

Perioperative Butorphanol as a Multimodal Analgesic Strategy to Reduces Emergence Agitation and Attenuates Systemic Inflammation in Elderly Patients Undergoing Transurethral Resection of the Prostate: A Pragmatic Randomized Controlled Trial

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Research Article

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Abstract

Background

Emergence agitation (EA) is a common complication after general anesthesia in elderly patients undergoing transurethral resection of the prostate (TURP), a procedure associated with multiple risk factors for EA. Butorphanol, a κ -opioid receptor agonist and μ -antagonist, may reduce EA through its sedative, analgesic, and anti-inflammatory properties. This randomized controlled trial evaluated the effect of perioperative butorphanol on EA incidence and explored its impact on postoperative pain, sleep quality, delirium, and systemic inflammation.

Methods

Seventy elderly patients (aged 65–80 years, ASA I - III) scheduled for elective TURP were randomized 1:1 to receive either butorphanol (Group T, 0.15 mg/kg at induction, plus 0.15 mg/kg in postoperative analgesia) or sufentanil (Group C, 0.5 μ g/kg at induction, plus 1.5 μ g/kg in analgesia). The primary outcome was the incidence and scores of EA at extubation (Richmond Agitation-Sedation Scale [RASS] score ≥ 1). Secondary outcomes included clinical assessments (pain via NRS, sleep via PSQI, delirium via 3D-CAM), recovery parameters (BIS, time to extubation, bladder irrigation duration and PCA consumption), and postoperative safety metrics (hemodynamic parameters and adverse events). Intraoperative anesthetic consumption and the total dosages of sufentanil or butorphanol were also recorded; these were standardized and compared using morphine equivalent units (10 μ g sufentanil = 10 mg morphine; 2 mg butorphanol = 10 mg morphine).

Results

Baseline characteristics were comparable. Butorphanol significantly reduced EA incidence (5.71% vs. 31.43%, $P = 0.006$) and RASS scores ($P = 0.001$). Pain scores at extubation were lower in Group T ($P < 0.001$), and sleep quality was improved on postoperative days 2 and 3 ($P < 0.05$). The time from drug discontinuation to extubation was longer in Group T than in Group C, while both the BIS value at extubation and the morphine equivalent dose were lower in Group T than in Group C ($P < 0.05$). Serum TNF- α and IL-10 levels at extubation were significantly lower in Group T ($P < 0.05$). No differences were observed in postoperative delirium incidence, adverse events, or hemodynamic profiles.

Conclusion

Perioperative butorphanol reduces EA, improves immediate postoperative analgesia and sleep quality, and attenuates systemic inflammation in elderly patients undergoing TURP, supporting its use as a safe and effective component of multimodal anesthesia in this high-risk population. This offers a practical, opioid-sparing alternative to conventional μ -opioid dominated regimens, directly facilitating individualized patient management in urological anesthesia practice.

Trial registration

1 Introduction

As the global population ages, the prevalence of benign prostatic hyperplasia (BPH) continues to rise, making transurethral resection of the prostate (TURP) one of the most commonly performed urological procedures in older men [1, 2]. Although TURP is considered minimally invasive with favorable surgical outcomes, elderly patients undergoing this procedure are particularly vulnerable to perioperative neurocognitive complications, especially emergence agitation (EA) [3, 4]. EA is characterized by confusion, restlessness, and hyperactive behavior during early emergence from general anesthesia, and is associated with serious consequences such as accidental extubation, hemodynamic instability, surgical site bleeding, and increased healthcare utilization [5–7].

The incidence of EA in adults ranges from 0.25% to 19%, with substantially higher rates in elderly and urological populations [8, 9]. A recent systematic review and meta-analysis identified male sex, urinary catheter placement, and postoperative pain as the strongest independent risk factors for EA [5]. Indeed, TURP uniquely combines multiple EA-promoting factors: advanced age, male sex, surgical trauma to the prostate, continuous bladder irrigation, and indwelling catheter stimulation [10, 11]. These factors contribute to visceral pain and discomfort, which are transmitted via A δ and C fibers and often inadequately managed by conventional μ -opioid analgesics [12]. Moreover, μ -opioid agonists such as sufentanil and fentanyl are frequently associated with nausea, vomiting, dizziness, and delayed recovery, which may paradoxically worsen EA or prolong agitation [13–15].

Butorphanol, a mixed κ -opioid receptor agonist and μ -opioid receptor partial agonist/antagonist, offers a distinct pharmacological profile that may address these limitations [16, 17]. Activation of κ -receptors produces effective visceral analgesia, particularly against catheter-related bladder discomfort (CRBD), while μ -antagonism may reduce the incidence of opioid-related adverse effects [18–20]. Preclinical studies have also demonstrated that butorphanol suppresses macrophage M1 polarization and reduces pro-inflammatory cytokine release via κ -receptor-dependent mechanisms [21]. Clinical studies have shown that pre-anesthetic butorphanol reduces EA in thoracic and sinus surgery [22, 23], and our previous pilot study suggested that butorphanol improves early postoperative cognition and modulates systemic inflammation in elderly surgical patients [24].

Despite these promising findings, no dedicated randomized controlled trial has systematically evaluated its effects in the high-risk elderly TURP population. Unlike standard surgical cohorts, TURP presents a unique convergence of continuous bladder irrigation, indwelling catheter-induced visceral pain, and prostatic tissue injury, all of which are notoriously refractory to conventional μ -opioid analgesia. This patient group is not only exposed to multiple EA triggers but also exhibits age-related neuroinflammation and diminished cognitive reserve, which may further predispose them to perioperative neurocognitive disorders [25–27]. Given the growing recognition that systemic inflammation and neuroinflammation

play pivotal roles in EA and postoperative delirium [28–30], an intervention capable of simultaneously providing effective analgesia, sedation, and anti-inflammatory effects could represent a meaningful advancement.

Therefore, we conducted this prospective, randomized, double-blind controlled trial to test the hypothesis that perioperative administration of butorphanol, compared with sufentanil, reduces the incidence of EA in elderly patients undergoing TURP. We further aimed to explore its effects on pain, sleep quality, delirium, and inflammatory markers (TNF- α and IL-10), thereby providing a multidimensional assessment of its clinical utility and mechanistic relevance.

2 Materials and Methods

2.1 Study Design and Ethics

This was a prospective, randomized, double-blind, parallel-group, controlled trial conducted at the First Affiliated Hospital of Dalian Medical University between April and December 2025. The study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University(PJ-KS-KY-2025-140[X]) and registered at the Chinese Clinical Trial Registry (ChiCTR2500114145). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legally authorized representatives before enrollment. This pragmatic randomized controlled trial was reported in accordance with the CONSORT 2025 guidelines.

2.2 Participants

Eligible patients were aged 65–80 years, with an American Society of Anesthesiologists (ASA) physical status of I to III, a body mass index (BMI) of 21–34 kg/m², scheduled for elective transurethral resection of the prostate (TURP) under general anesthesia. Exclusion criteria were: known contraindications or allergies to butorphanol or sufentanil; pre-existing dementia indicated by a Mini-Mental State Examination (MMSE, a widely used screening tool evaluates orientation, memory, attention, language and visuoconstructive ability[31]) score below the education-adjusted cutoff (literate > 23 points, illiterate > 20 points); severe visual, auditory, or communication disorders precluding assessment; severe cardiovascular, hepatic, or renal dysfunction; or a history of substance abuse. The basic cognitive functions were assessed by a psychiatrist specializing in mental health.

2.3 Randomization and Blinding

Patients were randomized 1:1 to either the butorphanol group (Group T) or the sufentanil group (Group C) using a computer-generated random number sequence concealed in sealed envelopes. Anesthesiologists performing the procedure, outcome assessors, and patients were blinded to group allocation.

2.4 Anesthesia Protocol

All patients underwent a standardized general anesthesia protocol. Upon arrival in the operating room, standard monitoring (electrocardiogram, pulse oximetry, non-invasive blood pressure) was applied, and the bispectral index (BIS, CBS-2000BIS, Shanghai Saniver Electronic Co., Ltd.) was monitored using a disposable sensor. A radial artery catheter was inserted under local anesthesia for continuous invasive blood pressure monitoring.

Anesthesia was induced with intravenous propofol (1–2 mg/kg) and cisatracurium (0.2 mg/kg). According to group assignment, patients received either butorphanol tartrate 0.15 mg/kg (Group T) or sufentanil citrate 0.5 µg/kg (Group C). After loss of consciousness and adequate neuromuscular blockade, tracheal intubation was performed. Mechanical ventilation was initiated with a tidal volume of 6–8 mL/kg, a respiratory rate of 12–14 breaths/min, and an FiO₂ of 0.5 to maintain end-tidal CO₂ between 35 and 40 mmHg.

Anesthesia was maintained with continuous intravenous infusion of propofol (1–3 mg/kg/h) and cisatracurium (0.1–0.12 mg/kg/h), supplemented with inhaled sevoflurane (1–2%). Additional boluses of the assigned opioid were administered as needed, and the total intraoperative consumption of butorphanol or sufentanil was recorded. Hemodynamic goals were to maintain mean arterial pressure (MAP) and heart rate (HR) within $\pm 20\%$ of baseline. BIS was maintained between 40 and 60.

At the end of surgery, cisatracurium infusion was stopped, and all patients were connected to a PCA pump. The PCA formulation for Group T was butorphanol 0.15 mg/kg + ramosetron 0.6 mg + flurbiprofen axetil 100 mg in 100 mL of 0.9% saline; for Group C, it was sufentanil 1.5 µg/kg + ramosetron 0.6 mg + flurbiprofen axetil 100 mg in 100 mL of 0.9% saline. The PCA settings were: bolus dose 2 mL, lockout interval 15 min, and background infusion 2 mL/h. After surgery, patients were transferred to the post-anesthesia care unit (PACU). Extubation was performed when standard criteria were met (e.g., spontaneous breathing with adequate tidal volume, response to verbal commands, and stable hemodynamics). Patients were discharged to the ward when the modified Aldrete score was ≥ 12 , with each component ≥ 1 .

2.5 Outcome Measures

Primary outcome

The primary outcome was the incidence and scores of emergence agitation (EA) at the time of extubation (D1) in the PACU. EA was defined as a Richmond Agitation-Sedation Scale (RASS) score ≥ 1 . We adopted a conservative threshold of RASS ≥ 1 to define EA. Unlike younger patients where only severe agitation (RASS $\geq +2$) requires intervention, in the frail elderly population, even mild agitation (RASS +1) at extubation can trigger immediate sympathetic surges leading to severe hemodynamic instability and cardiovascular events. Therefore, a more sensitive cutoff was clinically justified to capture the earliest signs of emergent distress.

Secondary outcomes:

1. Pain intensity: Assessed using the Numeric Rating Scale (NRS, 0–10, where 0 = no pain and 10 = worst imaginable pain) at extubation (D1), on postoperative day 1 (D2), and day 3 (D3).
2. Sleep quality: Assessed using the Pittsburgh Sleep Quality Index (PSQI) preoperatively on D2 and D3. A lower PSQI score indicates better sleep quality.
3. Postoperative Delirium (POD): Assessed using the 3-Minute Diagnostic Interview for CAM (3D-CAM) on D2 and D3 by a single trained psychiatrist who was blinded to group allocation. The psychiatrist underwent standardized training in 3D-CAM administration prior to the study to ensure consistency.
4. Perioperative Inflammatory Response: Serum levels of tumor necrosis factor- α (TNF- α) and interleukin-10 (IL-10) were measured using enzyme-linked immunosorbent assay (ELISA) at two time points: before induction of anesthesia (baseline, T1) and at extubation (D1). Blood samples (3 mL) were collected from the radial artery catheter, centrifuged at 1000 $\times$ g for 10 minutes, and the supernatant was stored at -80°C until analysis. All assays were performed in duplicate.
5. Hemodynamic and Anesthetic Parameters: MAP, HR, body temperature, and BIS were recorded at four time points: after entering the operating room (T1), immediately after intubation (T2), at surgical incision (T3), and at PACU discharge (T4). The time from discontinuation of anesthetic drugs to extubation was recorded. The total consumption of propofol, cisatracurium, and vasoactive drugs (methoxamine, atropine) was also documented. The intraoperative dosages of sufentanil citrate and butorphanol tartrate, converted according to morphine equivalent units (where 10 μg of sufentanil is equivalent to 10 mg of morphine, and 2 mg of butorphanol tartrate is also equivalent to 10 mg of morphine). Bladder irrigation duration and total PCA consumption were recorded.
6. Safety: The incidence of postoperative adverse events, including nausea, vomiting, and dizziness, was recorded during the first three postoperative days. Hemoglobin (THbc) levels were measured preoperatively (T1) and at extubation (D1) using a blood gas analyzer.

2.6 Sample Size Calculation

The sample size was calculated using PASS 15.0 based on a pilot study from our center, which suggested that butorphanol could reduce EA incidence by approximately 30%. Assuming an EA incidence of 30% in the control group, a two-sided significance level (α) of 0.05, and a power ($1-\beta$) of 0.80, a minimum of 31 patients per group was required. To account for a potential 10% dropout rate, we enrolled 35 patients per group, for a total of 70 patients.

2.7 Statistical Analysis

Data were analyzed using R statistical software (version 4.2.1). The normality of continuous data was assessed using the Shapiro-Wilk test. Normally distributed data are presented as mean $\pm$ standard deviation (SD) and were compared using independent-samples t-tests for between-group comparisons. Non-normally distributed data are presented as median with interquartile range (IQR) and were compared using the Mann-Whitney U test. Categorical variables are presented as counts (percentages) and were compared using Fisher's exact test.

For repeated measures data (MAP, HR, BIS, temperature), a linear mixed-effects model was used. This model included group (fixed effect), time (fixed effect), and their interaction (group × time), with patient as a random intercept. This approach allows for the analysis of incomplete data and accounts for within-subject correlation. The Satterthwaite method was used to estimate degrees of freedom.

3 Results

3.1 Disposition and Baseline Characteristics

A total of 86 patients were screened for eligibility between April and December 2025. Sixteen patients were excluded: 13 did not meet inclusion criteria and 3 declined participation. The remaining 70 patients were randomized (35 per group), and all completed the study and were included in the final analysis (Fig. 1). There were no missing data for the primary outcome or key secondary outcomes, as all patients completed the scheduled assessments. All cytokine measurements and hemodynamic recordings were successfully obtained. The two groups were well-balanced with respect to baseline demographic and clinical characteristics, including age, ASA physical status, BMI, and prevalence of hypertension and diabetes (all $P > 0.05$; Table 1). Preoperative cognitive function (MMSE) and sleep quality (PSQI) were also comparable (both $P > 0.05$; Table 1).

Table 1
Baseline demographic and clinical characteristics of the Study Population.

Characteristic	Group T (Butorphanol, n = 35)	Group C (Sufentanil, n = 35)	Test Statistic	P value
Age (years): mean ± SD	72.43 ± 4.40	70.80 ± 4.04	t = -1.614	0.111
ASA I–II / III: n (%)	30 (85.7) / 5 (14.3)	27 (77.1) / 8 (22.9)	$\chi^2 = 0.850$	0.356
BMI (kg/m ²): mean ± SD	24.75 ± 2.52	25.10 ± 2.14	t = 0.639	0.525
Hypertension: n (%)	16 (45.7)	14 (40.0)	$\chi^2 = 0.233$	0.629
Diabetes: n (%)	5 (14.3)	6 (17.1)	$\chi^2 = 0.108$	0.743
PSQI (D0), median (IQR)	6 (5, 7)	6 (5, 7)	Z = -0.288	0.774
MMSE(D0), median (IQR)	23(21, 23)	22(21.5, 23)	Z = -0.562	0.574
Note: Data are presented as mean ± SD, median (IQR), or n (%). T, butorphanol; C, sufentanil; ASA, American Society of Anesthesiologists; BMI, body mass index; D0, the day before surgery.				

3.2 Primary Outcome: Emergence Agitation

The incidence of EA at extubation (RASS ≥ 1) was significantly lower in the butorphanol group (Group T) compared with the sufentanil group (Group C) (5.71% vs. 31.43%; $P = 0.006$; Table 2, Fig. 2). The median RASS score was also lower in Group T (0 [IQR: -1, 0] vs. 0 [IQR: 0, 1]; $P = 0.001$; Table 2, Fig. 3).

Table 2
Comparison of Primary and Secondary Clinical Outcomes.

Outcome	Group T (n = 35)	Group C (n = 35)	Test Statistic	P value
Primary Outcome				
EA incidence at D1 (n, %)	2 (5.71)	11 (31.43)	Z = 7.652	0.006
RASS score (D1), median (IQR)	0 (-1, 0)	0 (0, 1)	Z = -3.290	0.001
Secondary Outcomes				
NRS pain (D1), median (IQR)	0 (0, 1)	2 (1, 2)	Z = -4.415	< 0.001
NRS pain (D2), median (IQR)	1 (0, 3)	1 (0, 2)	Z = -0.092	0.927
NRS pain (D3), median (IQR)	0 (0, 1)	0 (0, 1)	Z = -1.032	0.302
PSQI (D2), median (IQR)	6 (5, 7)	7 (6, 8)	Z = -2.182	0.029
PSQI (D3), median (IQR)	5 (5, 6)	6 (5, 7)	Z = -2.348	0.019
POD incidence at D2: n (%)	1 (2.86)	3 (8.57)	Z = 0.265	0.614
POD incidence at D3: n (%)	0 (0.00)	0 (0.00)	-	-
Adverse events: n (%)	15 (42.86)	14 (40.00)	Z = 0.059	0.808
Note: EA, emergence agitation; RASS, Richmond Agitation-Sedation Scale; NRS, Numeric Rating Scale; PSQI, Pittsburgh Sleep Quality Index; POD, postoperative delirium.				

3.3 Secondary Outcomes

Postoperative Pain and Sleep Quality: At extubation (D1), NRS pain scores were significantly lower in Group T (median 0 [IQR: 0, 1]) than in Group C (median 2 [IQR: 1, 2]; $P < 0.001$; Table 2, Fig. 4). This difference was no longer significant on D2 and D3 (both $P > 0.05$; Table 2). Within-group comparisons showed that NRS scores increased from D1 to D2 in both groups ($P < 0.05$). For sleep quality, PSQI scores were similar at baseline (D0) but were significantly better (lower) in Group T at both D2 (median 6 [5, 7] vs. 7 [6, 8]; $P = 0.029$) and D3 (median 5 [5, 6] vs. 6 [5, 7]; $P = 0.019$; Table 2, Fig. 5). Furthermore, Group T showed improved sleep from baseline at D3 ($P < 0.05$), whereas Group C showed worsened sleep from baseline at D2 ($P < 0.05$).

Postoperative Delirium

There were no significant differences in the incidence of POD between the two groups at D2 (2.86% vs. 8.57%; $P = 0.614$) or at D3 (0% vs. 0%; Table 2).

Inflammatory Markers: Preoperative serum levels of TNF- α and IL-10 were comparable between groups (both $P > 0.05$). At extubation (D1), both TNF- α and IL-10 levels were significantly lower in Group T compared with Group C (TNF- α : 14.50 [13.70, 15.80] pg/mL vs. 15.30 [14.30, 18.95] pg/mL, $P = 0.029$; IL-10: 15.10 [12.35, 16.20] pg/mL vs. 17.40 [15.15, 22.35] pg/mL, $P < 0.001$; Table 3, Fig. 6). Within Group T, both cytokines decreased significantly from preoperative levels ($P < 0.05$), while no significant within-group changes were observed in Group C.

Table 3
Perioperative Inflammatory Markers and Hemoglobin.

Marker	Time Point	Group T (n = 35)	Group C (n = 35)	Test Statistic	P value
TNF- α (pg/mL), median (IQR)	Preop	17.10 (15.30, 19.55)	15.80 (14.55, 17.90)	Z = -1.375	0.169
	Postop (D1)	14.50 (13.70, 15.80)	15.30 (14.30, 18.95)	Z = -2.180	0.029
IL-10 (pg/mL), median (IQR)	Preop	15.60 (14.25, 17.00)	16.10 (14.35, 21.10)	Z = -1.145	0.252
	Postop (D1)	15.10 (12.35, 16.20)	17.40 (15.15, 22.35)	Z = -3.536	< 0.001
THbc (g/L), mean $\pm$ SD	Preop	141.94 $\pm$ 15.43	146.29 $\pm$ 15.28	t = -1.183	0.241
	Postop (D1)	129.80 $\pm$ 16.64	136.00 $\pm$ 18.84	t = -1.459	0.149

Anesthetic and Hemodynamic Parameters

The time from discontinuation of anesthetics to extubation was significantly longer in Group T (median 25.0 [20.0, 37.0] min vs. 15.0 [10.0, 25.0] min; $P < 0.001$; Table 4). The BIS value at extubation was significantly lower in Group T (median 75 [70, 80] vs. 88 [85, 91]; $P < 0.001$; Table 4). There were no significant differences in total consumption of propofol, cisatracurium, methoxamine, or atropine, nor in PCA consumption or bladder irrigation duration (all $P > 0.05$; Table 4). The morphine equivalent dose were lower in Group T (median 25.00 [22.50, 27.50] mg vs. 37.50 [35.00, 40.00]mg; $P < 0.05$; Table 4).

Table 4
Intraoperative and Postoperative Anesthetic and Recovery Parameters.

Parameter	Group T (n = 35)	Group C (n = 35)	Test Statistic	P value
Propofol (mg), median (IQR)	201.29 ± 88.65	174.86 ± 74.76	t = -1.274	0.182
Cisatracurium (mg), median (IQR)	4.00 (1.50, 5.00)	4.00 (2.00, 4.00)	Z = -0.174	0.862
Methoxamine (mg), median (IQR)	5.00 (2.00, 10.00)	7.00 (3.00, 9.00)	Z = -0.779	0.436
Patients requiring atropine: n (%)	14 (40.0)	16 (45.7)	$\chi^2 = 0.233$	0.63
PCA consumption (mL), median (IQR)	59.00 (51.00, 63.00)	57.00 (52.00, 62.00)	Z = -0.388	0.698
Bladder irrigation duration (h), median (IQR)	24.00 (21.00, 26.00)	23.00 (20.00, 25.00)	Z = -0.954	0.34
Time to extubation (min), median (IQR)	25.00 (20.00, 37.00)	15.00 (10.00, 25.00)	Z = -4.047	< 0.001
BIS at extubation (D1), median (IQR)	75.00 (70.00, 80.00)	88.00 (85.00, 91.00)	Z = -6.202	< 0.001
Morphine equivalent dose(mg), median (IQR)	25.00 (22.50, 27.50)	37.50 (35.00, 40.00)	Z = -3.720	< 0.001

The linear mixed-effects model (LMM) revealed a significant main effect of time for MAP, HR, BIS, and temperature, indicating that all four parameters changed significantly during the perioperative period (all $P < 0.001$; Table 5). No significant main effect of group was found for any of these parameters (all $P > 0.05$). Importantly, the group-by-time interaction was not significant for any outcome (all $P > 0.05$), demonstrating that the temporal trajectories of these parameters were parallel between the two groups (i.e., the effect of the intervention did not change over time). Exploratory post-hoc comparisons at individual time points were performed to further characterize the temporal patterns. These comparisons were not pre-specified and were not adjusted for multiple testing; therefore, they should be interpreted as hypothesis-generating. These analyses showed that heart rate at T3 was higher in Group T (58.94 ± 9.18 bpm) than in Group C (53.66 ± 7.72 bpm; $P = 0.010$; Supplementary Table 1;Figure 7). Similarly, BIS at T4 was lower in Group T (67.29 ± 7.48) than in Group C (75.26 ± 11.77 ; $P = 0.001$; Supplementary Table 1;Figure 7).

Table 5
Linear Mixed-Effects Model Results for Intraoperative Parameters.

Parameter	Fixed Effect	β (95% CI)	SE	Z	P value
MAP	Group (T vs. C)	3.03 (-3.89, 9.95)	3.53	0.858	0.391
	Time	-3.71 (-5.42, -2.01)	0.87	-4.28	< 0.001
	Group $\times$ Time	-0.59 (-3.00, 1.81)	1.23	-0.484	0.628
Heart Rate	Group (T vs. C)	5.19 (-1.19, 11.56)	3.25	1.594	0.111
	Time	-3.97 (-5.33, -2.61)	0.69	-5.726	< 0.001
	Group $\times$ Time	-0.69 (-2.61, 1.24)	0.98	-0.7	0.484
BIS	Group (T vs. C)	3.91 (-7.39, 15.22)	5.77	0.679	0.497
	Time	-5.67 (-8.59, -2.75)	1.49	-3.807	< 0.001
	Group $\times$ Time	-2.06 (-6.19, 2.07)	2.11	-0.978	0.328
Temperature	Group (T vs. C)	0.03 (-0.21, 0.27)	0.12	0.248	0.804
	Time	-0.15 (-0.18, -0.12)	0.02	-9.175	< 0.001
	Group $\times$ Time	-0.04 (-0.09, 0.00)	0.02	-1.914	0.056
Linear mixed-effects models showed no significant group-by-time interactions for any parameter, indicating parallel trajectories between groups.					
Group T had a significantly lower EA incidence (5.71%) compared to Group C (31.43%). $P = 0.006$ (Fisher's exact test).					
Boxplots show median, IQR, and range. Group T had significantly lower RASS scores than Group C ($P = 0.001$, Mann-Whitney U test).					
Group T had significantly lower pain scores at extubation (D1) than Group C ($P < 0.001$). Data are presented as median with IQR.					
Group T had significantly better sleep quality (lower PSQI scores) at D2 and D3 compared to Group C ($P < 0.05$). Data are presented as mean $\pm$ SEM.					
TNF- α and IL-10 levels at baseline (preoperative) and at extubation (D1). Group T had significantly lower levels of both cytokines at extubation compared to Group C ($P < 0.05$). Data are presented as median with IQR.					

Hemoglobin and Safety

Preoperative hemoglobin levels were similar between groups. Both groups experienced a significant postoperative decrease in hemoglobin ($P < 0.05$), but the between-group difference was not significant ($P = 0.149$; Table 3). The incidence of adverse events, including nausea, vomiting, and dizziness, was comparable between Group T (42.86%) and Group C (40.00%; $P = 0.808$; Table 2). No serious adverse events related to the study drugs were reported.

4 Discussion

This prospective, randomized, double-blind trial demonstrates that perioperative administration of butorphanol significantly reduces the incidence and severity of EA in elderly patients undergoing TURP. The benefits extend to improved immediate postoperative analgesia, enhanced sleep quality, and attenuation of systemic inflammation, all without increasing adverse events or causing clinically significant hemodynamic instability. These findings provide robust evidence supporting the integration of butorphanol into multimodal anesthesia strategies for this high-risk population.

4.1 Clinical Efficacy: Analgesia, Sedation, and EA Reduction

Our finding that butorphanol reduces EA aligns with previous studies in thoracic and sinus surgery [22, 23], but this is the first dedicated trial to target the high-risk TURP population. The pathophysiology of EA is multifactorial, and TURP patients are particularly vulnerable due to the convergence of advanced age, male sex, indwelling urinary catheter, and ongoing bladder irrigation [5, 9]. The κ -agonist properties of butorphanol are likely central to its effectiveness. Unlike μ -opioids, which are less effective for visceral pain, κ -receptors are densely expressed in the spinal and supraspinal pathways mediating visceral sensation [12, 16]. This explains the significantly lower pain scores at extubation in the butorphanol group, a direct correlate of EA. The prolonged sedation observed (lower BIS at extubation, longer extubation time) may allow for more synchronized recovery of motor and cognitive functions, reducing the disorientation characteristic of EA [4, 32].

4.2 Mechanistic Insights: Attenuation of Systemic Inflammation

A key finding of our study is the significant reduction in both the pro-inflammatory cytokine TNF- α and the anti-inflammatory cytokine IL-10 in the butorphanol group. This simultaneous downregulation suggests that butorphanol does not merely shift the inflammatory balance but rather dampens the overall inflammatory response. This finding is consistent with preclinical data showing that κ -receptor activation inhibits M1 macrophage polarization and suppresses the release of multiple cytokines [21]. Given that perioperative tissue injury, ischemia, and pain trigger a systemic inflammatory cascade that can compromise the blood-brain barrier and activate neuroinflammation, this anti-inflammatory effect provides a plausible mechanistic hypothesis linking butorphanol use to improved neurobehavioral outcomes [28, 29, 33]. However, it is important to note that our inflammatory data are derived from peripheral blood; direct evidence of central nervous system inflammation (e.g., cerebrospinal fluid cytokines or neuroimaging) was not obtained in this study [34]. The reduction in IL-10, typically a compensatory anti-inflammatory mediator, is best interpreted as a consequence of the diminished pro-inflammatory stimulus [35, 36]. This nuanced finding supports the hypothesis that butorphanol may act on upstream inflammatory triggers (e.g., pain, surgical stress) rather than directly modulating downstream cytokine production.

4.3 Clinical Implications and Multimodal Anesthesia Integration

While the time from anesthetic discontinuation to extubation was objectively longer in Group T (median 25 vs. 15 min), we interpret this as a sign of a more gradual, synchronized emergence profile rather than a simple delay. Instead of abrupt awakening with sympathetic surges and disorientation—which can be catastrophic in frail elderly patients [7], the slower transition allows for smoother hemodynamic stabilization and improved cognitive re-orientation. This is particularly critical for the geriatric TURP population, where sudden surges in heart rate and blood pressure are strongly associated with surgical site bleeding and cardiovascular complications [6].

Furthermore, the significantly lower morphine equivalent dose (MED) in Group T (median 25.00 mg vs. 37.50 mg) provides direct evidence for optimized opioid utilization. By leveraging the distinct kappa-receptor agonism of butorphanol for visceral pain [12, 16], we achieved superior analgesia with approximately 33% less opioid burden. From a clinical practice standpoint, this reduced opioid load directly translates into a lower risk of delayed respiratory depression, postoperative ileus, and unwanted sedation. This aligns with current Enhanced Recovery After Surgery (ERAS) principles advocating for opioid-sparing multimodal analgesia. Therefore, butorphanol represents a practical, safe, and opioid-efficient choice for individualizing pain management in high-risk urological surgery.

While we observed a non-significant trend toward reduced POD incidence (2.86% vs. 8.57%, $P = 0.614$), our study was underpowered to detect a difference in this secondary outcome. The observed effect size ($OR = 0.31$) and the well-established link between EA and subsequent POD [37] suggest that a larger, adequately powered trial is warranted. The significantly improved sleep quality (PSQI) in the butorphanol group is another important finding. Perioperative sleep disturbance is increasingly recognized as an independent risk factor for both EA and POD [38, 39]. Butorphanol's sedative properties may help consolidate sleep architecture, and effective pain control reduces nocturnal awakenings, thereby improving overall sleep quality [19]. This, in turn, may contribute to a more favorable neurocognitive recovery trajectory.

4.4 Safety Profile

Importantly, the beneficial effects of butorphanol were not accompanied by an increase in adverse events. The comparable rates of nausea, vomiting, and dizziness are likely due to its μ -antagonist properties, which can counteract the emetogenic effects of μ -opioid receptor activation [40]. The linear mixed-effects models confirmed that the temporal changes in MAP, HR, BIS, and temperature were parallel between the two groups, indicating that butorphanol does not introduce significant hemodynamic instability. In addition, this study used morphine equivalent dose as a standardized analgesic dosage evaluation index to eliminate the comparison bias caused by differences in pharmacological potency among different analgesic drugs. The results showed that the morphine equivalent dose in the butorphanol tartrate group was lower than that in the sufentanil citrate group,

indicating that butorphanol may be a more efficient analgesic choice for elderly patients undergoing transurethral resection of the prostate, i.e., achieving similar analgesic effects with a lower morphine equivalent dose. This provides a new option for individualized clinical medication in this type of surgery.

4.5 Limitations

Several limitations must be acknowledged. First, the single-center design and relatively small sample size limit generalizability and precluded robust subgroup analyses. Second, the follow-up for POD was limited to postoperative day 3. Although this aligns with guidelines for early detection, we may have missed later-onset delirium cases [41]. Third, while our cytokine data provide valuable mechanistic clues, they are based on only two time points. A more dynamic assessment with serial sampling would better capture the trajectory of the inflammatory response[36]. Fourth, we did not incorporate advanced neurophysiological or neuroimaging measures, such as electroencephalography (EEG) burst suppression or functional MRI, which could provide deeper insights into the central effects of butorphanol. Consequently, while our peripheral cytokine data suggest an anti-inflammatory effect, the link to central neuroinflammation remains inferential. Fifth, our cytokine measurements were limited to two time points, which may not capture the full dynamic trajectory of the inflammatory response. Future studies incorporating serial sampling and central nervous system biomarkers are needed to validate these mechanistic hypotheses. Finally, the study was powered for the primary outcome (EA), and the null finding for POD should be interpreted with caution due to limited statistical power.

4.6 Conclusion

In conclusion, this randomized controlled trial provides compelling evidence that perioperative butorphanol reduces EA, improves immediate analgesia and sleep quality, and attenuates systemic inflammation in elderly patients undergoing TURP, with a favorable safety profile. The findings support its use as a safe and effective component of multimodal anesthesia in this vulnerable population. Future multi-center studies with larger sample sizes, extended follow-up, and integrated neuroimaging and electrophysiological assessments are warranted to confirm the effects on POD and to further elucidate the underlying mechanisms linking κ -opioid receptor activation to neuroprotection.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University(PJ-KS-KY-2025-140[X]) and was registered retrospectively (Registration No. ChiCTR2500114145, December 08 2025) due to an unforeseen delay in the institutional registration review process at the time of study launch. The study protocol was finalized and IRB approved prior to participant enrollment, and no outcome data were analyzed before registration. All participants or their legal surrogates provided written informed consent prior to enrolment. This pragmatic randomized controlled trial was reported in accordance with the CONSORT 2025 guidelines.

Consent for publication

Not applicable. No individual person's data, images or clinical details are included in this manuscript.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that Generative AI was not used in the creation of this manuscript.

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Author Contribution

YX: Writing – original draft, Methodology, Formal analysis, Data curation. DS: Project administration, Validation, Supervision, Funding acquisition, Writing – review & editing.

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An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR.

Data Availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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Figures

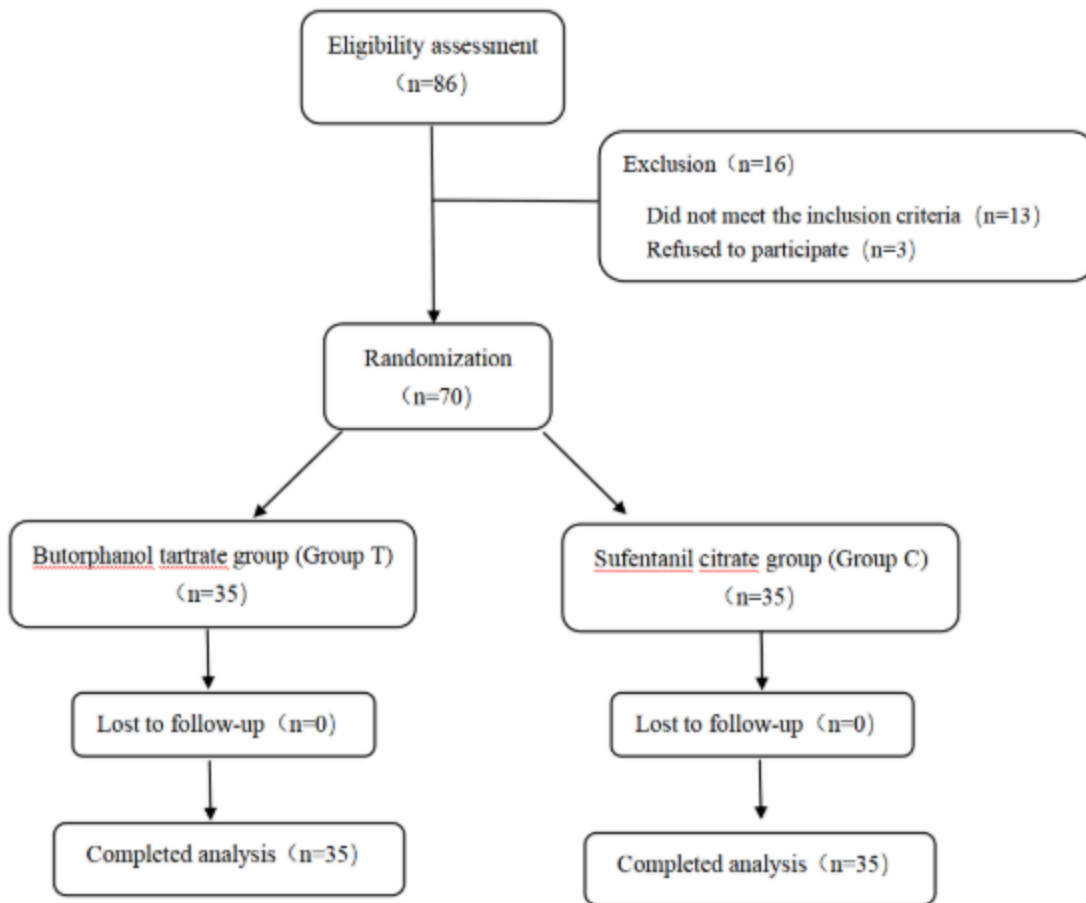


Figure 1

CONSORT flow diagram of patient enrollment and randomization.

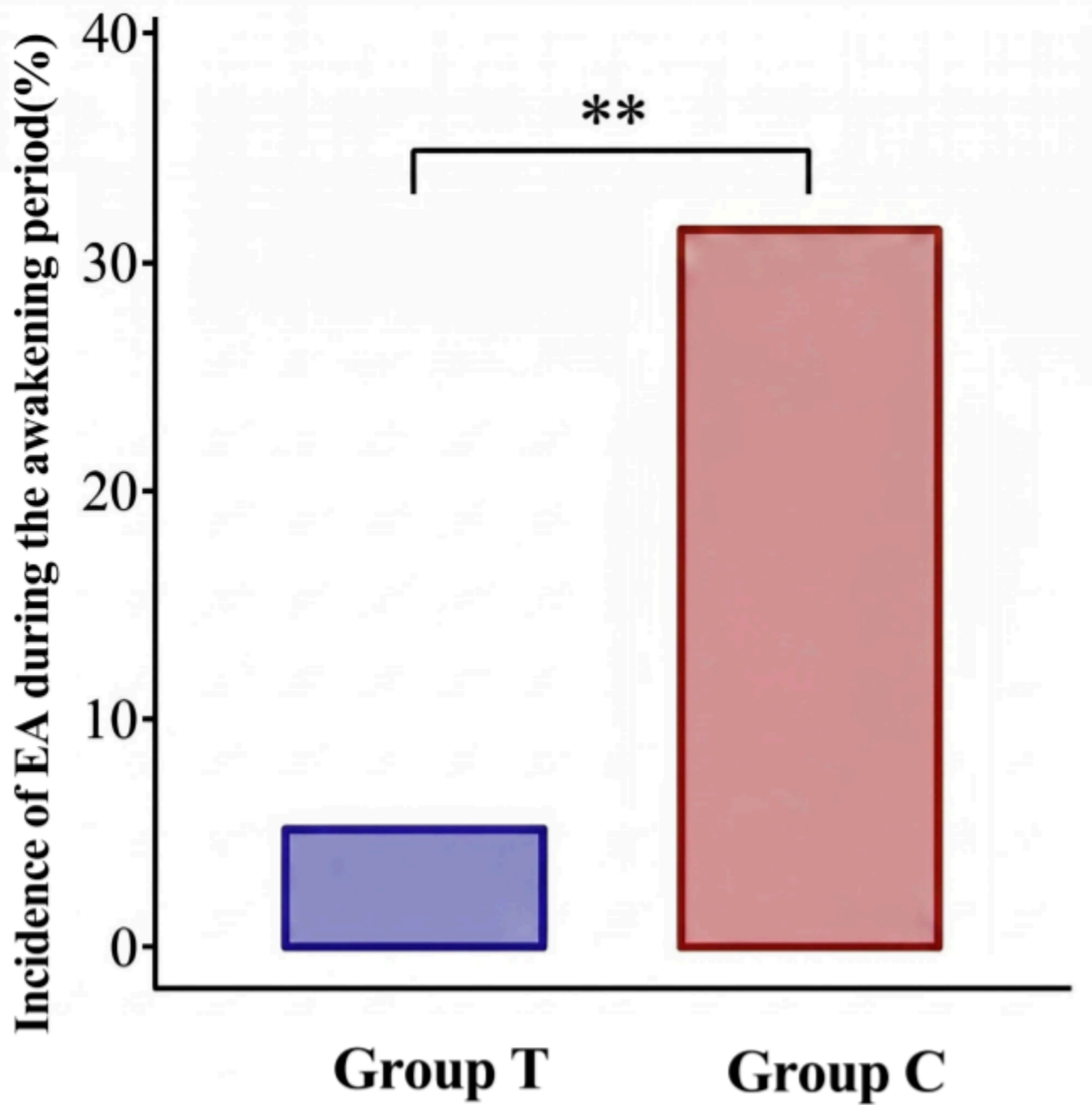


Figure 2

Incidence and scores of emergence agitation (EA) at extubation (D1).

Group T had a significantly lower EA incidence (5.71%) compared to Group C (31.43%). $P = 0.006$ (Fisher's exact test).

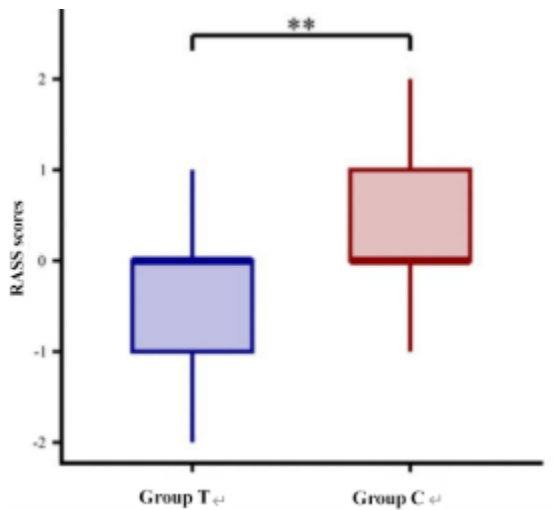


Figure 3

Richmond Agitation-Sedation Scale (RASS) scores at extubation (D1).

Boxplots show median, IQR, and range. Group T had significantly lower RASS scores than Group C ($P = 0.001$, Mann-Whitney U test).

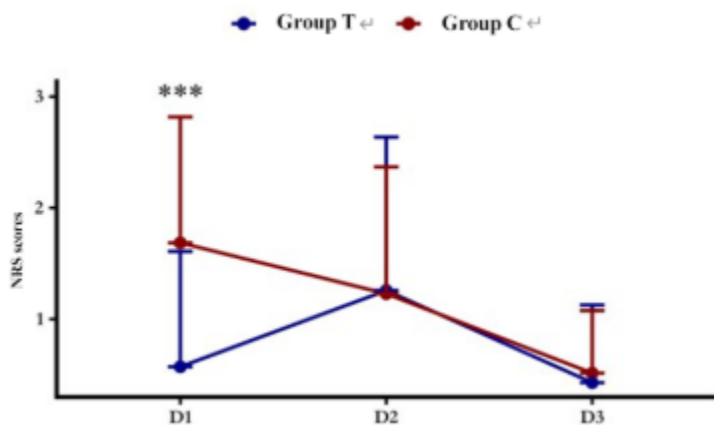


Figure 4

Postoperative pain scores (NRS) over time.

Group T had significantly lower pain scores at extubation (D1) than Group C ($P < 0.001$). Data are presented as median with IQR.

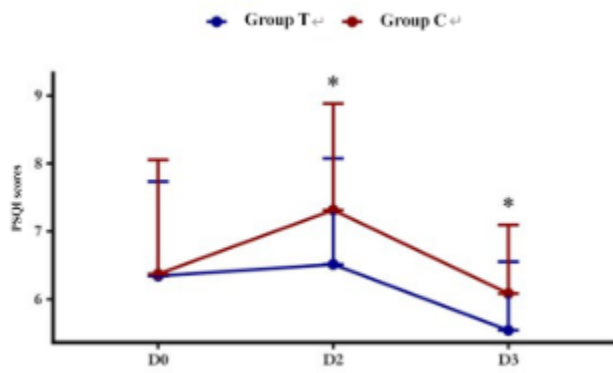


Figure 5

Sleep quality (PSQI) over time.

Group T had significantly better sleep quality (lower PSQI scores) at D2 and D3 compared to Group C ($P < 0.05$). Data are presented as mean $\pm$ SEM.

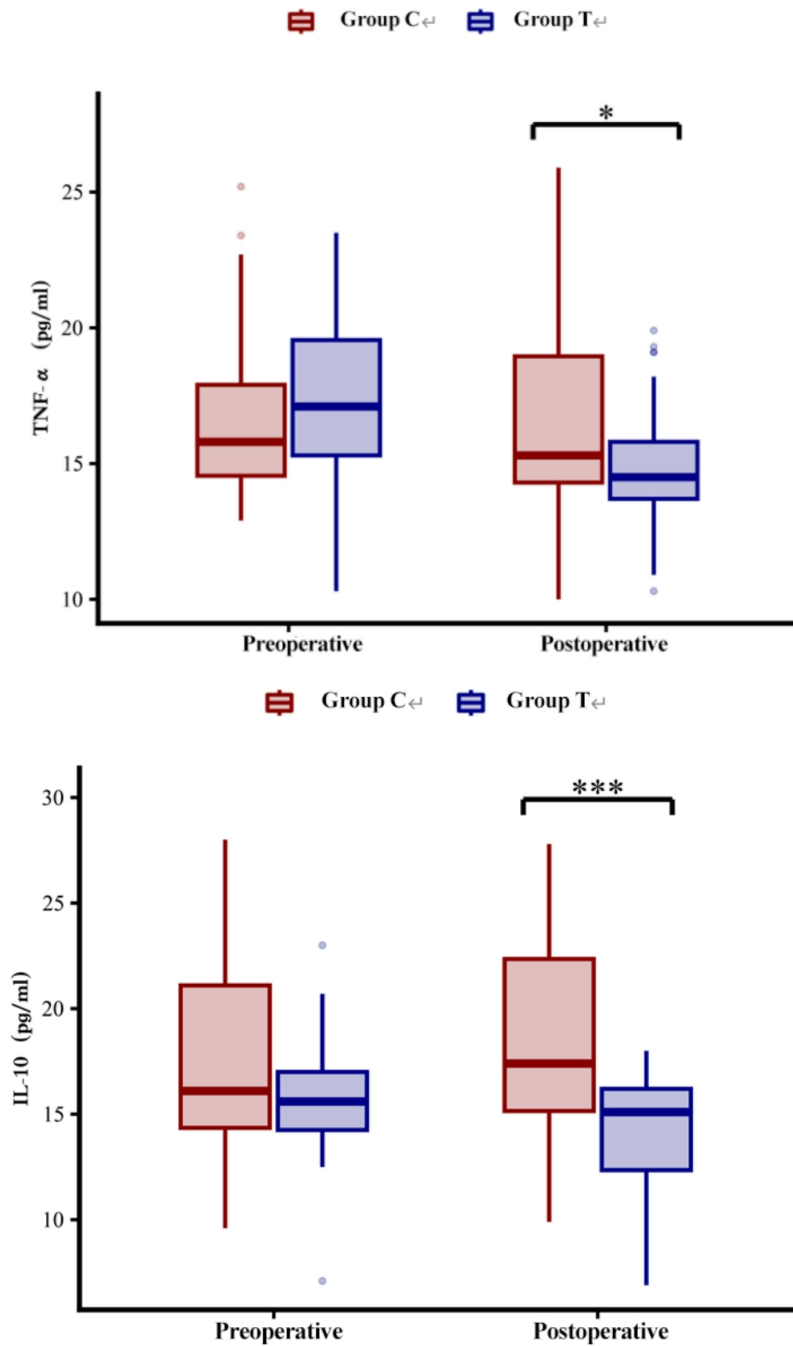


Figure 6

Perioperative changes in serum inflammatory markers.

TNF-α and IL-10 levels at baseline (preoperative) and at extubation (D1). Group T had significantly lower levels of both cytokines at extubation compared to Group C ($P < 0.05$). Data are presented as median with IQR.

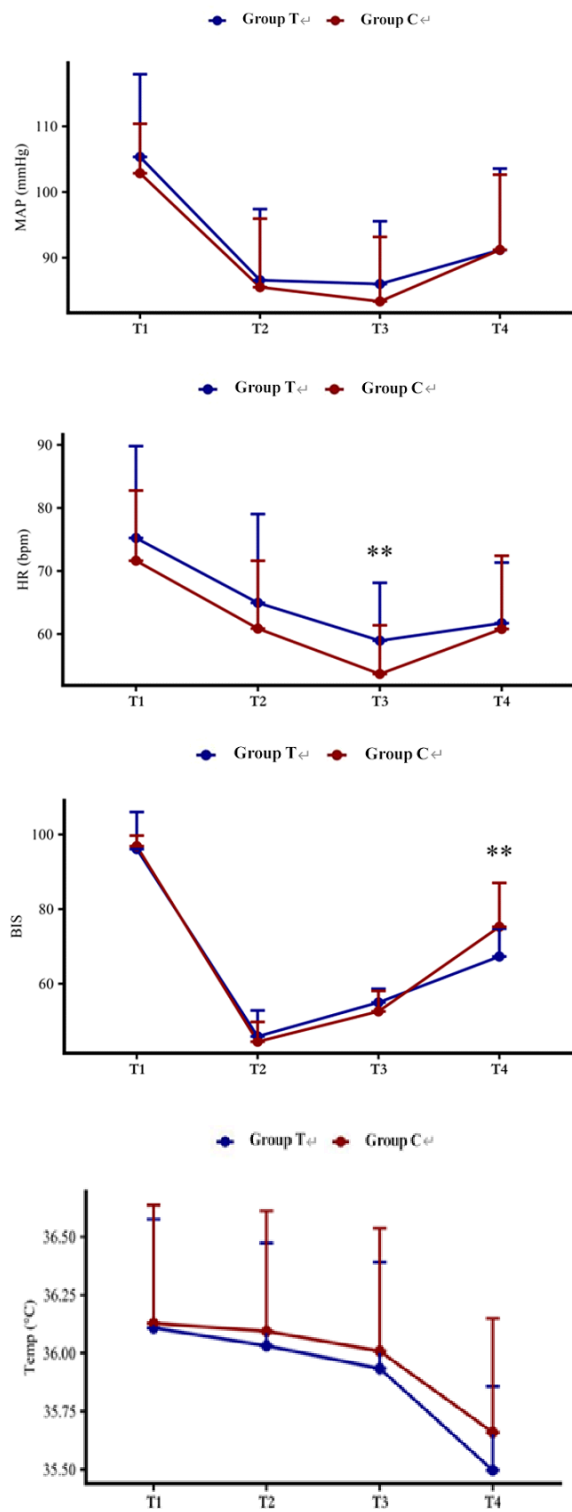


Figure 7

Temporal trends in intraoperative parameters.

MAP, Heart Rate, BIS, and Temperature across T1 (entry), T2 (intubation), T3 (incision), and T4 (PACU discharge). Data are presented as mean $\pm$ SEM.

Supplementary Files

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