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Paracetamol Plus Tramadol Versus Fentanyl as Pre-emptive Analgesia for Enhanced Recovery after Day-Case Surgeries: A Randomised Controlled Trial

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Abstract

Background: Effective perioperative pain control is central to enhanced recovery after day-case surgery, yet the optimal pre-emptive analgesic strategy for ambulatory procedures remains debated.

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This trial compared pre-emptive intravenous paracetamol plus tramadol with pre-emptive intravenous fentanyl for enhanced recovery following day-case surgery.

Methods: In this prospective, randomised controlled trial, 102 adult patients (ASA physical status I–II, aged 21–65 years, BMI 25–30 kg/m²) scheduled for elective day-case surgery lasting 1–2 hours were randomly allocated 1:1 to intravenous paracetamol (15 mg/kg) plus tramadol (1 mg/kg) (Group T, n=51) or intravenous fentanyl (1.5 µg/kg) (Group F, n=51) before induction of general anaesthesia. The primary outcome was the Enhanced Recovery Score (QoR-40), recorded 24 hours postoperatively. Secondary outcomes included postoperative VAS pain scores, time to first rescue analgesia, RASS scores, perioperative haemodynamics, hospital stay duration, and adverse events.

Results: Baseline characteristics were comparable between groups. The Enhanced Recovery Score was significantly higher in Group T than Group F (188.06±4.29 vs 179.82±5.17; p=0.0001). Group T had lower VAS scores on arrival and at 1 hour ($p<0.001$), whereas Group F had lower VAS scores from 4 hours onward ($p<0.001$); despite this, Group T had a markedly longer time to first rescue analgesia (median 6 vs 1 hour; $p<0.001$). Group T showed deeper sedation on RASS immediately after extubation and on arrival to the PACU ($p<0.001$), with no difference by 20 minutes. Postoperative heart rate was higher in Group F (76.61±9.74 vs 72.73±7.76 beats/min; p=0.028); other haemodynamic parameters and hospital stay did not differ significantly. No other adverse events occurred; nausea and vomiting occurred at a low, similar rate in both groups.

Conclusion: Pre-emptive paracetamol plus tramadol provided better early analgesia, markedly delayed the need for rescue analgesia, and was associated with a higher Enhanced Recovery Score than pre-emptive fentanyl in patients undergoing day-case surgery, despite higher pain scores from 4 hours onward and deeper early postoperative sedation. Both regimens showed a comparable safety profile.

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Trial registration: The trial was prospectively registered on 14th of August 2023 on Clinicaltrials.gov (NCT05990686) prior to enrolment of the first participant.

1 Introduction

Enhanced recovery after surgery (ERAS), also described as "fast-track" surgery or an "enhanced recovery protocol" is a multimodal perioperative care pathway designed to reduce major morbidity and length of hospital stay, while promoting accelerated postoperative recovery and minimizing postoperative fatigue (1-3). It integrates a range of perioperative interventions from anaesthetic, surgical, nursing, and allied health disciplines that together aim to attenuate the surgical stress response and facilitate early mobilisation.

While effective postoperative pain management relieves suffering and promotes earlier mobilisation, a shorter hospital stay, reduced costs and greater patient satisfaction, inadequate control of postoperative pain has significant physical and physiological consequences that can precipitate complications extending well beyond the immediate postoperative period (4). Postoperative pain management must be individualised according to the patient's medical, psychological and physical status, the surgical procedure and the response to the therapeutic agents administered, as no single analgesic regimen suits all patients (5).

Pre-emptive analgesia refers to the administration of an analgesic agent before the onset of a painful stimulus, with the aim of preventing the central sensitization and rebound hyperalgesia that follow tissue injury. This is vital as surgical injury disrupts the normal processing of nociceptive afferent input to the central nervous system through increased spinal cord excitability, which could be attenuated by the pre-emptive administration of opioids (6).

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Paracetamol is a centrally acting analgesic that inhibits prostaglandin synthesis and central cyclooxygenase activity (7). Spinal serotonergic pathways and other central mechanisms have also been implicated in its antinociceptive action (7). Tramadol is a centrally acting, atypical opioid analgesic with a dual mechanism of action, combining weak μ-opioid receptor agonism with inhibition of norepinephrine and serotonin reuptake (8). In contrast, Fentanyl is a potent synthetic opioid structurally related to morphine but about 50 -100 times more potent as a pure μ-opioid receptor agonist. Each of these medications has been used during the perioperative period, with widely varying results in the quality of pain relief (9).

Management of perioperative pain can be considered challenging to clinicians as it is particularly important for attenuating the surgical stress response and supporting enhanced recovery in day-case surgeries. Multiple analgesic strategies have been proposed in this setting, including non-steroidal anti-inflammatory drugs, opioids and epidural techniques, each having recognised limitations and expected side effects. The pre-emptive use of a combination of paracetamol and tramadol versus fentanyl has not been well explored. Therefore, this trial was designed to compare the two pre-emptive analgesic strategies in the context of enhanced recovery using the Enhanced Recovery Score as the primary outcome and postoperative pain, sedation, haemodynamic stability, hospital stay length and adverse events as secondary outcomes (10).

2 Methods

2.1 Study Design and Setting

This prospective, two-arm, parallel-group, superiority, randomised, controlled clinical trial was conducted in the Department of Anaesthesia, Intensive Care and Pain Management at Zagazig University Hospital, Zagazig, Egypt, between 1 June 2025 and 31 December 2025.

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The study was approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (ZU-IRB 459 /14-July 2024) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. The trial was prospectively registered on 14th of August 2023 on Clinicaltrials.gov (NCT05990686) prior to enrolment of the first participant (https://clinicaltrials.gov/study/NCT05990686). Patient enrolment did not begin until 1 June 2025 due to delays in finalising staffing and logistical arrangements at the study site. Written informed consent was obtained from all participants before enrolment. Patients retained the right to withdraw from the study at any time without affecting their subsequent medical or surgical care.

The trial protocol is available from the corresponding author upon reasonable request. No separate statistical analysis plan document exists beyond the analysis described in Section 2.6. Patients and the public were not involved in the design, conduct, or reporting of this trial. This trial is reported in accordance with the CONSORT 2025 guidelines; the participant flow diagram is presented in Figure 1 (11).

2.2 Study Population

2.2.1 Eligibility Criteria

Adult patients aged 21-65 years who have American Society of Anesthesiologists (ASA) physical status I or II, body mass index (BMI) 25-30 kg/m^2, anticipated surgical duration of 1-2 hours and who presented during the study time frame were included in the study.

Patients who were not cooperative, had a diagnosed psychological disorder, had hepatic or renal impairment, known allergy to any of the drugs included in the study, chronic pain, and current use of analgesic therapy for a pre-existing condition, or did not present during the study time frame were excluded.

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2.2.2 Sample Size

The sample size was calculated using G*Power (version 3.1.9.7), based on the expected moderate effect size (Cohen's d = 0.5) between the paracetamol-tramadol and fentanyl groups, a statistical power of 80 %, a 95 % confidence interval and a 1:1 allocation ratio. This yielded a required sample of 102 patients, 51 per group.

2.3 Randomisation and Blinding

Simple randomisation was used without stratification or blocking in this trial. Patients were enrolled by the attending anesthesiologist on the surgical list. After eligible patients had been identified from the surgical list, a random allocation computer-generated sequence was accessed and applied by an independent investigator not involved in patient care. This was used to allocate them in a 1:1 ratio to Group T (paracetamol plus tramadol) or Group F (fentanyl). Postoperative pain and sedation scores were assessed by an anaesthesiologist independent of the anaesthetic team and not involved in drug administration. A formal allocation concealment mechanism was not used; this was acknowledged as a limitation.

This was an assessor-blinded trial. The anaesthetist administering the study drugs was not blinded to group allocation due to the difference in the volume and appearance of administration between the two regimens. Postoperative pain and sedation assessments were performed by an anaesthesiologist independent of the anaesthetic team and unaware of group allocation.

2.4 Interventions

Standard monitoring (pulse oximetry, non-invasive blood pressure, and electrocardiography) was applied, and a recording of the baseline heart rate, mean arterial pressure, and peripheral oxygen

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saturation was obtained. An intravenous peripheral line was secured, and fluid requirements were calculated as the sum of the estimated fluid deficit and maintenance requirements to be administered.

Patients in Group T received an intravenous infusion of paracetamol (15 mg/kg) with tramadol (1 mg/kg), completed immediately before induction of anaesthesia. Group F received a single intravenous injection of fentanyl 1.5 µg/kg before induction. General anaesthesia was induced with propofol 2 mg/kg and cisatracurium 0.15 mg/kg to facilitate endotracheal intubation, and maintained with inhaled isoflurane and incremental doses of muscle relaxant if needed. Intraoperative monitoring of heart rate, mean arterial blood pressure, oxygen saturation and end-tidal CO_2 were recorded every 5 minutes.

At the end of the surgery, inhalational anaesthesia was discontinued, and neuromuscular blockade was reversed using neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. Extubation was done when the patient met standard extubation criteria. Rescue analgesia (intravenous Ketorolac 30 mg) was administered if tachycardia and/or hypertension occurred postoperatively, defined as an increase in heart rate or blood pressure of more than 25 % from baseline, or if the VAS score was 5 or higher.

Aside from the study interventions, all patients received identical standard perioperative care, with no other analgesic, sedative, or antiemetic agents administered outside the protocol-defined criteria described above.

2.5 Outcome measures

The primary outcome of the study was the Enhanced Recovery Score, derived from the 40-item Quality of Recovery questionnaire (QoR-40), a previously validated and published patient-reported outcome measure that assesses five dimensions of postoperative recovery: emotional state, physical comfort, psychological support, physical independence and pain (10). Each of the 40 items is scored

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from 1 (worst) to 5 (best), yielding a total score ranging from 40 to 200. The QoR-40 was administered 24 hours after the surgery by an anaesthesiologist independent of the anaesthetic team and not involved in drug administration (10).

Secondary outcomes included assessing postoperative pain intensity, which was done using the 10 cm visual analogue scale (VAS; 0 = no pain, 10 = worst pain imaginable) and the patient was instructed to mark along the line which pain intensity is currently being experienced on arrival to the recovery room and at 1, 2, 4, 6, and 12 hours postoperatively. Other data collected included time to first request for postoperative rescue analgesia, postoperative sedation/agitation, assessed using the Richmond Agitation-Sedation Scale (RASS) (12). This 10-point scale ranges from -5 (unarousable) through 0 (alert and calm) to +4 (combative), with negative scores indicating sedation and positive scores agitation. RASS was recorded immediately after extubation, on arrival to the Post Anaesthesia Care Unit (PACU) and at 10 and 20 minutes after arrival to the PACU.

Perioperative haemodynamics, including systolic and diastolic blood pressure, mean arterial pressure and heart rate, were recorded preoperatively and postoperatively. The duration of the postoperative hospital stay and the incidence of adverse events were recorded. Adverse events included nausea and vomiting, treated with intravenous ondansetron 8 mg; hypotension, defined as a decrease in mean arterial pressure exceeding 20 % of baseline readings and treated with intravenous crystalloid infusion and 5 mg boluses of ephedrine; and bradycardia, defined as a heart rate below 50 beats per minute and treated with atropine 0.2–0.5 mg.

2.6 Data Analysis and Statistics

All collected data were de-identified and assigned unique study codes to ensure confidentiality. The Excel sheet was stored in a password-coded folder on the principal investigator's laptop. De-identified data were shared with all participating authors. Data were analysed using IBM Statistical

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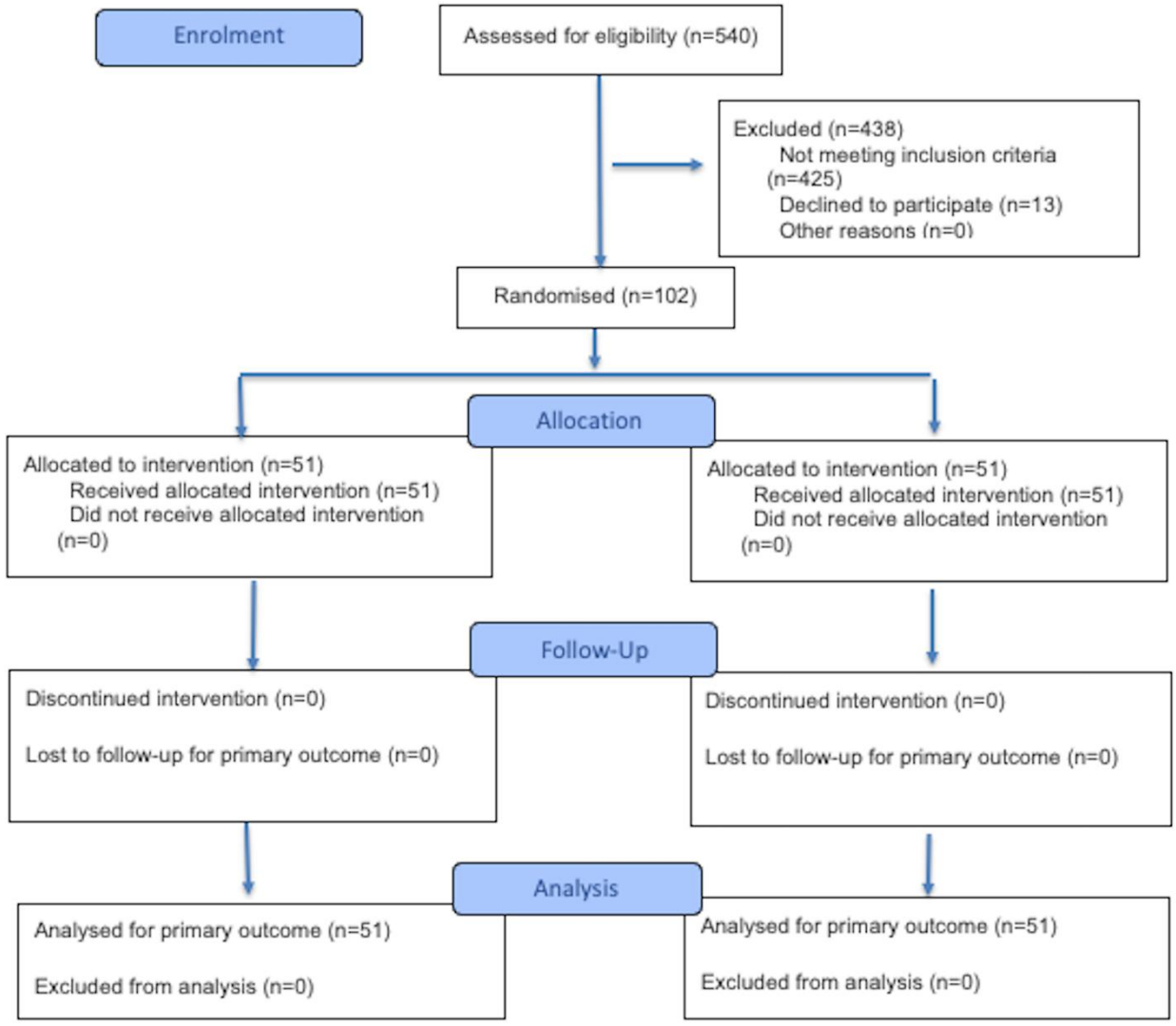
Package for Social Sciences (SPSS version 23.0). The normality of quantitative data was assessed using the Shapiro-Wilk test. Normally distributed quantitative variables are presented as means with standard deviation (SD) and were compared between groups using the independent-samples t-test. Paired preoperative and postoperative values within each group were compared using the paired t-test. Non-normally distributed quantitative variables are presented as medians and interquartile ranges (IQR) and were compared using the Mann-Whitney U test. Categorical variables are presented as numbers and percentages and were compared using the chi-square test, or Fisher's exact test when the expected count in any cell was less than 5. A two-sided p-value < 0.05 was considered statistically significant. No interim analyses or formal stopping guidelines were planned or performed; data were analysed only after all the participants had completed the 24-hour follow-up period. All 102 randomised participants were included in the analysis as there were no losses to follow-up, withdrawals, missing data, or protocol deviations in either group.

3 Results

During the study period, 540 patients underwent day-case surgery, of whom 438 were excluded (425 did not meet eligibility criteria and 13 declined to participate). The remaining 102 patients were enrolled and completed the study, with 51 in each group. No patients withdrew or were lost to follow-up (Figure 1). Recruitment continued until the pre-specified target sample size was reached, at which point enrolment was closed as planned. Baseline demographic and surgical characteristics were comparable between the two groups (Table 1). Age, BMI, sex distribution, the distribution of surgical procedures and operative time did not differ significantly between Group T and Group F.

Figure 1 CONSORT flow diagram of patient enrolment, randomisation, allocation, follow-up, and analysis

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193 **Table 1 Demographic and surgical characteristics**

Variable	Group T (n=51)	Group F (n=51)	Test statistic	p value
Age [years, mean ± SD]	43.08 ± 10.49	42.37 ± 9.78	t = 0.352	0.726
BMI [kg/m², mean ± SD]	27.27 ± 1.66	26.71 ± 1.36	t = 1.890	0.062
Sex [n (%)]			$\chi^2 = 0.158$	0.691
Female	27 (52.9)	29 (56.9)		
Male	24 (47.1)	22 (43.1)		
Type of surgery [n (%)]			$\chi^2 = 1.98$	0.739
Breast biopsy	12 (23.5)	9 (17.6)		
Cystoscopy	13 (25.5)	12 (23.5)		

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Cystoscopy + ureteric stent	1 (2.0)	0 (0.0)		
Hysteroscopy	10 (19.6)	13 (25.5)		
Haemorrhoidectomy	15 (29.4)	17 (33.3)		
Operative time [minutes, mean ± SD]	68.33 ± 19.56	63.43 ± 15.54	t = 1.406	0.163

SD standard deviation, t independent-samples t test, χ^2 chi-square test. $p < 0.05$ was considered statistically significant.

Mean age was similar between Group T and Group F (43.08 ± 10.49 vs 42.37 ± 9.78 years; p = 0.726), as was BMI (27.27 ± 1.66 vs 26.71 ± 1.36 kg/m²; p = 0.062). The sex distribution did not differ significantly between groups, with a similar proportion of female patients in Group T and Group F (52.9 % vs 56.9 %; $\chi^2 = 0.158$, p = 0.691). The distribution of surgical procedures was also comparable across the five case types (breast biopsy, cystoscopy, cystoscopy with ureteric stenting, hysteroscopy, and haemorrhoidectomy), with no significant difference in case-mix between groups ($\chi^2 = 1.98$, p = 0.739). Mean operative time was somewhat longer in Group T than in Group F, but this difference did not reach statistical significance (68.33 ± 19.56 vs 63.43 ± 15.54 minutes; p = 0.163) (Table 1). These findings confirm that randomisation produced two groups that were well matched at baseline, supporting the validity of the between-group comparisons.

The Enhanced Recovery Score at 24 hours was 8 points higher on the QoR-40 in Group T than in Group F (188.06 ± 4.29 vs 179.82 ± 5.17; p = 0.0001), indicating a significantly better overall quality of recovery in patients who received pre-emptive paracetamol plus tramadol (Table 2). Duration of postoperative hospital stay was nearly identical between groups (10.24 ± 2.07 vs 10.28 ± 2.0 hours; p = 0.923).

Table 2 Primary outcome (Enhanced Recovery Score) and duration of hospital stay

Variable	Group T (n=51)	Group F (n=51)	Test statistic	p value
Duration of hospital stay [hours, mean ± SD]	10.24 ± 2.07	10.28 ± 2.0	t = 0.097	0.923
Enhanced Recovery Score (QoR-40) [mean ± SD]	188.06 ± 4.29	179.82 ± 5.17	t = 8.751	<0.001*

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*SD standard deviation, t independent-samples t test, QoR-40 40-item Quality of Recovery score (range 40–200). * $p < 0.05$ was considered statistically significant.*

Table 3 shows that the preoperative systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate were comparable between groups ($p > 0.05$), confirming haemodynamic equivalence at baseline. Within Group T, all four parameters fell significantly from the preoperative to the postoperative measurement: systolic blood pressure from 125.88 ± 12.91 to 118.73 ± 12.28 mmHg, diastolic blood pressure from 75.49 ± 11.41 to 72.45 ± 9.77 mmHg, mean arterial pressure from 92.29 ± 11.49 to 87.88 ± 10.04 mmHg, and heart rate from 78.63 ± 9.51 to 72.73 ± 7.76 beats/min (all $p = 0.0001$ by paired t test). No corresponding within-group change reached statistical significance in Group F for any of the four parameters ($p > 0.05$). Comparing the two groups directly, postoperative heart rate was significantly higher in Group F than in Group T (76.61 ± 9.74 vs 72.73 ± 7.76 beats/min; $p = 0.028$), while postoperative systolic blood pressure, diastolic blood pressure, and mean arterial pressure did not differ significantly between groups (all $p > 0.05$) (Table 3).

Table 3 Perioperative haemodynamic variables

Variable	Group T (n=51)	Group F (n=51)	Test statistic (t)	p value
Preoperative systolic BP [mmHg, mean ± SD]	125.88 ± 12.91	121.57 ± 12.31	1.727	0.087
Postoperative systolic BP [mmHg, mean ± SD]	118.73 ± 12.28	122.35 ± 13.72	1.407	0.163
Within-group paired p (preoperative vs postoperative)†	<0.001*	0.697	—	—
Preoperative diastolic BP [mmHg, mean ± SD]	75.49 ± 11.41	74.12 ± 9.63	0.656	0.513
Postoperative diastolic BP [mmHg, mean ± SD]	72.45 ± 9.77	73.92 ± 8.85	0.797	0.427
Within-group paired p (preoperative vs postoperative)†	<0.001*	0.881	—	—
Preoperative mean arterial pressure [mmHg, mean ± SD]	92.29 ± 11.49	89.94 ± 10.09	1.098	0.275
Postoperative mean arterial pressure [mmHg, mean ± SD]	87.88 ± 10.04	90.07 ± 9.97	1.105	0.272

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Within-group paired p (preoperative vs postoperative)†	<0.001*	0.929	—	—
Preoperative heart rate [beats/min, mean ± SD]	78.63 ± 9.51	75.63 ± 7.9	1.732	0.086
Postoperative heart rate [beats/min, mean ± SD]	72.73 ± 7.76	76.61 ± 9.74	2.226	0.028*
Within-group paired p (preoperative vs postoperative)†	<0.001*	0.348	—	—

*BP blood pressure; t independent-samples t test (between-group rows). † Paired t test (within-group rows). * p < 0.05 was considered statistically significant.*

Postoperative pain scores are shown in Table 4. On arrival to the recovery room, the median VAS was 0 (IQR 0–0) in Group T versus 3 (IQR 0–3) in Group F, and at 1 hour 1 (0–2) versus 2 (2–4), respectively (both $p < 0.001$). At 2 hours the groups were statistically indistinguishable (Group T 2 (2–3) vs Group F 2 (2–4); $p = 0.215$). From 4 hours onward the pattern reversed, with significantly lower VAS scores in Group F than in Group T at 4, 6, and 12 hours (all $p < 0.001$). The median time to first rescue analgesia was substantially longer in Group T than in Group F with 6 (5–7) vs 1 (1–2) hours ($p < 0.001$).

Table 4 Postoperative VAS pain scores at rest and time to first rescue analgesia

Variable	Group T (n=51)	Group F (n=51)	Test statistic (U)	p value
VAS on arrival to recovery room (0 h)	0 (0–0)	3 (0–3)	6.456	<0.001*
VAS at 1 hour	1 (0–2)	2 (2–4)	6.678	<0.001*
VAS at 2 hours	2 (2–3)	2 (2–4)	1.240	0.215
VAS at 4 hours	3 (2–3)	2 (1–2)	6.530	<0.001*
VAS at 6 hours	3 (2–4)	1 (1–2)	6.953	<0.001*
VAS at 12 hours	1 (0–1)	0 (0–0)	4.322	<0.001*
Time to first rescue analgesia [hours]	6 (5–7)	1 (1–2)	8.458	<0.001*

*Values are median (interquartile range). VAS visual analogue scale (0–10), U Mann-Whitney U test. * p < 0.05 was considered statistically significant.*

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After extubation, Group T showed sedation (median RASS -2 (IQR -2–1)) while Group F showed mild agitation (median RASS 1 (-1–1)); the difference was significant ($p < 0.001$). The same pattern held on arrival to the PACU (-2 (-2–1) vs 1 (-1–1)) and at 10 minutes (-1 (-1–0) vs 0 (-1–0)) (Table 5). By 20 minutes, all patients in both groups had returned to RASS 0 (alert and calm), so no between-group comparison was applicable at this time point.

Table 5 Richmond Agitation-Sedation Scale (RASS) scores

Variable	Group T (n=51)	Group F (n=51)	Test statistic (U)	p value
RASS immediately after extubation	-2 (-2 – 1)	1 (-1 – 1)	5.699	<0.001*
RASS on arrival to PACU	-2 (-2 – 1)	1 (-1 – 1)	5.289	<0.001*
RASS 10 minutes after PACU arrival	-1 (-1 – 0)	0 (-1 – 0)	4.108	<0.001*
RASS 20 minutes after PACU arrival	0 (0 – 0)	0 (0 – 0)	Not estimable‡	Not estimable‡

*Values are median (interquartile range). PACU post-anaesthesia care unit, U Mann-Whitney U test. * $p < 0.05$ was considered statistically significant. ‡ Absence of variance precluded a computation of a test statistic.*

Nausea and vomiting were infrequent and did not differ significantly between Group T and Group F (5.9 % vs 3.9 %; $p = 0.99$) (Table 6). No patients in either group developed hypotension or bradycardia meeting the predefined thresholds, and no other adverse events were observed.

Table 6 Incidence of adverse events

Variable	Group T (n=51)	Group F (n=51)	p value
Nausea and vomiting [n (%)]	3 (5.9)	2 (3.9)	0.99
Hypotension [n (%)]	0 (0.0)	0 (0.0)	—
Bradycardia [n (%)]	0 (0.0)	0 (0.0)	—

p-value from Fisher's exact test.

4 Discussion

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Our randomised controlled trial was designed to compare pre-emptive intravenous administration of paracetamol plus tramadol with pre-emptive intravenous administration of fentanyl for enhanced recovery of day-case surgeries. Patients who received paracetamol plus tramadol have shown significantly higher Enhanced Recovery scores, reported lower pain scores in the immediate postoperative period and required rescue analgesia considerably later than those who received fentanyl. This aligns with the principles underlying enhanced recovery after surgery (ERAS) protocols, which emphasise that multimodal, opioid-sparing analgesic strategies reduce the surgical stress response and accelerate functional recovery in comparison to reliance on a single potent opioid (1-3). Furthermore, Kehlet and Zargar-Shoshtari et al. reported that fast-track, multimodal perioperative pathways produce measurable improvements in postoperative recovery and reduce morbidity when compared with conventional, opioid-centred approaches (1-3).

Kannan et al. found a clinically and statistically significant reduction in hospital stay length, varying between 3 and 8 days, associated with ERAS pathways when used in colorectal surgery compared with conventional perioperative care (13). It was also reported that ERAS patients had faster gastrointestinal recovery and reduced postoperative complications and opioid consumption and significantly lower VAS scores (13). On the other hand, our trial, which found no significant difference in the hospital stay between groups, likely reflects the short nature of day-case surgeries, where discharge timing can be less sensitive to analgesic technique than it is after major abdominal surgery.

Our findings also align with Liu et al., whose meta-analysis of 15 randomised clinical trials found that opioid-free anaesthesia improved global QoR-40 scores at 24 hours compared with opioid-based anaesthesia (14). Moreover, Kovač et al. reported a 10-point advantage in QoR-40 scores with a multimodal or regional approach compared with a single intravenous opioid agent, suggesting a consistent pattern across varying surgical settings (15). The approximately 8-point QoR-40 advantage

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we observed sits within the same range, reinforcing that the benefit of multimodal analgesia on early recovery is reproducible across surgical contexts.

Regarding postoperative pain, patients who received paracetamol plus tramadol showed notably lower VAS scores immediately upon arrival at the recovery room and at 1 hour, but from 4 hours onward, their scores were higher than those in the fentanyl group. They also had a longer median time before requesting rescue pain relief (6 hours versus 1 hour). This may reflect tramadol's combined opioid and monoaminergic mechanisms, consistent with safety data showing that intravenous tramadol provides prolonged analgesia across various surgeries without early breakthrough pain (16, 17). Conversely, fentanyl's rapid redistribution and short context-sensitive half-life, despite its high receptor affinity, may account for its strong early analgesia followed by an earlier need for rescue (18). The lower VAS pain scores in the fentanyl group after 4 hours should be interpreted with caution, as the majority of these patients had already received rescue analgesia by then. These findings can be considered clinically relevant, especially in the context of day-case anaesthesia, as it would enhance patient satisfaction and support earlier and more comfortable discharge.

A further finding in our trial was a significantly lower postoperative heart rate in the paracetamol-tramadol group compared with the fentanyl group, accompanied by a downward trend in blood pressure that reached significance only within the paracetamol-tramadol group. This is in keeping with Arslan et al., who showed that pre-emptive intravenous paracetamol not only reduced opioid requirements but also blunted the sympathetic response to surgery in patients undergoing cholecystectomy (19). Adverse events, specifically nausea and vomiting, were noted to have a similar incidence between the groups, which may be explained by the relatively low, single pre-emptive doses used in both groups.

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Taken together, our findings suggest that pre-emptive combination of paracetamol and tramadol offers a clinically meaningful advantage over fentanyl for enhanced recovery after day-case surgery. This combination may represent a practical, cost-effective option for anaesthesiologists managing ambulatory surgical pathways.

5 Limitations

Our trial had several limitations which need to be considered. First, this was a single-centre study, possibly limiting the generalizability of the findings to other institutional settings and patient populations. Second, this trial included a small sample size, further studies should be done to compare the same drug combinations in a larger population. Third, this trial compared a two-drug combination against a single agent, which does not fully isolate the individual contribution of each component of the combination regimen. A three- or four-arm design, including paracetamol and tramadol individually, would be needed to disaggregate these effects. Fourth, the Enhanced Recovery Score (QoR-40) was used as the primary outcome in the final analysis, whereas postoperative VAS pain score was designated the primary outcome in the original trial registration (NCT05990686); this deviation from the registered protocol was not pre-specified and should be considered when interpreting the primary outcome result. Additionally, a formal allocation concealment mechanism was not used, as the same investigator who generated the random allocation sequence also oversaw its application; this raises the possibility of selection bias in the enrolment process, despite the separation between the enrolling clinician and the person applying the sequence. Finally, our outcomes were only assessed for 24 hours postoperatively, precluding conclusions about longer-term recovery or the persistence of analgesic benefit beyond this time window.

6 Conclusion

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In patients undergoing day-case surgery, pre-emptive paracetamol-tramadol produced a significantly higher Enhanced Recovery Score (QoR-40) than pre-emptive intravenous fentanyl, together with superior analgesia in the first postoperative hour and a notably longer time to first rescue analgesia. Both regimens were associated with stable haemodynamics and a low incidence of adverse events. These findings support the use of pre-emptive paracetamol-tramadol as an effective combination for enhanced recovery pathways in ambulatory surgery. Multicentre trials with longer follow-up are warranted to confirm these findings.

7 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

8 Ethics Approval

This study was approved by the Institutional Review Board / Research Ethics Committee of the Faculty of Medicine, Zagazig University (ZU-IRB 459 /14-July 2024) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent to participate was obtained from all participants.

9 Trial Registration

The trial was prospectively registered on 14th of August 2023 on Clinicaltrials.gov (NCT05990686) prior to enrolment of the first participant (https://clinicaltrials.gov/study/NCT05990686).

10 Author Contributions

WMMA - data acquisition; statistical analysis; data interpretation

AH - data acquisition; original draft of the manuscript.

MAS – study design and conceptualisation; data acquisition; manuscript review

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KS - data acquisition; manuscript review

SSEIE: contributed to data acquisition; critically reviewed and revised the manuscript for important intellectual content.

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13 Data Availability Statement

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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