, parallel-group, randomized controlled trial with a 1:1 allocation ratio conducted at two tertiary care hospitals in Erbil City, Iraq, between June 2024 and September 2025. The trial was conducted in accordance with the Declaration of Helsinki and adhered to the guidelines of Good Clinical Practice (GCP). Ethical approval was obtained from the institutional review boards of both participating hospitals before patient enrollment. The study was prospectively registered on ClinicalTrials.gov (NCT07019103), and written informed consent was obtained from all participants prior to enrollment. Ethical approval was obtained from the Institutional Review Boards of Rizgary and Soran teaching hospital prior to patient recruitment (Approval No. 2429 from Hawler Medical University college of Nursing Ethics Committee dated 22-August 2024).

Patients

Adult patients scheduled for elective abdominal surgery at either participating hospital were screened for eligibility through preoperative clinic visits and surgical scheduling lists. Patients satisfied the inclusion criteria if they met all of the following criteria: (1) age ≥ 18 years; (2) planned for elective abdominal surgery including cholecystectomy, appendectomy, hernia repair, or bowel resection; (3) American society of anesthesiologists (ASA) physical status classification I-III; (4) capable of providing written informed consent; and (5) able to comprehend and comply with the study protocol, including pain assessments and follow-up requirements.

Patients were excluded if they met any of the following criteria: (1) scheduled for emergency or urgent laparotomy; (2) Chronic pain disorder requiring daily opioid use (more than 30 milligrams morphine equivalents [MME] per day) for ≥ 3 months prior to surgery; (3) history of substance use

disorder within the past 5 years; (4) marked hepatic insufficiency (Child-Pugh class C) or compromised renal function (estimated glomerular filtration rate < 30 mL/min/1.73m²); (5) allergic reactions or clinical contraindications to any component of the multimodal pain management protocol; (6) cognitive deficits preventing reliable self-reporting of pain scores; or (7) pregnancy or breastfeeding.

Randomization

Eligible study participants were randomly assigned to either the intervention or control group in a 1:1 ratio using computer-generated random numbers. To adjust for the multicenter designed, we used stratified randomization by hospital. Within each hospital, we applied permuted block randomization with variable block sizes of 2, 4, or 6 to maintain balance between groups. Randomization was performed using the “block Rand” package in R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). Randomization lists were prepared separately for each hospital. Randomization sequences were packaged in sequentially numbered, opaque envelopes to ensure allocation concealment. Each envelope contained the treatment assignment card and was opened by the attending physician only after patient eligibility was confirmed, informed consent obtained, and baseline assessments completed. Research coordinators responsible for outcome assessment were not involved in the randomization process.

Intervention

The multimodal protocol for the intervention group included 4 distinct phases: preoperative, intraoperative, postoperative, and discharge phases. In the preoperative phase, patients received structured education delivered by trained pain management specialists during a dedicated preoperative session. The educational intervention included interactive explanation of the surgical procedure, expected pain trajectories, and accessible pain management options strategies. Patients were instructed on the proper use of the (VAS) pain scale for pain reporting. As part of preemptive analgesia, gabapentin 300 mg was administered orally two hours before surgery, unless contraindicated.

Intraoperatively, general anesthesia followed a structured protocol including pre-medication with midazolam (0.02–0.04 mg/kg IV), induction with propofol (1.5–2.5 mg/kg IV), and maintenance with isoflurane or sevoflurane (0.5–1.5 minimum alveolar concentration [MAC]).

In the postoperative phase, both non-pharmacological and pharmacological interventions were employed. Non-pharmacological measures included: (1) early mobilization; (2) physical therapy beginning on postoperative day 1, supervised by licensed physical therapists; (3) transcutaneous electrical nerve stimulation (TENS) units made available for patient use with instruction on proper application provided by researcher.

The medication regimen consisted of scheduled non-opioid analgesics as the foundation of pain control. According to local institutional protocol, patients received either ibuprofen 400 mg orally every 6 hours or diclofenac 50 mg orally every 8 hours for the first 48 hours postoperatively, unless contraindicated. This was complemented by acetaminophen 1,000 mg orally every 6 hours, not exceeding 4,000 mg/day. For breakthrough pain (VAS > 4 despite scheduled analgesics),

tramadol 50–100 mg orally every 6 hours was administered on an as-needed basis. Adjuvant medications included gabapentin 100–300 mg orally three times daily, titrated based on patient response and tolerability, and cyclobenzaprine 5 mg orally three times daily as needed for muscle spasms.

At discharge, patients and family members received training on proper use of pharmacological and non-pharmacological interventions at home. Patients were provided with written instructions for pain management and warning signs requiring medical attention.

Participant in the control group received standard perioperative care according to each hospital's existing protocols. This typically included general anesthesia with standard intraoperative management, postoperative pain control primarily with opioid-based regimens (morphine or fentanyl patient-controlled analgesia or scheduled intramuscular/intravenous opioids), supplemented with non-opioid analgesics at the physician discretion. (physical therapy, CBT, TENS), and preemptive gabapentin were not routinely provided. Patients received standard preoperative counseling and discharge instructions as per usual care.

Blinding

Complete blinding was not possible in this trial because of the multimodal intervention's nature. Treatment allocation was not concealed from patients or the treating professionals (surgeons, anesthesiologists, and nurses in charge of administering the intervention). However, the study coordinators who collected outcome data and assessed pain were not involved in the intervention's administration and were blinded to group assignment. Until the primary analysis was finished, an analyst who was blind to treatment allocation conducted statistical analyses.

Outcomes

The primary end point was the area under the curve (AUC) for pain intensity over the first 72 hours following surgery completion (i.e., from the time of arrival to the post-anesthesia care unit), calculated using the trapezoidal rule (Lang-Illievich et al. 2020). Pain intensity was assessed using an 11-point visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst imaginable pain) at 2, 6, 12, 24, 48, and 72 hours postoperatively. Pain assessments were conducted by trained research nurses who were not involved in delivering the interventions and who received standardized training on VAS administration prior to study initiation. Recovery milestones were assessed daily and time to each milestone included: (1) time to first ambulation (defined as walking at least 10 meters with or without assistance); (2) time to first oral intake (defined as tolerating at least 100 mL of clear liquids without vomiting); (3) time to first flatus (patient-reported passage of intestinal gas); and (4) length of hospital stay (time from surgery completion to hospital discharge). Overall recovery time was defined as the maximum of these four milestones. Cumulative opioid consumption was measured at 24, 48, and 72 hours postoperatively. All opioid medications were converted to oral morphine milligram equivalents (MME) using standard conversion factors.¹⁵ The Quality of Recovery-15 (QoR-15) questionnaire was administered preoperatively (within 24 hours before surgery) and on postoperative day 7 or discharge, whichever

comes first. The QoR-15 is a validated 15-item instrument assessing five aspects of recovery: physical comfort (5 items), emotional state (4 items), physical independence (2 items), psychological support (2 items), and pain (2 items).¹⁶

Patient experience and satisfaction with pain management was assessed at 24 hours postoperatively, 48 hours postoperatively, and at hospital discharge using a 5-point Likert scale: 1 = strongly dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, and 5 = strongly satisfied. The incidence of specific adverse events was prospectively monitored from surgery completion through postoperative day 7 or hospital discharge, whichever occurred first. Adverse events were actively solicited at each postoperative assessment through structured inquiry by research nurses, rather than passive spontaneous reporting, to ensure systematic and complete capture of all clinically relevant events.

Sample Size and Statistical Analysis

Based on the findings from the previous literature, we assumed a 20% reduction in VAS-time AUC is a clinically meaningful difference in at 72 hours postoperative (Viscusi et al. 2019). Considering a two-sided alpha of 0.05, power of 80%, and an additional 10% to account for potential dropouts and between-hospital variability, we estimated that the sample size should be at least 132 patients using two-sided t-test.

Continuous variables were summarized as the mean $\pm$ SD or median (IQR), based on a normality check performed using the Shapiro-Wilk test. Normally distributed data were compared using an independent t-test; otherwise, Wilcoxon rank test was utilized for non-parametric comparison. Categorical variables were presented as counts (percentages) and were compared using Pearson χ^2 or Fisher's exact tests as appropriate. Linear mixed-effects regression models accounting for hospital clustering were employed for continuous outcomes, with fixed effects for treatment, age, sex, weight, ASA status, surgery type, and surgical approach, and random intercepts for hospital. Since the dependent variable was the AUC of the VAS-time curve at 72 hours, no additional adjustment for intra-individual variability was performed. All hypothesis tests were two-sided with statistical significance defined as $P < 0.05$. Missing data were handled using complete case analysis, given $<10\%$ missingness for all outcomes. All analyses were performed using R software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants' Characteristics

A total of 150 candidates for elective abdominal surgeries were initially recruited. Of these, 132 patients met our selection criteria and were randomly assigned to the multimodal (intervention) group ($n = 67$) or the control group ($n = 65$). All randomized patients completed the study and were included in the current analysis (Figure 1).

Baseline characteristic of participants and clinical parameters were comparable between the study groups (Table 1), confirming that randomization achieved adequate balance across all key prognostic variables. The mean age was 52.3 ± 7.4 years, with 48% being male. The majority of our patients (73%) were classified as ASA class I or II. Abdominal

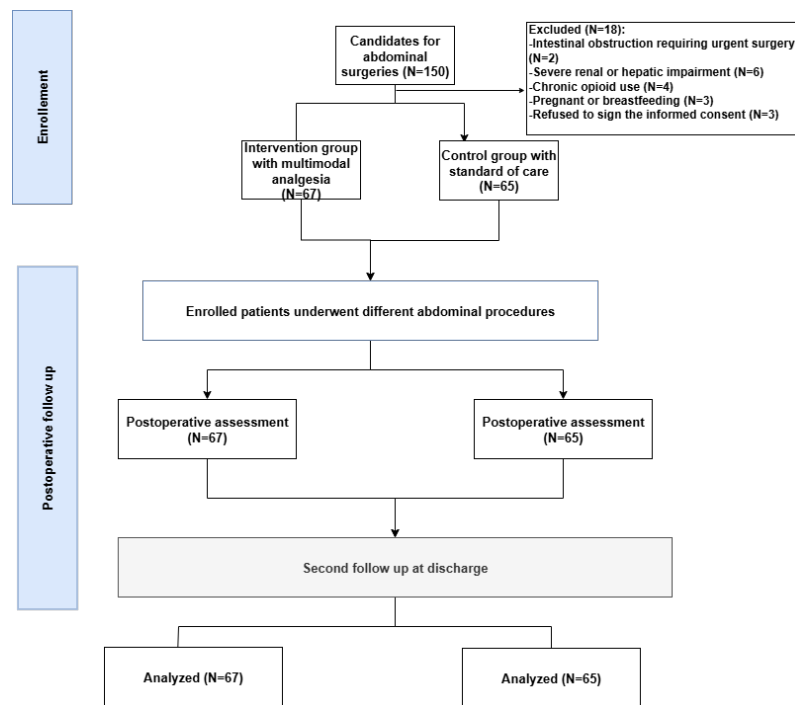


Fig. 1 Consort flow chart.

Table 1. Comparing baseline demographic and clinical characteristics between the study groups

Characteristic	Overall N = 132	Control N = 65	Intervention N = 67	P-value
Age (years)	52.3 ± 7.4	52.7 ± 8.1	51.9 ± 6.8	0.8 ²
Sex				0.12 ³
Female	68 (52%)	38 (58%)	30 (45%)	
Male	64 (48%)	27 (42%)	37 (55%)	
Height (cm)	169.7 ± 14.6	168.0 ± 15.4	171.4 ± 13.8	0.2 ²
Weight (kg)	82.0 ± 17.8	79.1 ± 15.6	84.9 ± 19.3	0.08 ²
Body mass index (kg/m ²)	28.4 ± 5.0	28.0 ± 4.4	28.8 ± 5.6	0.6 ²
ASA physical status				0.4 ³
I	41 (31%)	20 (31%)	21 (31%)	
II	56 (42%)	31 (48%)	25 (37%)	
III	35 (27%)	14 (22%)	21 (31%)	
Surgery type				0.2 ³
Appendectomy	28 (21%)	13 (20%)	15 (22%)	
Bowel resection	24 (18%)	13 (20%)	11 (16%)	
Cholecystectomy	50 (38%)	29 (45%)	21 (31%)	
Hernia repair	30 (23%)	10 (15%)	20 (30%)	
Surgical approach				0.8 ³
Laparoscopic	95 (72%)	46 (71%)	49 (73%)	
Open	37 (28%)	19 (29%)	18 (27%)	
Surgery duration (min)	76.5 (63.0, 105.0)	72.0 (61.0, 94.0)	87.0 (65.0, 146.0)	0.087 ²
Estimated blood loss (mL)	80.0 (71.0, 167.5)	80.0 (71.0, 167.0)	81.0 (70.0, 168.0)	0.9 ²
Regional block	40 (30%)	0 (0%)	40 (60%)	<0.001 ³
Preoperative VAS	1.5 (1.0, 2.0)	2 (1, 3)	1 (1, 2)	0.4 ²
Preoperative QoR-15 score	127.6 ± 16.8	127.5 ± 14.7	127.7 ± 18.8	0.6 ²

¹Mean ± SD; n (%); Median (Q1, Q3). ²Wilcoxon rank sum test. ³Pearson's Chi-squared test.

procedures were either appendectomy (21%), bowel resection (18%), cholecystectomy (38%), or hernial repair (23%). Most cases (72%) underwent laparoscopic rather than open surgery (28%). No significant differences were demonstrated in baseline VAS ($P = 0.4$) or QoR scores ($P = 0.6$). The only difference is the use of regional block in 40 cases (60%) of the intervention groups, since it was a part of our protocol for multimodal analgesia.

Pain Profiles

Pain trajectories assessed at 2, 6, 12, 24, 48, and 72 hours showed a consistent reduction in pain intensities across the intervention group compared to the controls. At 2 hours postoperatively, the difference was not statistically significant (median VAS 6 vs. 7 in the intervention group and control, respectively; $P = 0.12$). However, all the subsequent time points showed a significant reduction in VAS scores associated with the intervention compared to controls (Table 2, Figure 2). The median pain AUC over 0–72 hours was significantly lower in the intervention group (162 [78–293] VAS×h) compared with the control group (318 [199–446] VAS×h; $P < 0.001$).

Recovery Milestones

Patients in the intervention group achieved all recovery milestones significantly faster than those in the control group (Table 3). The median time to first ambulation was 18 hours vs 28 hours ($P < 0.001$), and the median time to first oral intake was 12 hours vs. 20 hours ($P < 0.001$). The median time to first flatus was also shorter in the intervention group (36 hours vs 51 hours; $P < .001$). Consequently, the median recovery time (72 hours vs 120 hours; $P < 0.001$) and length of hospital stay (3 days vs 5 days; $P < 0.001$) were significantly reduced in the intervention group.

Opioid Consumption

The use of multimodal analgesia was associated with a consistent pattern of reduced opioid consumption at 24, 48, and 72 hours ($P < 0.001$ for all). The intervention group required significantly lower rescue tramadol doses (median [IQR], 1 [0–2]) compared to controls (median [IQR], 2 [1–3]; $P < 0.001$). A summary of opioid consumption of both groups is depicted in Table 4.

Table 2. Comparing pain trajectories between the study groups

Characteristic	Overall N = 132	Control N = 65	Intervention N = 67	P-value
VAS at 2 h	6 (4, 8)	7 (4, 8)	6 (3, 7)	0.12 ²
VAS at 6 h	5 (3, 6)	6 (4, 7)	4 (2, 5)	<0.001 ²
VAS at 12 h	5 (2, 7)	6 (3, 7)	3 (1, 6)	0.004 ²
VAS at 24 h	3 (1, 6)	4 (3, 7)	3 (0, 5)	0.002 ²
VAS at 48 h	3 (0, 6)	4 (2, 7)	1 (0, 3)	<0.001 ²
VAS at 72 h	2 (0, 4)	3 (1, 5)	1 (0, 3)	<0.001 ²
Pain AUC over 0–72 h (VAS×h)	236 (121, 365)	318 (199, 446)	162 (78, 293)	<0.001 ²

¹Median (Q1, Q3); ²Wilcoxon rank sum test.

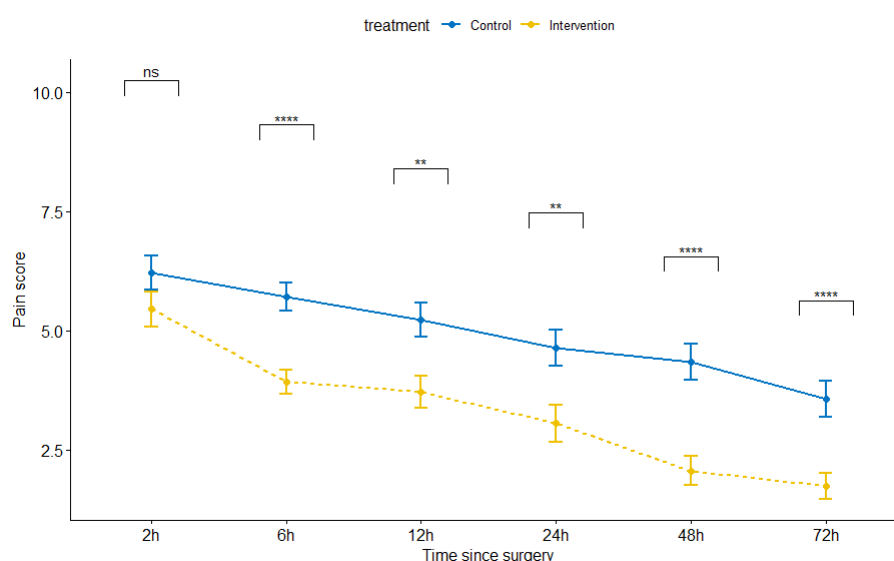


Fig. 2 Postoperative pain trajectories across 72 hours postoperatively. Data are presented as mean $\pm$ SD. P values calculated at each time point using Wilcoxon-rank sum test; “ns” denotes non-significant difference, **: $P < 0.01$, ***: $P < 0.001$, ****: $P < 0.0001$.

Table 3. Comparing time to recovery milestones between the study groups

Characteristic	Overall N = 132	Control N = 65	Intervention N = 67	P-value
Time to first ambulation (h)	24 (18, 28)	28 (27, 30)	18 (16, 20)	<0.001 ²
Time to first oral intake (h)	16 (12, 20)	20 (18, 23)	12 (11, 14)	<0.001 ²
Time to first flatus (h)	43 (36, 51)	51 (50, 54)	36 (34, 38)	<0.001 ²
Recovery time (h)	96 (72, 120)	120 (96, 120)	72 (48, 96)	<0.001 ²
Length of stay (days)	4 (3, 5)	5 (4, 5)	3 (2, 4)	<0.001 ²

¹Median (Q1, Q3); ²Wilcoxon rank sum test.

Table 4. Comparing opioid consumption between study groups

Characteristic	Overall N = 132	Control N = 65	Intervention N = 67	P-value
Cumulative opioid consumption to 24 h (MME)	19.6 ± 12.0	26.6 ± 10.1	12.9 ± 9.7	<0.001 ²
Cumulative opioid consumption to 48 h (MME)	37.4 ± 25.4	53.7 ± 22.6	21.6 ± 16.5	<0.001 ²
Cumulative opioid consumption to 72 h (MME)	52.3 ± 40.2	78.1 ± 38.1	27.3 ± 22.9	<0.001 ²
Number of rescue tramadol doses	2(1–3)	2(1–3)	1(0–2)	<0.001 ²

¹Mean ± SD; Median(Q1-Q3); ²Wilcoxon rank sum test.

Adverse Events

Despite the statistically non-significant difference ($P = 0.052$), the incidence of overall opioid-related adverse events was marginally lower in the intervention group (28% vs. 45%) (Table 5). Constipation, the most common opioid-related complication, occurred significantly less frequently in the intervention group (18% vs. 37%, $P = 0.014$). Also, PONV was significantly lower in the intervention group (24% vs. 74%, $p < 0.001$). Moderate to severe PONV (grades 2–3) occurred in 7.5% of intervention patients versus 26% of controls.

Respiratory depression occurred in 3 patients, all of them were from the control group. Other opioid-related adverse events, including pruritus (1.5% vs. 0%, $P > 0.9$), urinary retention (4.5% vs. 6.2%, $P = 0.7$), and excessive sedation (9.0% vs. 15%, $P = 0.32$), showed no significant differences between groups.

Post operative complications, including incisional infections, wound dehiscence, and postoperative ileus, were presented with an overall rate between 4–7%, with no differences between the study groups. The mean number of adverse events per patient was non-significantly lower in the intervention group (0.4 vs. 0.7, $P = 0.078$). A summary of the adverse event rates in both groups is depicted in Table 5.

Functional Recovery and Satisfaction

A significant enhancement in both quality of life and satisfaction measures were demonstrated with the intervention group compared with the control. The mean QoR-15 was significantly higher in the intervention (141.2 ± 15.4 vs. 127.8 ± 21.6; $P < 0.001$; Figure 3). Compared to baseline, this is translated to a median of a 12-point increase in QoR-15 in the intervention compared to a 1-point increase in control. Rates of satisfaction or strong satisfaction were also consistently higher in the intervention group at 24 hours (92% vs 65%; $P < 0.001$),

48 hours (100% vs 62%; $P < 0.001$), and at discharge (89% vs 40.2%; $P < 0.001$) (Table 6).

Prediction of the Area Under VAS-Time Curve

To account for the treatment effect of our multimodal analgesic intervention, a multivariable mixed-effects linear regression model was constructed, controlling for age, sex, weight, ASA category, surgery type, and the surgical approach (laparoscopic vs. open surgeries) regarding the primary outcome (the area under the VAS-time curve between zero and 72 hours). The intervention showed a significant decrease in AUC of 133 (95% CI -84, -183) compared to control ($P < 0.001$). Compared to appendectomy, all surgery types were associated with a significantly increased AUC, ranging from 7.4 for bowel resection to 83 for hernial repair ($P = 0.036$). Age, sex, weight, ASA, and surgical approach were not significantly associated with a change in AUC (Table 7).

Discussion

This study evaluated a structured four-phase multimodal analgesia (MMA) protocol for postoperative pain management following elective abdominal surgery. The findings of the study suggest that MMA is associated with significant reduction in pain scores, opioid consumption, and adverse event rates. Furthermore, our multimodal approach significantly enhanced postoperative recovery, as evidenced by improvement in time to first ambulation, oral intake, and passage of flatus. Collectively, these favorable outcomes were associated with significant reduction in length of stay and superior satisfaction with the MMA approach, compared to traditional opioid-based pain control strategies across multiple domains, including pain intensity, opioid consumption, safety, recovery, and patient satisfaction.

Table 5. Comparing adverse effects between the study groups

Characteristic	Overall N = 132	Control N = 65	Intervention N = 67	P-value
Any opioid-related adverse event	48 (36%)	29 (45%)	19 (28%)	0.052 ²
Constipation	36 (27%)	24 (37%)	12 (18%)	0.014 ²
PONV overall score				<0.001 ³
None	68 (52%)	17 (26%)	51 (76%)	
Mild	42 (32%)	31 (48%)	11 (16%)	
Moderate	15 (11%)	12 (18%)	3 (4.5%)	
Severe	7 (5.3%)	5 (7.7%)	2 (3.0%)	
Respiratory depression	3 (2.3%)	3 (4.6%)	0 (0%)	0.12 ³
Pruritus	1 (0.8%)	0 (0%)	1 (1.5%)	>0.9 ³
Urinary retention	7 (5.3%)	4 (6.2%)	3 (4.5%)	0.7 ³
Excessive sedation	16 (12%)	10 (15%)	6 (9.0%)	0.3 ²
Surgical site infection	7 (5.3%)	4 (6.2%)	3 (4.5%)	0.7 ³
Wound dehiscence	2 (1.5%)	0 (0%)	2 (3.0%)	0.5 ³
Postoperative ileus	4 (3.0%)	2 (3.1%)	2 (3.0%)	>0.9 ³
Number of adverse events	0.6 ± 0.8	0.7 ± 0.9	0.4 ± 0.7	0.078 ⁴

¹n (%); Mean ± SD; ²Pearson's Chi-squared test; ³Fisher's exact test; ⁴Wilcoxon rank sum test.

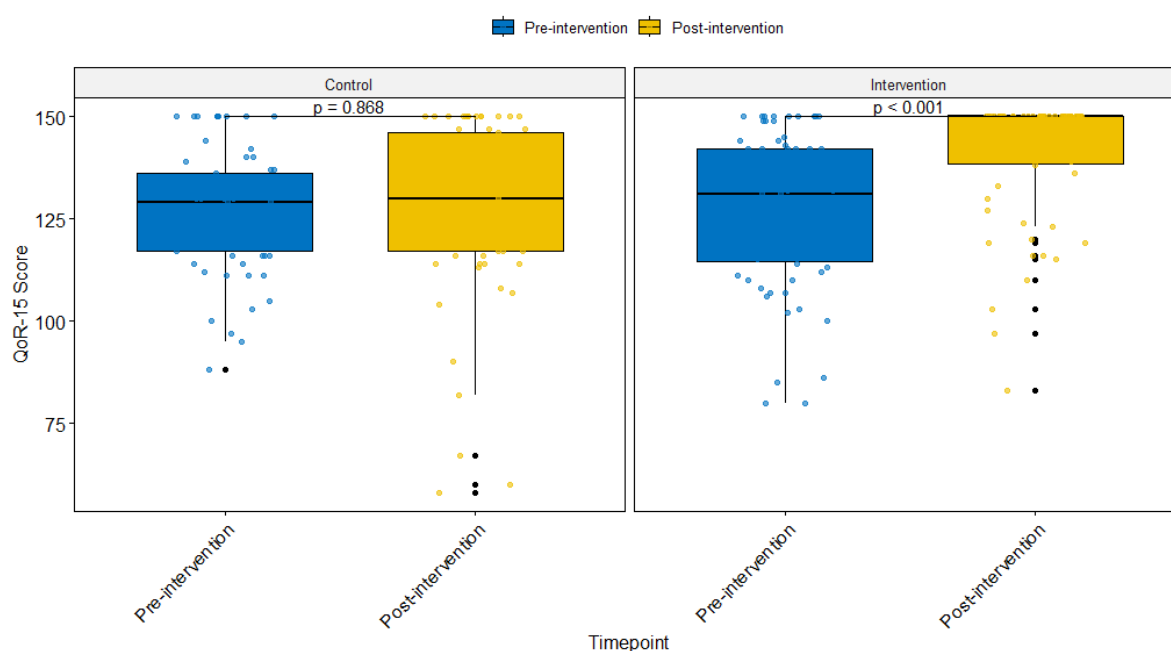


Fig. 3 Boxplots comparing the mean QoR-15 scores before surgery and discharge across the study groups. For each comparison, *P*-value was calculated using paired-t-test.

The superior efficacy of MMA compared to opioid therapy was consistently shown in the current literature. A recent meta-analysis including 37 RCTs demonstrated a significant reduction of postoperative opioid consumption associated with MMA in patients who underwent different obesity surgeries. This study showed that dexmedetomidine, ketamine, lidocaine, magnesium, and gabapentin significantly reduced postoperative opioid consumption after surgery.¹⁷ It was demonstrated that VAS pain scores in the multimodal

group were consistently and significantly lower at 2, 4, and 8 hours postoperatively compared to unimodal analgesia in a prospectively analyzed cohort of 60 adult patients undergoing abdominal surgeries. Additionally, they showed that patients in the MMA group required significantly fewer rescue doses of fentanyl and experienced a longer duration of analgesia before their first analgesic request, with a significantly lower incidence of sedation.¹⁸ Elsabeeny et al. demonstrated statistically significant reductions in intraoperative fentanyl consumption

Table 6. Comparing functional recovery and satisfaction profiles between the study groups

Characteristic	Overall N = 132	Control N = 65	Intervention N = 67	P-value
QoR-15 on POD 7	134.6 ± 19.8	127.8 ± 21.6	141.2 ± 15.4	<0.001 ²
Change in QoR-15 at POD 7	7.5 (0.0 – 17.0)	1.0 (–6.0 – 10.0)	12.0 (3.0 – 20.0)	<0.001 ²
Satisfaction at 24 h				<0.001 ³
Dissatisfied	11 (8.3%)	11 (17%)	0 (0%)	
Neutral	17 (13%)	12 (18%)	5 (7.5%)	
Satisfied	46 (35%)	31 (48%)	15 (22%)	
Strongly satisfied	58 (44%)	11 (17%)	47 (70%)	
Satisfaction at 48 h				<0.001 ⁴
Dissatisfied	6 (4.5%)	6 (9.2%)	0 (0%)	
Neutral	19 (14%)	19 (29%)	0 (0%)	
Satisfied	39 (30%)	27 (42%)	12 (18%)	
Strongly satisfied	68 (52%)	13 (20%)	55 (82%)	
Overall satisfaction at discharge				<0.001 ⁴
Strongly dissatisfied	8 (6.1%)	8 (12%)	0 (0%)	
Dissatisfied	11 (8.3%)	10 (15%)	1 (1.5%)	
Neutral	27 (20%)	21 (32%)	6 (9.0%)	
Satisfied	33 (25%)	20 (31%)	13 (19%)	
Strongly satisfied	53 (40%)	6 (9.2%)	47 (70%)	

¹Mean ± SD; Median(Q1-Q3); n (%); ²Wilcoxon rank sum test; ³Pearson's Chi-squared test; ⁴Fisher's exact test.

Table 7. Multivariable linear mixed-effects model predicting the area under the VAS-time curve at 72 hours postoperatively

Characteristic	Beta	95% CI	P-value
Treatment			<0.001
Control	—	—	
Intervention	–133	–183, –84	
Age (years)	–1.3	–4.6, 2.1	0.5
Sex			0.8
Female	—	—	
Male	15	–116, 145	
Weight (kg)	0.50	–6.6, 7.6	0.9
ASA category			0.6
I	—	—	
II	25	–31, 82	
III	27	–38, 92	
Surgery type			0.036
Appendectomy	—	—	
Bowel resection	7.4	–71, 86	
Cholecystectomy	80	12, 147	
Hernia repair	83	8.6, 157	
Surgical approach			0.2
Laparoscopic	—	—	
Open	40	–16, 96	

CI; Confidence interval.

($P < 0.001$) and 24-hour morphine consumption ($P = 0.001$) with preventive MMA versus morphine alone in 40 cancer patients undergoing major abdominal operations.¹⁹

The study suggests that the improved efficacy and safety outcomes demonstrated in the current study are primarily attributed to combining patient education with a variety of synergistically working non-pharmacologic and pharmacologic pain control strategies, including the use of NSAIDs, regional blocks, TENS, and adjuvants at different phases from the preoperative stage to discharge. The impact of preoperative education was shown in a recent meta-analysis of 37 RCTs, suggesting that combining patient education with analgesia resulted in significantly improved postoperative pain in orthopedic surgery patients. However, authors showed that education alone could not provide additional benefit for improved postsurgical recovery.²⁰

The addition of NSAIDs and paracetamol postoperatively was previously demonstrated to reduce opioid consumption with improved pain scores. A recent meta-analysis of 10 RCTs showed that the addition of 2 or more analgesic methods with different mechanisms, including opioids, NSAIDs, local anesthetics, and adjuncts, resulted in a statistically significant decrease in 24-hour postoperative pain scores with MMA and adverse events, and shortened hospital stay for hepatocellular carcinoma patients who underwent hepatectomy¹². In particular, paracetamol was shown to significantly decrease opioid consumption and opioid-related adverse effects in a meta-analysis of 5 studies, including 271 patients who underwent orthopedic surgeries.²¹

The role of regional block in MMA is presented with conflicting evidence in the current literature. A meta-analysis

of 8 studies, including 525 patients who underwent bariatric surgery, showed that TAP blocks when added to MMA reduced pain scores at all evaluated timepoints, decreased opioid requirements ($P < 0.001$), and shortened time to ambulation ($P = 0.009$), with no significant difference in the rates of opioid-related adverse effects.²² Geng et al. found that preoperative TAP block added to multimodal analgesia in open gynecological surgery significantly reduced rescue morphine requirements within 24 hours, lowered pain scores at early timepoints (1, 2, and 6 hours), reduced nausea incidence at 48 hours (25.8% versus 50%, $P = 0.039$), and improved patient satisfaction. Importantly, they also demonstrated sustained benefits at 30 days postoperatively, with higher SF-36 bodily pain scores in the TAP group (59 ± 13 versus 49 ± 16 , $P = 0.023$).²³ Conversely, Yu et al. demonstrated that TAP blocks did not significantly reduce the need for oxycodone rescue when added to an MMA protocol in a randomized controlled trial of 159 women undergoing cesarean delivery under spinal anesthesia.²⁴ However, their findings should be interpreted cautiously since their patients received intrathecal opioids as part of spinal anesthesia, which provides prolonged postoperative analgesia and may have created a ceiling effect that obscured TAP block benefits. Furthermore, their follow-up was limited to 24 hours, potentially missing later-emerging benefits. Also, cesarean delivery involves different pain mechanisms and recovery trajectories compared to major abdominal surgery. Importantly, the choice of VAS-time area under the curve (AUC) at 72 hours instead of the final VAS scores was intended to represent both the magnitude and duration of pain in the postoperative period. It represents the individual variabilities of treatment effects across the whole evaluation period, without the need for multiple comparisons of pain scores at different time points, which potentially inflates type I errors.²⁵

The current study demonstrated that the implementation of MMA resulted in a 65% reduction of opioid requirements at 72 hours postoperatively. In their meta-analysis involving 26 studies with 1,646 patients, Bailey et al. showed a mean reduction of 31.52 MME in opioid consumption in the multimodal analgesia group compared to continuous peripheral nerve block (CPNB) in patients undergoing midline laparotomy.²⁶ However, their findings did not show a significant improvement in pain scores compared to controls. Furthermore, unlike the current findings, they showed a 1.41-day reduction in the length of hospital stay in CPNB compared to multimodal or epidural analgesia. This contradictory finding suggests that the superior efficacy of the multimodal approach in our study is contributed from the multiphasic approach of patient education, non-pharmacologic, and pharmacologic interventions implemented at different phases from preoperative to discharge phases.

The nature of the multimodal approach also matters. Yang et al. evaluated oxycodone-based versus sufentanil-based MMA following major laparoscopic gastrointestinal surgery in a randomized double-blind trial of 40 patients. Their multimodal protocol included bilateral TAP blocks, intraoperative dexmedetomidine infusion, flurbiprofen axetil, and patient-controlled analgesia with either oxycodone or sufentanil. The study found that oxycodone reduced 24-hour time-weighted average visceral pain at rest by 0.60 points ($P = 0.039$) and on coughing by 0.98 points ($P = 0.006$) compared to sufentanil.²⁷ In contrast, our protocol achieved

clinically meaningful pain reductions at most timepoints from 6 hours onward, with median VAS differences consistently exceeding 1-2 points between intervention and control groups. This discrepancy may reflect several factors: our control group received standard opioid-based care rather than optimized PCA with alternative opioids; our open surgical approach may have produced different pain characteristics compared to their laparoscopic procedures; and our integration of preoperative education, early mobilization, and cognitive behavioral therapy may have provided synergistic benefits beyond pharmacological optimization alone.

Although the overall adverse event rate was non-significantly different between the study groups, the rates of constipation, nausea, and vomiting were significantly lower in the multimodal group compared to the standard of care. This could be related to the reduced opioid consumption in the multimodal group, which significantly reduced opioid exposure and, therefore, the incidence of adverse effects. Similar to the current findings, Mao et al. investigated nalbuphine with flurbiprofen in MMA combined with TAP block for elderly patients undergoing open gastrointestinal surgery. Their study of 158 patients found that postoperative pain intensity and the incidence of postoperative nausea and vomiting (PONV) were similar across different nalbuphine doses, though the severity of PONV was decreased with lower nalbuphine doses. Importantly, no patients experienced respiratory depression, pruritus, or hypotension in any group.²⁸ Although our study did not examine nalbuphine, the absence of respiratory depression in their TAP block cohorts parallels our finding of zero respiratory depression events in the intervention group compared to 4.6% in controls. This consistency across studies suggests that MMA protocols incorporating regional anesthesia may substantially mitigate respiratory depression risk, a critical safety consideration in opioid-based analgesia.

The significant reduction in length of stay and improved satisfaction with MMA demonstrated in our study could therefore be related to improved analgesia, enhanced recovery, and reduced adverse event rates. Similarly, a recent meta-analysis of 58 randomized controlled clinical trials investigated the efficacy of MMA compared to control in different surgery types. Their findings suggested superior satisfaction (MD 0.88; $P = 0.009$) with MMA compared to control. However, unlike the current findings, no significant differences were demonstrated in terms of recovery, length of stay, or quality of life.⁹ This contradiction could be interpreted based on different surgeries (abdominal and non-abdominal) and multimodal protocols investigated in this meta-analysis compared to the current study.

A range of limitations should be acknowledged. First, the open-label design may have introduced potential performance and detection biases. However, due to the nature of our comprehensive MMA protocol, blinding was not feasible in the current study. Second, assessment of pain scores was limited to the first 72 hours subsequent to surgery, where the highest pain intensity is usually presented. We did not investigate the effects of our MMA on the long-term postoperative phase. Third, although MMA exhibited a marginally lower overall incidence of opioid-related adverse events, the study was insufficiently powered to detect statistically significant differences in adverse event rates between groups. Future studies are required to investigate the differential efficacy of each single component of our studied MMA program on the pain and

satisfaction outcomes through a factorial design with a larger sample size. Additionally, the favorable findings of our MMA need to be externally validated in different surgery types, including non-abdominal ones. In terms of generalizability, the results of this study are most directly applicable to adult patients who are scheduled for elective abdominal surgery in tertiary care hospital settings and who have access to multi-disciplinary perioperative pain management resources, such as licensed physical therapists, chemists who can administer intricate multimodal regimens, and trained pain management specialists. The study was carried out at two hospitals in Erbil, Iraq, and it is unclear whether our findings can be applied to other healthcare systems, environments with limited resources, or non-abdominal surgery populations. Furthermore, individuals with significant organ dysfunction, cognitive impairment, or chronic opioid use were not included in our cohort; consequently, care should be taken when extrapolating these results to such populations. However, the fundamental tenets of the multiphasic MMA approach which include preoperative patient education, scheduled non-opioid analgesics, regional techniques, and early mobilization align with generally accepted ERAS guidelines and are probably broadly applicable in a variety of surgical and clinical settings.

Conclusion

This research provides strong evidence for a multiphasic structured MMA protocol demonstrated superior efficacy in reducing postoperative pain intensity. Combining preoperative patient education with different pharmacologic and non-pharmacological pain management strategies across the different phases from preoperative to discharge reduced opioid

consumption and opioid-related adverse events, with a significant improvement in both recovery and patient satisfaction.

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AI use Disclosure

In preparing this manuscript, the authors used AI-assisted language tools for grammar and syntax review of draft text. All scientific content, data, analyses, and intellectual contributions are solely the work of the authors. The authors take full responsibility for the integrity of the data and the accuracy of the analysis.

Ethical Approval

The study was approved by the Ethical committee of research in the college of nursing/Hawler Medical University. Issue Number (2429), Date: 22/8/2024. The trial was prospectively registered on ClinicalTrials.gov (NCT07019103) prior to enrollment. All participants provided written informed consent before any study procedures were initiated.

Conflicts of Interest

The author declares no conflicts of interest throughout this study. ■

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