Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Effects of Different Doses of Butorphanol on Perioperative Analgesia, Recovery, and Immune Function in Patients Undergoing Cytoreductive Surgery for Ovarian Cancer: A Randomized Controlled Trial

Guizhi Wang[1], Mengmeng Xu[2], Chuanyao Li[2], Na Zhang[2], Tingting Tian[2], Chen Gao[2], Wei Zhang[1,2]

[1]Graduate School, Bengbu Medical University, Bengbu, Anhui, People's Republic of China; [2]Department of Anesthesiology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, People's Republic of China

Correspondence: Wei Zhang, Graduate School, Bengbu Medical University, 2600 Donghai Avenue, Bengbu, Anhui, 233030, People's Republic of China, Email doctor_zw97079@163.com; Chen Gao, Department of Anesthesiology, The First Affiliated Hospital of University of Science and Technology of China, No. 17 Lujiang Road, Luyang District, Hefei, 230001, People's Republic of China, Email gaochen8805@126.com

Purpose: To investigate the optimal dose of butorphanol for patient-controlled intravenous analgesia (PCIA) by evaluating its effects on perioperative pain control and immune function in patients undergoing ovarian cancer surgery.

Patients and Methods: Patients undergoing ovarian cancer surgery between May 2023 and March 2025 were randomized into four PCIA groups: Group S (sufentanil 0.04 $\mu g \cdot kg^{-1} \cdot h^{-1}$), B1 (low-dose butorphanol 3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$), B2 (medium-dose butorphanol 3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and B3 (high-dose butorphanol 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Postoperative pain visual analog scale scores (VAS) were recorded for each group at T1 (2 h), T2 (6 h), T3 (12 h), T4 (24 h), and T5 (48 h). The number of PCIA button presses, rescue analgesia frequency, adverse reactions, inflammatory biomarkers, postoperative recovery indicators, and the level of lymphocyte subsets and NK cells were recorded.

Results: VAS score at T3 was lower in group B3 than in S ($P = 0.042$). VAS scores at T3 and T4 were lower in groups B2 ($P = 0.007$ and $P < 0.001$) and B3 ($P = 0.005$ and $P < 0.001$) than in B1. Compared to group S, B1 showed an increased area under the curve of VAS time ($AUC_{VAS\text{-}time}$) over 48 hours ($P = 0.010$), whereas group B3 exhibited a decrease in $AUC_{VAS\text{-}time}$ ($P = 0.004$). Group B3 had shorter postoperative time to ambulate than group S ($P = 0.041$). In group S, NK cells at T5 were lower than those at T0 ($P = 0.007$). In group B1, levels of CD4+ T cells, and CD4+/CD8+ ratio were higher at T5 than at T0 ($P = 0.007$ and $P = 0.014$), whereas CD8+ T cell count was lower ($P = 0.011$).

Conclusion: High-dose butorphanol PCIA effectively relieves postoperative pain and reduces time to early ambulation without affecting immune indicators within 48 h postoperatively.

Keywords: butorphanol, postoperative analgesia, cytoreductive surgery, immune function

Introduction

Ovarian cancer is the third most common gynecological malignancy globally, with a five-year survival rate of 40–45%.[1–3] Cytoreductive surgery serves as the first-line treatment for ovarian cancer and requires multi-organ resection.[4] The surgical trauma associated with this operation results in various types of pain, including incision, inflammatory, and visceral pain, leading to severe postoperative pain for patients. Therefore, pain management following primary cytoreductive surgery remains a major challenge. Improved opioid analgesics should be prioritized in the analgesic strategy for cytoreductive surgery, aligning with the requirements of Enhanced Recovery After Surgery protocols.[5]

Received: 17 June 2025
Accepted: 19 November 2025
Published: 8 December 2025

Butorphanol, a synthetic opioid receptor agonist-antagonist, exhibits a potency ratio of 25:4:1 against κ, μ, and δ receptors, respectively. Varying affinities for these receptors results in distinct clinical effects.[6] Compared to pure μ receptor agonists, butorphanol is more effective at suppressing visceral pain while reducing opioid-associated adverse effects and opioid dependence risk. A study by Du et al[7] on postoperative analgesia in patients undergoing laparoscopic hysterectomy showed that dexmedetomidine combined with butorphanol patient-controlled intravenous analgesia (PCIA) significantly decreased postoperative visual analog scale (VAS) scores and postoperative nausea and vomiting, thus improving patient satisfaction. Similarly, butorphanol has been shown to reduce postoperative visceral pain in patients undergoing microwave ablation for liver tumors.[8] However, its application in large open abdominal surgeries, such as ovarian cancer surgery has not been reported. Considering the existing literature, pharmacological characteristics of butorphanol, and lack of reported effective perioperative analgesia for ovarian cancer, we anticipate that butorphanol PCIA will provide effective analgesia with fewer adverse reactions in postoperative ovarian cancer. However, the optimal dosage remains to be determined.

Furthermore, patients with tumors often experience a suppressed immune function, making them susceptible to immune dysfunction during the perioperative period. Surgical trauma, perioperative stress, inflammatory responses, and anesthetic agents facilitate dissemination of tumor cells.[9] In vitro studies have demonstrated that butorphanol protects PC12 cells from inflammation and apoptosis induced by oxygen-glucose deprivation/reperfusion.[10] Additionally, butorphanol may inhibit malignant biological behavior of ovarian cancer cells by downregulating the expression of TMEFF1 (Tomoregulin-1, a transmembrane protein with an epidermal growth factor-like domain and two follistatin-like structural domains).[11] Consequently, we hypothesized that butorphanol PCIA as an opioid agonist-antagonist in postoperative patients undergoing primary cytoreductive surgery for ovarian cancer may stabilize the immune status of these patients.

Materials and Methods

Patients

This was a prospective, double-blind, randomized controlled trial. This study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (approval number: 2021KY [258]). This study was registered in the Chinese Clinical Trial Registry (Registration Number: ChiCTR 2300069879). Compliance with the Declaration of Helsinki and CONSORT standards was ensured during the trial. All patients signed an informed consent form. We enrolled patients who underwent primary cytoreductive surgery for ovarian cancer at the First Affiliated Hospital of the University of Science and Technology of China (Anhui Provincial Hospital) between May 2023 and March 2025. Four groups were formed by dividing the patients according to the postoperative use of sufentanil or different doses of butorphanol PCIA: S (sufentanil 0.04 $\mu g \cdot kg^{-1} \cdot h^{-1}$), B1 (butorphanol 3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$), B2 (butorphanol 3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and B3 (butorphanol 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$).

The following inclusion criteria were applied: American Association of Anesthesiologists (ASA) classification I, II, or III; ovarian cancer confirmed by surgical and pathological diagnosis; no history of allergies to the study drugs; International Federation of Gynecology and Obstetrics classification I, II, or III; and age 18–65 years. Patients who had multiple chronic diseases, were unable to tolerate surgical anesthesia, had severe cardiopulmonary or renal insufficiency, had coagulation dysfunction, were allergic to sufentanil or butorphanol, had severe sequelae of neurological disorders, had advanced ovarian cancer with cachexia, had a recent history of opioid use, had recent infections or immune system diseases, or were pregnant or lactating were excluded from the study. The removal criteria were as follows: intraoperative bleeding volume more than 2000 mL, surgical duration >6 h, or need for a second procedure within 48 h postoperatively.

Anesthesia and Analgesia

All patients fasted for 8 h before surgery and had no oral intake for 4 h. General anesthesia was administered via endotracheal intubation. Upon entering the operating room, patient information was verified and intravenous access was established. Heart rate, electrocardiography, oxygen saturation, and end-tidal carbon dioxide were continuously monitored. Under local anesthesia, radial artery catheterization was performed to monitor arterial pressure and internal jugular vein catheterization was performed to monitor central venous pressure. All groups of patients were induced with

intravenous administration of midazolam (0.05 mg/kg), sufentanil (0.5 μg/kg), etomidate (0.3 mg/kg), and rocuronium (0.8 mg/kg). Following satisfactory muscle relaxation, endotracheal intubation was performed and intermittent positive pressure ventilation was initiated. Target-controlled infusion was used to maintain a target plasma concentration of propofol between 2.0~4.0 μg/mL and remifentanil between 2.0~6.0 ng/mL during the surgery, with inhalation of 1–2% sevoflurane and intermittent bolus doses of cisatracurium (0.1 mg/kg) to maintain a Bispectral Index value between 40 and 60. Intraoperative monitoring included nasal temperature measurements and temperature management was implemented for thermal protection. The acid–base balance, electrolyte levels, blood glucose levels, and other parameters were adjusted according to the arterial blood gas results.

After completion of surgery, all patients underwent bilateral, four-point transversus abdominis plane (TAP) block under ultrasound guidance, and 15 mL of 0.25% ropivacaine was injected at each injection site through different puncture pathways.[12,13]

Postoperatively, all the patients received PCIA. The study protocols were sealed in envelopes and were randomly distributed to each participant. The study drugs for the PCIA pump were prepared by an independent anesthetic nurse, with an anesthesiologist handling the recording of study outcomes. The PCIA formulations were as follows: sufentanil 0.04 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for group S, low-dose butorphanol (3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) for group B1, medium-dose butorphanol (3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) for group B2, and high-dose butorphanol (4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) for group B3, with background infusion of 2 mL/h, a bolus dose dose of 1 mL and a lockout interval of 30 minutes. When the patients' VAS scores exceeded 4, rescue analgesia was administered via intravenous injection of 50 mg flurbiprofen axetil as analgesic rescue.

Data Collection

The patients' general characteristics were recorded, including age, height, weight, body mass index (BMI), and ASA classification. Surgical parameters, such as operative time, intraoperative blood loss, urine output, fluid intake, extubation time, and surgical complexity scores were also documented. Additionally, postoperative pain VAS scores at T1 (2 h), T2 (6 h), T3 (12 h), T4 (24 h), and T5 (48 h), the curve of VAS time ($AUC_{VAS\text{-}time}$) over 48 hours, the number of PCA button presses, the frequency of rescue analgesia, the occurrence of adverse reactions, postoperative recovery indicators and preoperative and postoperative inflammatory indicators, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) were recorded for each group.

Levels of T lymphocytes (CD3+), B lymphocytes (CD19+), helper/inducer T lymphocytes (CD3+CD4+), suppressor/cytotoxic T lymphocytes (CD3+CD8+), and natural killer cells (CD3-CD16+ and CD56+), as well as the CD4+/CD8+ ratio were determined at baseline and 48 h postoperatively by flow cytometry using an Attune NxT flow cytometer. A schematic diagram of the gating strategy for the flow cytometry of various lymphocyte subsets and representative data of different parameters for each group are shown in Figure 1. To minimize the potential confounding effect of neoadjuvant chemotherapy on hematological parameters, patients who had received preoperative chemotherapy were excluded from this study. Furthermore, all postoperative blood samples were collected prior to administering any postoperative chemotherapy.

Statistical Analysis

A preliminary trial was conducted with 10 patients in each group, followed by recording postoperative VAS scores at 12 h (B1: 3.5 ± 0.85; B2: 2.80 ± 0.63; B3: 2.60 ± 0.70; S: 2.9 ± 0.74). Sample size was calculated using PASS 15.0 statistical software, with 90% power and a two-sided α value of 0.05. The required sample sizes for the four qualifying groups were computed using one-way analysis of variance (ANOVA) and averaged, resulting in a required sample size of 69. Considering a 20% loss to follow-up rate, a total sample size was set at 88 patients, with 22 patients allocated to each group.

Data analysis was performed using SPSS 25.0 statistical software. Results for normally distributed parameters are expressed as mean ± standard deviation ($\overline{X} \pm s$), while non-normally distributed parameters are presented as median and interquartile range. ANOVA was used for multigroup measurements to compare means among the three groups, with Bonferroni post-hoc tests for multiple comparisons. Categorical variables were analyzed using appropriate non-parametric tests based on data distribution. Ordered categorical data were analyzed using rank-sum tests, whereas unordered

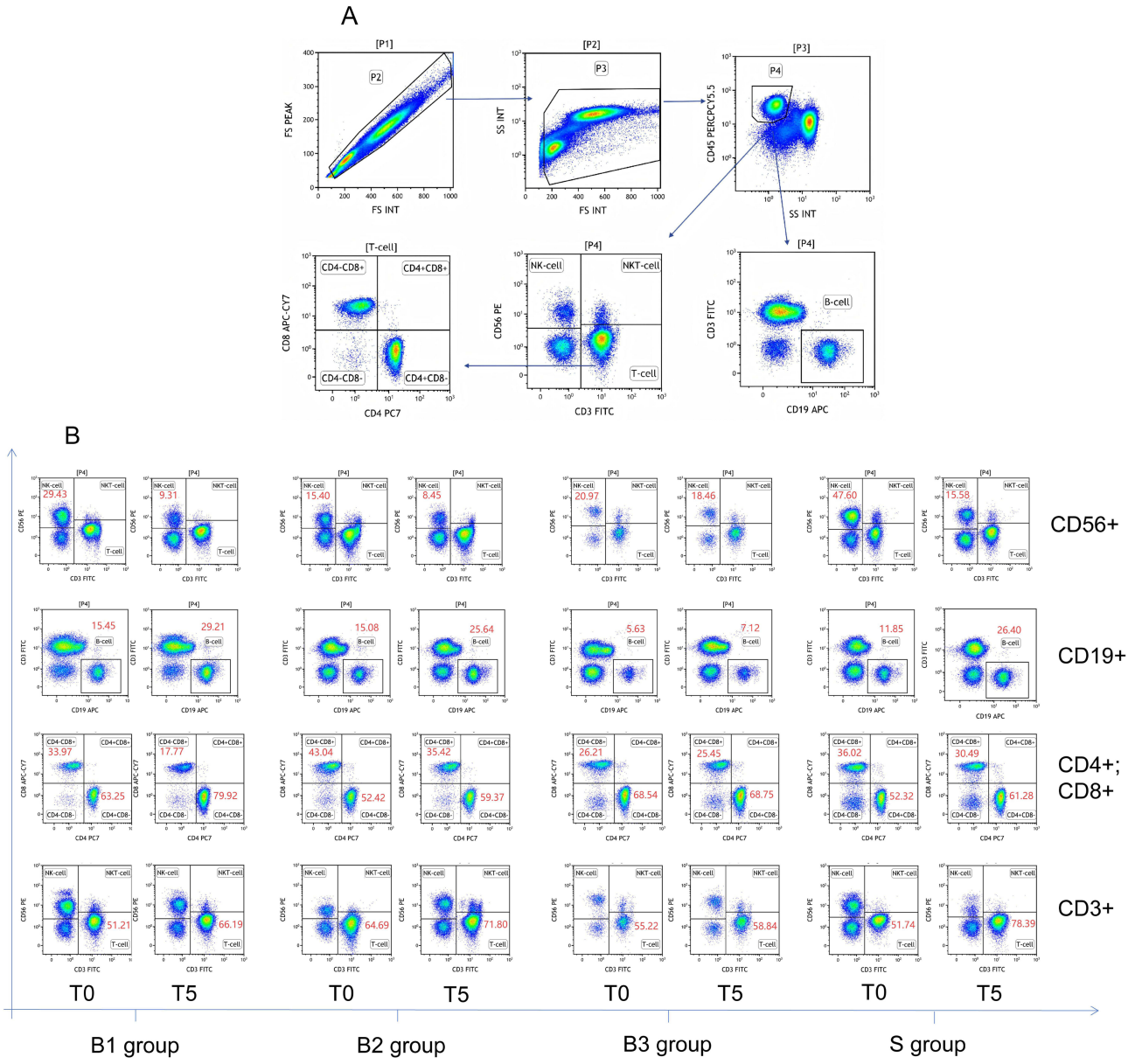

Figure 1 Flow cytometry workflow and representative plots of each group. (**A**) Gating strategy for lymphocyte subpopulation analysis by flow cytometry. (**B**) Representative flow cytometry plots showing the percentages of CD3+ T cells, CD19+ B cells, CD4+ T cells, CD8+ T cells, CD4+/CD8+ ratio, and NK cells across four groups at different time points.

categorical data were analyzed using chi-square tests. The Fisher's exact test was used when the cell frequency was less than 5. The significance level was set at a two-sided $\alpha = 0.05$.

Results

Patient Characteristics

Among the 119 patients who underwent ovarian cancer cytoreductive surgery under general anesthesia between May 2023 and March 2025, 88 were included in this study and randomized into four groups (Figure 2). As shown in Table 1, no statistically significant differences in age, BMI, ASA scores, comorbidities, blood loss, operative time, extubation time, surgical complexity scores, intraoperative fluid volume, or bleeding volume were observed among the four groups ($P > 0.05$).

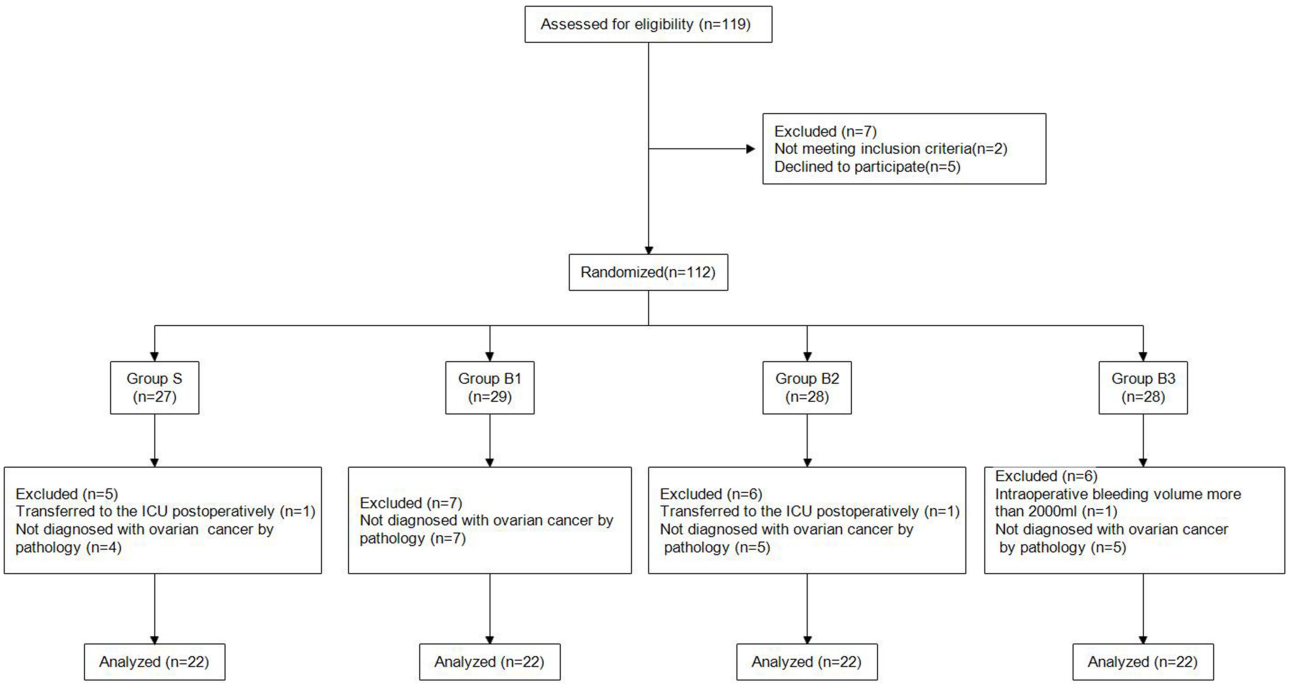

Figure 2 Flow diagram of participants in the study.

Postoperative Pain Score

At 2 and 6 h postoperatively, no statistically significant differences in pain VAS scores were observed among the groups ($P = 0.789$ and $P = 0.154$, respectively). At 24 h postoperatively, the VAS score in group B3 was significantly lower than

Table 1 Demographic and Clinical Characteristics of the Patients Included

	S (n=22)	B1 (n=22)	B2 (n=22)	B3 (n=22)	*P* value
Age (years), mean ± SD	50.09±9.38	52.82±7.20	53.55±5.62	50.05±8.37	0.311
BMI (kg/m^2), mean ± SD	23.04±3.57	23.10±3.04	23.59±2.79	23.03±2.81	0.918
ASA physical status, n (%)					0.713
I	5 (22.7)	3 (13.6)	2 (9.1)	3 (13.6)	
II	8 (36.4)	10 (45.5)	6 (27.3)	8 (36.4)	
III	9 (40.9)	9 (40.9)	14 (63.6)	11 (50.0)	
Hypertension, n (%)	5 (22.7)	4 (18.2)	7 (31.8)	3 (13.6)	0.557
Diabetes, n (%)	1 (4.5)	1 (4.5)	2 (9.1)	2 (9.1)	1.000
Heart disease, n (%)	0	0	0	1 (4.5)	1.000
Preoperative hemoglobin (g/L), mean ± SD	117.77±16.68	118.41±12.52	119.45±13.63	122.05±15.63	0.782
Preoperative albumin (g/L), mean ± SD	42.23±4.17	41.67±4.39	41.70±3.35	42.08±4.04	0.956
Duration of surgery (h), mean ± SD	3.65±1.33	3.71±1.45	3.40±0.95	3.43±1.07	0.780
Extubation time (h), mean ± SD	0.81±0.46	0.88±0.46	0.86±0.49	0.81±0.43	0.951
Intraoperative fluid infusion volume (mL), mean ± SD	2461.36±957.42	2427.27±674.84	2263.64±607.33	2363.64±663.00	0.822
Blood transfusion volume (mL), median (IQR)	200 (0, 800)	0 (0, 800)	0 (0, 450)	0 (0, 725)	0.308
Intraoperative albumin infusion (g), median (IQR)	40 (0, 60)	40 (22.5, 60)	40 (20, 45)	40 (0, 60)	0.751
Volume of blood loss (mL), median (IQR)	500 (175, 800)	300 (175, 800)	350 (200, 500)	350 (200, 800)	0.756
Urine volume (mL), median (IQR)	200 (100, 450)	300 (200, 500)	300 (175, 425)	200 (200, 300)	0.470
Ascites (mL), median (IQR)	0 (0, 225)	700 (0, 000)	275 (0, 1625)	300 (37.5, 1000)	0.103
Surgical complexity scores (SCS)	4.5 (4, 6.25)	5 (4, 7.5)	4 (3, 5.25)	4.5 (4, 6)	0.521

Notes: Group S, sufentanil; Group B1, low-dose butorphanol 3.0 μg·kg^{-1}·h^{-1}; Group B2, medium-dose butorphanol 3.5 μg·kg^{-1}·h^{-1}; Group B3, high-dose butorphanol 4.0 μg·kg^{-1}·h^{-1}.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

https://doi.org/10.2147/DDDT.S545111

that in group S ($P = 0.042$). Additionally, the VAS scores at 12 and 24 h were lower in groups B2 ($P = 0.007$ and $P < 0.001$, respectively) and B3 ($P = 0.005$ and $P < 0.001$, respectively) than in group B1. However, no statistically significant differences in VAS scores were observed between groups B2 and B3 at the time points of 2, 6, 12, 24, and 48 h ($P = 1.000$, $P = 1.000$, $P = 1.000$, $P = 0.663$, and $P = 1.000$, respectively) (Figure 3). Compared with that in group S, the $AUC_{VAS\text{-}time}$ was higher in group B1 and lower in group B3 ($P = 0.010$ and $P = 0.004$, respectively). Furthermore, the $AUC_{VAS\text{-}time}$ was lower in groups B2 and B3 than in group B1 ($P < 0.001$), as shown in Figure 4.

PCIA and Rescue Analgesia

The number of effective presses for PCIA was lower in group B3 than in group S ($P = 0.045$). Group B3 also exhibited a lower number of effective presses on the analgesic pump compared with group B1 ($P = 0.005$). However, no statistically significant differences in the total number of presses on the analgesic pump were observed among the four groups ($P = 0.075$). Additionally, the proportion of patients requiring rescue analgesia was lower in group B3 than in group B1 ($P = 0.002$), as shown in Table 2.

Comparison of Adverse Effects and Postoperative Rehabilitation Indexes Among the Four Groups

No statistically significant differences in postoperative nausea and vomiting, dizziness, drowsiness, or respiratory depression were observed among the four groups ($P > 0.05$). Additionally, no statistically significant differences in the

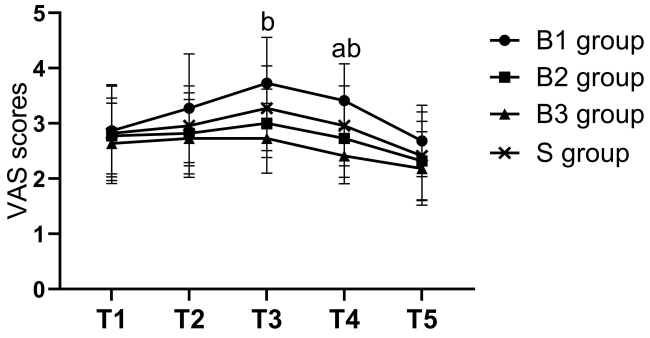

Figure 3 Postoperative VAS scores were measured at 2, 6, 12, 24, and 48 hours after surgery. The VAS score in group B3 compared with group S, [a]$P<0.05$. The VAS score in group B2 and group B3 compared with group B1, [b]$P<0.05$.

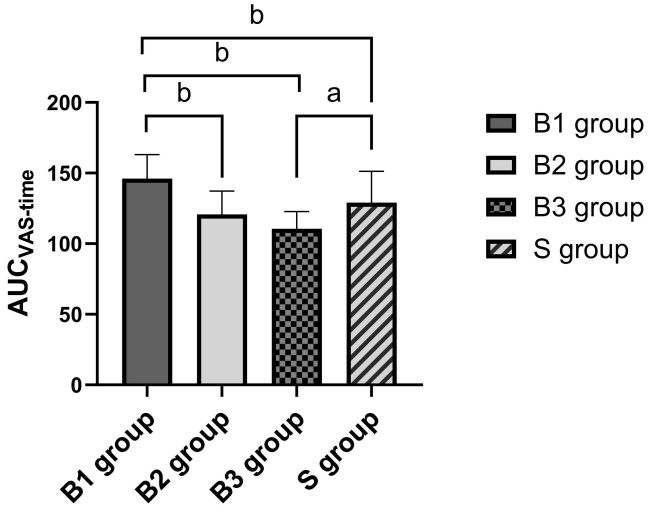

Figure 4 The area under the VAS-time curve ($AUC_{VAS\text{-}time}$) over 48 hours. $AUC_{VAS\text{-}time}$: The area under the VAS-time curve ($AUC_{VAS\text{-}time}$) over 48 hours was calculated using the trapezoidal rule, which represents the cumulative pain intensity. Compared with group S, [a]$P<0.05$, Compared with group B1, [b]$P<0.05$.

Table 2 PCIA and Rescue Analgesia Among the Four Groups

	Group S	Group B1	Group B2	Group B3	*P* value
The total number of pressing the analgesic pump, median (IQR)	4 (2.75, 5)	4 (3, 5)	3 (2, 4.25)	2.5 (1.75, 4)	0.075
The effective number of pressing the analgesic pump, median (IQR)	3 (2, 4.25)	3 (3, 4)	2.5 (2, 3.25)	2 (0.75, 3)[a,b]	0.004
The proportion of remedial analgesia, n (%)	11 (50)	15 (68.2)	8 (36.4)	5 (22.7)[b]	0.018

Notes: Group S, sufentanil; Group B1, low-dose butorphanol 3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$; Group B2, medium-dose butorphanol 3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$; Group B3, high-dose butorphanol 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$; Compared with group S, [a]*P*<0.05; Compared with group B1, [b]*P*<0.05.

Table 3 Adverse Effects and Postoperative Rehabilitation Indexes Among Four Groups

	Group S	Group B1	Group B2	Group B3	*P* value
Dizziness, n (%)	3 (13.6)	2 (9.1)	3 (13.6)	4 (18.2)	0.856
Somnolence, n (%)	3 (13.6)	3 (13.6)	4 (18.2)	6 (27.3)	0.608
Nausea and vomiting, n (%)	5 (22.7)	4 (18.2)	5 (22.7)	4 (18.2)	0.964
Respiratory depression, n (%)	0	0	0	0	1.000
Intestinal fistula, n (%)	3 (13.6)	1 (4.5)	0	0	0.099
Postoperative pulmonary complications, n (%)	5 (22.7)	3 (13.6)	1 (4.5)	0	0.063
Poor wound healing, n (%)	0	1 (4.5)	3(13.6)	1(4.5)	0.258
Time to first flatus (h), median (IQR)	58 (38.75, 109)	68 (53.75, 85)	57.5 (32, 80)	53.5 (32.25, 80)	0.336
Time to first ambulation (h), mean ± SD	34.73±8.15	31.77±9.83	30.32±6.69	28.00±5.83[a]	0.041
Time of first chemotherapy after surgery(d), median (IQR)	15 (9.5, 22.5)	14 (9.5, 23)	11 (9, 23.5)	14 (10, 22)	0.887
Length of hospital stay (d), median (IQR)	11.5 (9, 19.25)	13 (9.75, 18.25)	10.5 (9, 13.25)	11 (8, 14.25)	0.460

Notes: Group S, sufentanil; Group B1, low-dose butorphanol 3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$; Group B2, medium-dose butorphanol 3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$; Group B3, high-dose butorphanol 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$; Compared with group S, [a]*P*<0.05.

incidence of complications, such as enteric fistula, pulmonary complications, and wound healing were observed among the four groups ($P > 0.05$), as shown in Table 3. The differences in time to first flatus, time to first ambulation, and length of hospital stay among the four groups were not statistically significant ($P > 0.05$). However, the time to ambulation was significantly shorter in group B3 than in group S ($P = 0.031$) (Table 3).

Comparison of Inflammatory Biomarkers Among the Four Groups

Within each group, patients exhibited a significant postoperative increase in PLR and NLR compared to preoperative values, whereas LMR showed a significant postoperative decrease. No statistically significant differences were observed among the four groups, either preoperatively or postoperatively (Figure 5).

Expression of CD3+, CD4+, CD8+, CD4+/CD8+, and CD3-CD16+CD56+

Intergroup comparisons at T0 (preoperative) and T5 showed no significant differences in immune markers among the four groups ($P > 0.05$), as illustrated in Figure 6. Group S exhibited a lower NK cell count ($P = 0.007$) and a significantly higher CD19+ B cell count ($P = 0.005$) at T5 than at T0. Group B1 showed an increase in CD19+ B cells ($P = 0.012$), CD4+ T cell levels ($P = 0.007$), and the CD4+/CD8+ ratio ($P = 0.014$) at T5 compared to T0, whereas CD8+ T cell count decreased ($P = 0.011$). No statistically significant differences were observed in T cell subsets and NK cell levels between groups B2 and B3 at T5 compared with those at T0 ($P > 0.05$) (Figure 6).

Discussion

In the present study, we evaluated the clinical effects of butorphanol for PCIA on pain relief and immune function in patients undergoing cytoreductive surgery for ovarian cancer. Our results suggest that butorphanol PCIA at a high dose of 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in patients undergoing intubated general anesthesia for ovarian surgery results in optimal analgesic

https://doi.org/10.2147/DDDT.S545111

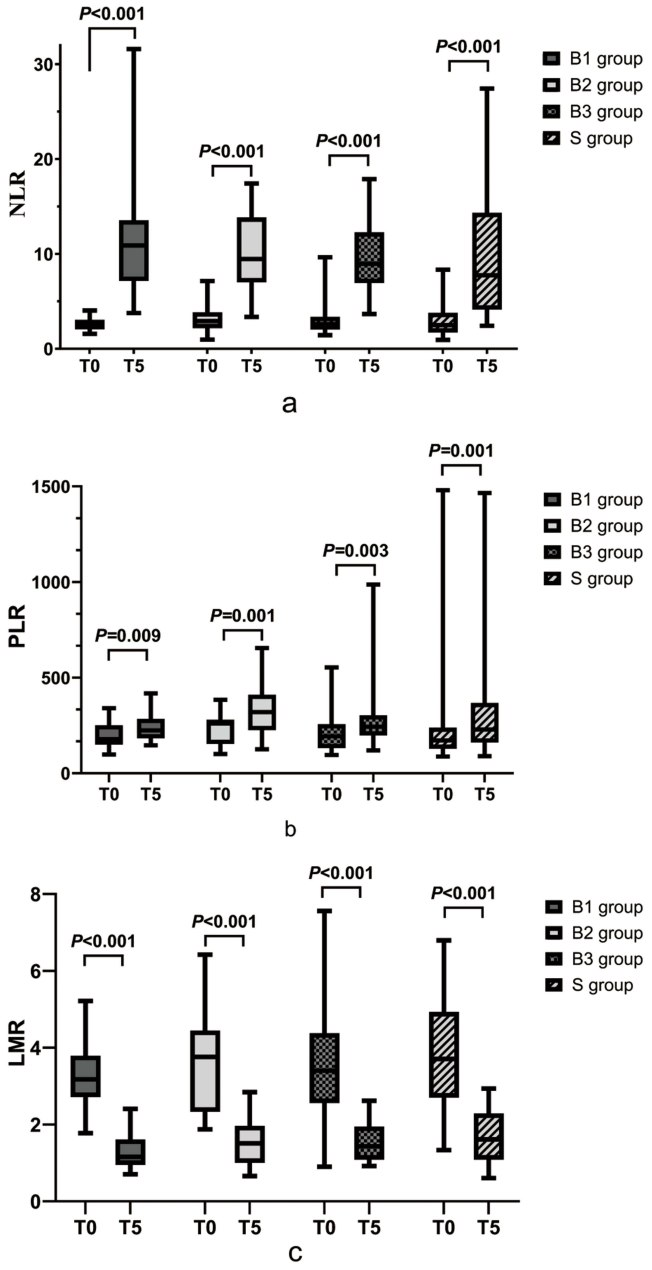

Figure 5 Box plots of NLR (**a**), PLR (**b**) and LMR (**c**) for the four groups of patients at different time points. T0: preoperative, T5: 48 hours postoperatively.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

outcomes without increasing the incidence of adverse events, and does not significantly impact patient immune markers, demonstrating its safe application for postoperative analgesia.

Several studies have indicated that[14] the postoperative analgesic efficacy of sufentanil is approximately 1000 times greater than that of morphine, whereas the analgesic potency of butorphanol is 5–8 times that of morphine. This indicates that 1 mg sufentanil may be equivalent to the analgesic effect of 200 mg butorphanol. A study investigating the postoperative analgesic effects of dexmedetomidine combined with sufentanil or butorphanol in patients undergoing laparoscopic gastrointestinal tumor resection has demonstrated that sufentanil (2.0 μg/kg) or butorphanol (0.15 mg/kg) combined with dexmedetomidine can be safely used for postoperative pain management in these patients.[15] In light of the increasing adverse reactions associated with higher doses, our study compared butorphanol dosages of 3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, 3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$, and 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ with sufentanil at 0.04 $\mu g \cdot kg^{-1} \cdot h^{-1}$.

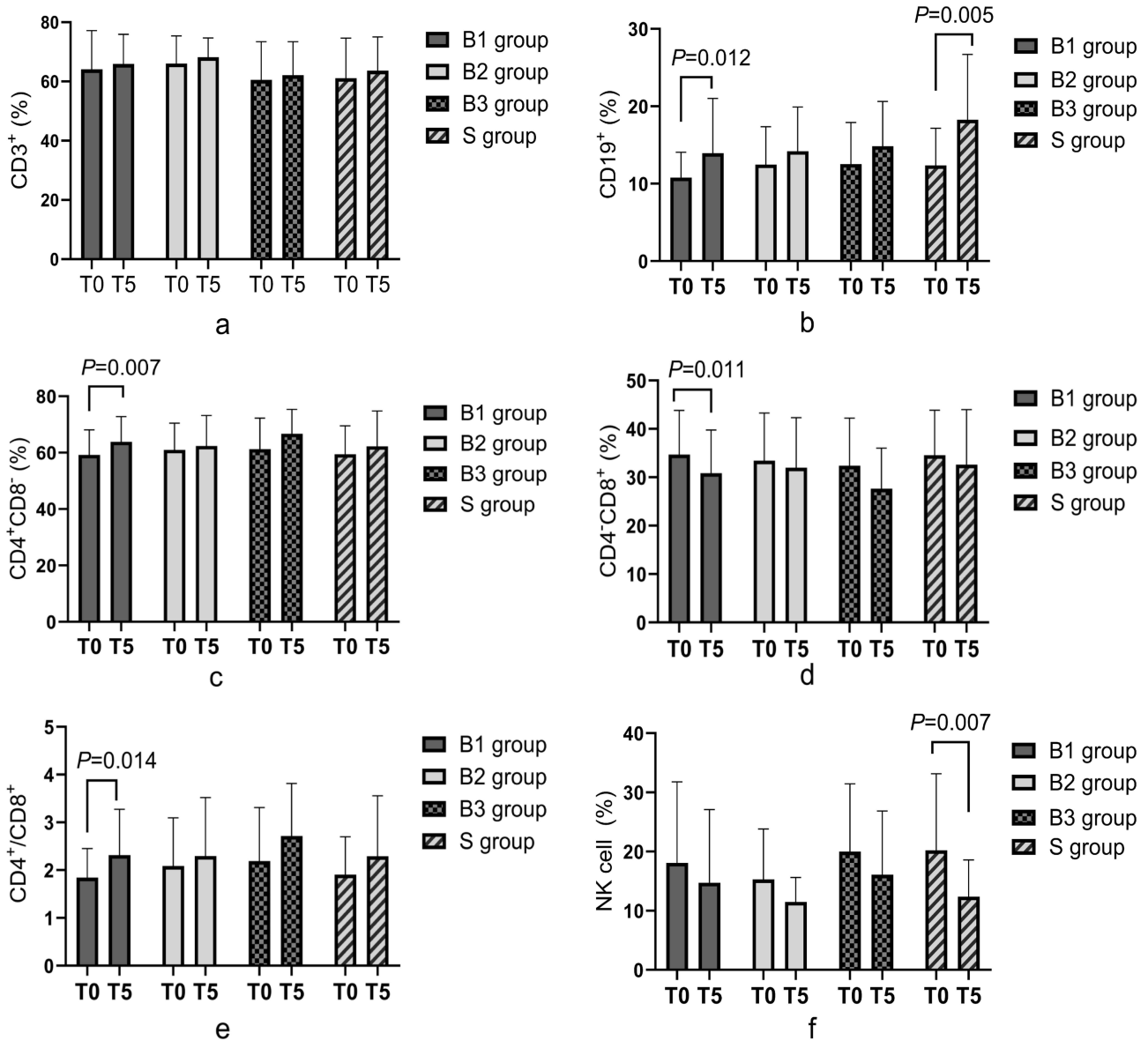

Figure 6 The level of lymphocyte subsets and NK cells in the four groups at different time points. The percentages of CD3+T cells (**a**), CD19+B cells (**b**), CD4+T cells (**c**), CD8+T cells (**d**) T lymphocytes, CD4+/CD8+ ratio (**e**), NK cells (**f**) in the four groups at different time points.

Butorphanol, with its unique mechanism of action and specific efficacy against visceral pain, can enhance analgesic effects of opioids while reducing the occurrence of common opioid-related adverse reactions.[7] The TAP block is recognized for its efficacy in managing somatic or incisional pain; however, it does not provide analgesia for visceral pain caused by intra-abdominal surgeries. Studies have shown that the analgesic duration of TAP block typically ranges from 12 to 24 h, depending on the type of injected medication and individual patient differences.[16,17] Our study showed that the VAS scores for four groups peaked at 12 h postoperative (mean ± standard deviation): B1 (3.27 ± 0.77), B2 (3.73 ± 0.83), B3 (3.00 ± 0.62), and B4 (2.73 ± 0.63). Some patients used PCIA or rescue analgesics when their VAS score exceeded 4, with a subsequent decline in VAS scores observed after the 12-h mark. We interpret this to be due to the gradual metabolism of local anesthetic agents from the TAP block at 12 h postoperatively, resulting in diminished analgesic effects from TAP and the need to incrementally increase the intensity of PCIA analgesia to provide supplementary pain relief. Consequently, the high (4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and medium (3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) dose butorphanol groups demonstrated superior analgesic benefits beyond the 12-h period. Statistically significant differences in VAS

https://doi.org/10.2147/DDDT.S545111

scores were observed at the 12-h and 24-h time points ($P < 0.001$). At 12 h postoperative, the VAS scores of groups B2 ($P = 0.007$ and $P < 0.001$) and B3 ($P = 0.005$ and $P < 0.001$) were significantly lower than that of group B1, indicating that high (4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and medium doses (3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) of butorphanol PCIA provided stronger analgesic efficacy compared to low dose butorphanol (3.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) PCIA. This suggests that low-dose butorphanol PCIA was insufficient for pain management. At 24 h postoperative, group B3 had lower VAS scores compared to group S ($P = 0.042$), thus indicating that postoperative analgesia with 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ butorphanol provides better pain relief for ovarian cancer patients. At the time points of 2, 6, 12, 24, and 48 h, no statistically significant differences in analgesic efficacy were observed between the medium-dose butorphanol (3.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and the sufentanil groups (0.04 $\mu g \cdot kg^{-1} \cdot h^{-1}$) ($P > 0.05$), suggesting similar analgesic efficacy and intensity between the two groups.

The area under the VAS-time curve ($AUC_{VAS\text{-}time}$) was calculated for 48 h postoperatively to compare cumulative pain intensity.[18] Compared to group S, the $AUC_{VAS\text{-}time}$ for group B1 increased ($P = 0.010$), while the $AUC_{VAS\text{-}time}$ for group B3 decreased ($P = 0.004$). Compared to group B1, the $AUC_{VAS\text{-}time}$ for groups B2 and B3 decreased ($P < 0.001$). These results suggest that PCIA with butorphanol or sufentanil combined with TAP can efficiently relieve postoperative pain in the short term. Importantly, the butorphanol dose in group B1 was inadequate to address postoperative pain in patients with ovarian cancer. Group B3 demonstrated superior analgesic efficacy compared to the S group. Additionally, the effective press counts on the analgesic pump and the need for rescue analgesia in group B3 were significantly lower than those in groups B1 and S. The present study revealed that butorphanol PCIA at a dose of 4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ resulted in optimal analgesic effects.

The results on adverse reaction incidence demonstrate no statistically significant differences across the groups. A meta-analysis indicated that butorphanol in PCA significantly reduces adverse events such as nausea, vomiting, pruritus, and dizziness.[19] Although six patients in group B3 experienced postoperative drowsiness (a common butorphanol-associated adverse reaction), this was not statistically significant compared to group S.[20] All six patients were mildly drowsy, easily awakened, and did not require special intervention. No instances of respiratory depression were observed in any group. Additionally, group B3 ambulated earlier than postoperatively than group S, likely due to better pain relief, conditions favoring early mobilization, and enhanced recovery. This finding may be influenced by the study's single-center design and modest sample size. Therefore, future research should plan to adopt a multicenter approach to increase sample size and explore the occurrence of adverse reactions among groups.

Various inflammatory markers have been widely used in cancer patients, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR).[21,22] NLR might be a reliable indicator of opioid-related immunosuppression after after thoracoscopic Surgery.[23] This study demonstrated a significant increase in postoperative PLR and NLR, along with a decrease in LMR, indicating that surgical stress induces inflammation and promotes a hypercoagulable state, predisposing patients to postoperative thrombotic events. Intergroup comparisons revealed no statistically significant differences in these hematological indices, at either preoperative or postoperative timepoints ($P > 0.05$), suggesting uniform inflammatory dynamics across all groups. Postoperative inflammatory marker changes were consistent across groups, indicating that butorphanol PCIA may exert similar effects to sufentanil in modulating these responses, with no observed intergroup differences.

NK cells are a major component of innate immunity, which can kill cells, promote the production of proinflammatory cytokines, and enhance the cytotoxicity and persistence of NK cells in vivo. NK cells are one of the targeted therapies for cancer and play an important role in tumor defense.[24] Group S exhibited a significant reduction in NK cell levels at 48 h postoperatively compared to preoperative levels ($P = 0.007$). It indicated that sufentanil suppresses NK cell activity in patients with ovarian cancer. This was consistent with previous studies.[25] In contrast, NK cell levels in the three butorphanol groups showed no significant differences at 48 h postoperatively compared to the preoperative levels ($P > 0.05$), suggesting that butorphanol does not adversely affect NK cell function in patients with ovarian cancer.

Opioids can not only directly affect immune cells, such as neutrophils, macrophages and NK cells, but also affect immune function through the hypothalamic pituitary-adrenal (HPA) axis. In addition, opioids can also regulate sympathetic nerve activity to affect immune function. In this study, group B1 showed significantly higher CD19+ B lymphocyte levels ($P = 0.012$), CD4+ T lymphocyte levels ($P = 0.007$), and CD4+/CD8+ ratio ($P = 0.014$) at 48 h postoperatively (T5) compared with preoperative (T0), along with a lower CD8+ T cell levels ($P = 0.011$). In contrast, no significant differences were

observed between groups B2 and B3. In the vast majority of physiological and pathological processes, CD4+ T cells serve as the initiators and regulators of immune responses, while CD8+ T cells act as the key effector executors—both are indispensable. In this study, patients in the low-dose group exhibited elevated CD4+ T lymphocyte levels and decreased CD8+ T lymphocyte levels postoperatively, suggesting that their immune function remained somewhat compromised. In contrast, no significant differences were observed in any parameters between groups B2 and B3. Moderate to high doses of butorphanol could partially alleviate surgery-induced stress and pain-related immunosuppression in ovarian cancer patients, with minimal impact on their postoperative immune status. Previous research has shown that μ-receptor agonists can inhibit T cell proliferation and macrophage activity, thereby affecting immune response.[26] Studies have shown that opioids enhance the proliferation and metastatic potential of tumor cells through μ-receptor expression while inhibiting immune cell function.[27] Research conducted by Gupta et al showed that morphine suppresses macrophage and T cell activity by activating the μ-opioid receptor, which helps to reduce the antitumor immune response.[28] Butorphanol enhances analgesia for visceral pain through κ-receptor activation while mitigating tumor-associated immunosuppression in recurrence and metastasis processes through reduction of μ-opioid receptor overexpression. In vivo experiments have shown that butorphanol provides protective effects against ischemia-reperfusion injury in rat myocardial tissue,[29] which enhances macrophage phagocytic activity and balances cytokine production. This indicates that butorphanol may enhance immune factor activity and bolster overall immune function, which is consistent with the results of this study.

In this study, the analgesic efficacy in group B1 was insufficient, allowing groups B2 and B3 to achieve better pain relief without adversely affecting immune function. Although butorphanol did not demonstrate significant immunoenhancement effects in this study, moderate to high doses partially alleviated surgery-induced immunosuppression. Importantly, higher doses of butorphanol may play a crucial role in preserving perioperative immune function and potentially improving clinical outcomes in ovarian cancer patients. Therefore, the use of butorphanol in Ovarian cancer patients needs to weigh the pros and cons. High-dose butorphanol (4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) PCIA may also be an option for postoperative analgesia in patients undergoing cytoreductive surgery for ovarian cancer, although it can not Up-regulation immune function.[30] This study has several limitations. First, its single-center design, despite an adequate calculated sample size, limits broader applicability due to the relatively small number of ovarian cancer patients included. Future studies should adopt a multicenter design to increase the sample size for a more comprehensive clinical assessment. Second, our study assessed outcomes only up to 48 h postoperatively; a longer follow-up period may be required to fully understand subsequent outcomes and prognosis. Third, while our assessment of immune cell functional status focuses on overall immune cell quantity and function, interpreting individual lymphocyte subsets may lack strong clinical guidance; therefore, future investigation should explore additional laboratory markers for comprehensive diagnostic evaluations. In addition, this study are applicable to the studied population of ovarian cancer patients aged 18–65 and that dose adjustments may be necessary for other groups, such as the elderly or pediatric patients, which should be determined by future dedicated studies.

Conclusion

High-dose butorphanol (4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) PCIA effectively relieves postoperative pain and reduces the time to early ambulation, without affecting immune indicators within 48 h postoperatively. Therefore, high-dose butorphanol (4.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) PCIA is recommended for postoperative analgesia in adults patients undergoing primary cytoreductive surgery for ovarian cancer.

Data Sharing Statement

The individual deidentified participant data will not be made available for public sharing. The data contain sensitive clinical information of participants. The informed consent documents signed by participants do not include provisions for public data sharing. Researchers may submit a methodologically sound proposal to the corresponding author (Wei Zhang, doctor_zw97079@163.com) for access to the deidentified data. Data requests will be reviewed by the study's steering committee. Approval will be granted subject to a signed data access agreement.

Funding

This work was supported by Rui Research Special Funds of Chen xiao-ping foundation for the development of science and technology of Hubei province.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Zhu B, Gu H, Mao Z, et al. Global burden of gynaecological cancers in 2022 and projections to 2050. *J Glob Health*. 2024;14. doi:10.7189/jogh.14.04155
3. Zhu CC, Zhu J, Qian LL, et al. Clinical characteristics and prognosis of ovarian clear cell carcinoma: a 10-year retrospective study. *Bmc Cancer*. 2021;21(1). doi:10.1186/s12885-021-08061-7
4. Armstrong DK, Alvarez RD, Backes FJ, et al. NCCN Guidelines® Insights: ovarian cancer, version 3.2022. *J National Compr Cancer Network*. 2022;20(9):972–980. doi:10.6004/jnccn.2022.0047
5. Nelson G, Altman AD, Nick A, et al. Guidelines for postoperative care in gynecologic/oncology surgery: enhanced Recovery After Surgery (ERAS®) Society recommendations - Part II. *Gynecologic Oncol*. 2016;140(2):323–332. doi:10.1016/j.ygyno.2015.12.019
6. Ji J, Lin W, Vrudhula A, et al. Molecular interaction between butorphanol and κ-opioid receptor. *Anesthesia Analg*. 2020;131(3):935–942. doi:10.1213/ANE.0000000000005017
7. Du J, Li J-W, Jin J, et al. Intraoperative and postoperative infusion of dexmedetomidine combined with intravenous butorphanol patient-controlled analgesia following total hysterectomy under laparoscopy. *Exp Ther Med*. 2018;16(5):4063–4069. doi:10.3892/etm.2018.6736
8. Wang B, Wang N, Zhao Z, et al. Effectiveness of Butorphanol in alleviating intra- and post-operative visceral pain following microwave ablation for hepatic tumor: a dual-central, randomized, controlled trial. *Sci Rep*. 2024;14(1).
9. Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? *Ann Surg Oncol*. 2003;10(8):972–992. doi:10.1245/aso.2003.02.007
10. Yang Z, Wang L, Hu Y, et al. Butorphanol protects PC12 cells against OGD/R-induced inflammation and apoptosis. *Mol Med Rep*. 2020;22(3):1969–1975. doi:10.3892/mmr.2020.11290
11. Wang B, Li Y, Shen Y, et al. Butorphanol inhibits the malignant biological behaviors of ovarian cancer cells via down-regulating the expression of TMEFF1. *Onco Targets Ther*. 2020;13:10973–10981. doi:10.2147/OTT.S244928
12. Borglum J, Maschmann C, Belhage B, et al. Ultrasound-guided bilateral dual transversus abdominis plane block: a new four-point approach. *Acta Anaesthesiol Scand*. 2011;55(6):658–663. doi:10.1111/j.1399-6576.2011.02430.x
13. Griffiths JD, Barron FA, Grant S, et al. Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block. *Br J Anaesth*. 2010;105(6):853–856. doi:10.1093/bja/aeq255
14. Van De Donk T, Ward S, Langford R, et al. Pharmacokinetics and pharmacodynamics of sublingual sufentanil for postoperative pain management. *Anaesthesia*. 2018;73(2):231–237. doi:10.1111/anae.14132
15. Zhang X-K, Chen Q-H, Wang W-X, et al. Evaluation of dexmedetomidine in combination with sufentanil or butorphanol for postoperative analgesia in patients undergoing laparoscopic resection of gastrointestinal tumors A quasi-experimental trial. *Medicine*. 2016;95(50):e5604. doi:10.1097/MD.0000000000005604
16. Mitchell KD, Smith CT, Mechling C, et al. A review of peripheral nerve blocks for cesarean delivery analgesia. *Reg Anesth Pain Med*. 2020;45(1):52–62. doi:10.1136/rapm-2019-100752
17. Tsai H-C, Yoshida T, Chuang T-Y, et al. Transversus abdominis plane block: an updated review of anatomy and techniques. *Biomed Res Int*. 2017;2017:1–12. doi:10.1155/2017/8284363
18. Abdallah FW, Cil T, Maclean D, et al. Too deep or not too deep?: a propensity-matched comparison of the analgesic effects of a superficial versus deep serratus fascial plane block for ambulatory breast cancer surgery. *Reg Anesth Pain Med*. 2018;43(5):480–487. doi:10.1097/AAP.0000000000000768
19. Zhu Z, Zhang W. Efficacy and safety of butorphanol use in patient-controlled analgesia: a meta-analysis. *Evid Based Complement Alternat Med*. 2021;2021:1. doi:10.1155/2021/9854850
20. Zhang L, Shu R, Zhao Q, et al. Preoperative butorphanol and flurbiprofen axetil therapy attenuates remifentanil-induced hyperalgesia after laparoscopic gynaecological surgery: a randomized double-blind controlled trial. *Br J Anaesth*. 2016;117(4):504–511. doi:10.1093/bja/aew248
21. Hayama T, Ozawa T, Asako K, et al. Impact of colon cancer location on the prognostic significance of nutritional indexes and inflammatory markers. *In Vivo*. 2021;35(2):1261–1269. doi:10.21873/invivo.12377
22. Dolan RD, Mcsorley ST, Park JH, et al. The prognostic value of systemic inflammation in patients undergoing surgery for colon cancer: comparison of composite ratios and cumulative scores. *Br J Cancer*. 2018;119(1):40–51. doi:10.1038/s41416-018-0095-9
23. Chen Q, Liang J, Liang L, et al. Neutrophil-to-lymphocyte ratio as an indicator of opioid-induced immunosuppression after thoracoscopic surgery: a randomized controlled trial. *J Pain Res*. 2022;15:1855–1862. doi:10.2147/JPR.S371022
24. Myers JA, Miller JS. Exploring the NK cell platform for cancer immunotherapy. *Nat Rev Clin Oncol*. 2021;18(2):85–100. doi:10.1038/s41571-020-0426-7
25. Shavit Y, Ben-Eliyahu S, Zeidel A, et al. Effects of fentanyl on natural killer cell activity and on resistance to tumor metastasis in rats - Dose and timing study. *Neuroimmunomodulation*. 2004;11(4):255–260. doi:10.1159/000078444
26. Liu K, Tang L, Wang J, et al. Effect of combined general/epidural anesthesia on postoperative NK cell activity and cytokine response in gastric cancer patients undergoing radical resection. *Hepato-Gastroenterology*. 2014;61(132):1142–1147.

27. Lennon FE, Mirzapoiazova T, Mambetsariev B, et al. The Mu opioid receptor promotes opioid and growth factor-induced proliferation, migration and Epithelial Mesenchymal Transition (EMT) in human lung cancer. *PLoS One*. 2014;9(3):e91577. doi:10.1371/journal.pone.0091577
28. Gupta K, Kshirsagar S, Chang LM, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. *Cancer Res*. 2002;62(15):4491–4498.
29. Wu Y, Wan J, Zhen W-Z, et al. The effect of butorphanol postconditioning on myocardial ischaemia reperfusion injury in rats. *Interact Cardiovasc Thorac Surg*. 2014;18(3):308–312. doi:10.1093/icvts/ivt516
30. Rossaint J, Zarbock A. Anesthesia-induced immune modulation. *Curr Opin Anaesthesiol*. 2019;32(6):799–805. doi:10.1097/ACO.0000000000000790