Original Article

Effects of perioperative oxycodone as the sole opioid on immunity within a multi-modal analgesia framework in patients undergoing cervical cancer surgery: A randomised controlled trial

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ABSTRACT

Background and Aims: Current views on oxycodone's effects on immunity are inconsistent. Our objective was to compare the effects of perioperative oxycodone as the sole opioid in a multi-modal analgesia regimen with conventional opioid regimens on immunity in cervical cancer. **Methods:** In this randomised controlled trial (RCT), patients scheduled for laparoscopic radical hysterectomy for cervical cancer were randomised to receive either oxycodone (Group O) or conventional opioid regimens (Group C). The primary outcome was the $CD4^+/CD8^+$ ratios postoperatively at 24 and 48 h. Student's *t*-test was used for normally distributed variables, the non-parametric Wilcoxon test for non-normally distributed variables, and Chi-square/Fisher's exact test for qualitative variables, with differences significant set at $P < 0.05$. **Results:** We included 56 patients in the final analysis. The postoperative $CD4^+/CD8^+$ ratios were comparable between groups. However, the mean arterial pressures (MAPs) at extubation and 5 minutes thereafter were lower in Group O than in Group C (both $P < 0.001$), as were the heart rates (HRs) ($P = 0.001$ and 0.018, respectively). Within 24 h postoperatively, the visual analogue scale (VAS) scores for resting and movement-evoked pain were lower in Group O than in Group C (all $P < 0.001$), and the same was observed at 48 h postoperatively (both $P = 0.002$), as was the incidence of catheter-related bladder discomfort ($P = 0.001$). The VASs for postoperative analgesia satisfaction were higher in Group O than in Group C ($P = 0.006$). **Conclusion:** In laparoscopic surgery for cervical cancer, perioperative oxycodone as the sole opioid within a multi-modal analgesia framework does not yield anticipated benefits in immunopreservation compared to conventional opioid regimens but improves postoperative pain management and haemodynamic stability.

Keywords: Analgesia, analgesics, cancer, haemodynamics, immunity, immunomodulation, immunoprotective, immunosuppression, opioid, oxycodone, uterine cervical neoplasms

INTRODUCTION

Cervical cancer profoundly impacts global women's health, with incidence rates ranging from 9.80 to 12.39 per 100,000 individuals.[1] Laparoscopic radical hysterectomy, though a key minimally invasive treatment, has been associated with shorter overall and disease-free survival than open surgery, potentially due to residual cancer cells.[2] This raises concerns about perioperative immunosuppression driven by

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surgical stress and anaesthetic-analgesic techniques,[3] potentially affecting the short- and long-term outcomes and survival prospects of these patients.

Opioids are crucial in onco-anaesthesia, particularly for perioperative pain management.[4] While fentanyl derivatives and morphine are known for their immunosuppressive effects, studies have indicated that oxycodone may either not impact or only minimally affect immunity, especially in postoperative analgesia.[5] Wan *et al*.[6] reported that oxycodone, combined with flurbiprofen axetil for patient-controlled intravenous analgesia (PCIA) after colorectal cancer surgery, improved immunological markers, including increased T helper cells ($CD4^+$) counts and $CD4^+$/cytotoxic T lymphocytes ($CD8^+$) ratios while decreasing levels of tumour necrosis factor (TNF)-α and interleukin (IL)-6 compared to sufentanil combinations. These findings imply that oxycodone may help mitigate the perioperative immunosuppression. Given the higher intraoperative opioid demand, utilising oxycodone as the sole opioid throughout the perioperative period in laparoscopic surgery for cervical cancer may offer immunoprotective benefits. However, research is needed on this hypothesis.

Oxycodone, unlike full agonists of the μ-opioid receptor (MOR) such as fentanyl derivatives and morphine, targets both MOR and κ-opioid receptor (KOR), with a strong affinity for KOR, making it potentially more effective for managing visceral pain with fewer side effects, particularly in intricate laparoscopic surgeries. Recent studies have corroborated its efficacy in anaesthesia induction and as the sole perioperative opioid, showing robust analgesic effectiveness and a favourable safety profile during intra and postoperative phases.[7,8] Consequently, we designed this randomised controlled trial (RCT) to compare the effects of perioperative oxycodone versus conventional opioids on immunity and recovery in laparoscopic surgery for cervical cancer. The primary objective was to assess the $CD4^+/CD8^+$ ratios at 24 and 48 h post surgery. Secondary objectives included evaluating the overall immune response, pain management, and recovery metrics. We hypothesised that patients receiving oxycodone as the sole opioid would have significantly higher $CD4^+/CD8^+$ ratios at these time points compared to those receiving conventional opioids and that the oxycodone group would achieve better pain management, lower complication rates, and higher patient satisfaction.

METHODS

This assessor-blinded, single-centre RCT was conducted from February to August 2023. It was approved by the Institutional Ethics Committee (vide approval number 2022–138, dated 7 October 2022) and registered at http://www.chictr.org.cn (ChiCTR2300068377, dated 16 February 2023) before patient enrolment. Manuscript preparation adhered to Consolidated Standards of Reporting Trials (CONSORT) guidelines, and written informed consent was obtained from all participants for their involvement in the study and the use of their data for research and educational purposes. The study was carried out using the principles of the Declaration of Helsinki (2013) and Good Clinical Practice guidelines.

Patients diagnosed with cervical cancer and scheduled for laparoscopic radical hysterectomy with bilateral pelvic lymph node dissection under general anaesthesia were assessed for eligibility. Of 105 patients initially assessed, 58 were recruited and randomised. Inclusion criteria were: age 18–64 years; American Society of Anesthesiologists (ASA) physical status ≤ III; and the ability to understand the study's rationale. Exclusion criteria were: body mass index (BMI) >30 kg/m^2 or ≤18.4 kg/m^2; cognitive or language impairments; severe systemic or organ disorders such as severe hypertension (systolic blood pressure [SBP] ≥180 mmHg or diastolic blood pressure [DBP] ≥110 mmHg), severe liver, kidney or lung dysfunction, preoperative left ventricular ejection fraction <30%, myasthenia gravis, thyroid disorders, or gastroduodenal ulcer, etc.; allergies to study drugs; history of alcohol abuse or drug use or addiction or long-term use of opioids or other analgesic drugs (≥3 months); long-term use of anti-depressants; prior chemoradiotherapy or conditions affecting immunity; or refusal to participate. Enroled patients were withdrawn from the study if they switched to open surgery, experienced severe perioperative complications, failed to follow up, or had specimen haemolysis.

Block randomisation was performed using the block and package of R software version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) with a fixed block size of 6; allocation concealment was ensured using sequentially numbered, sealed, and opaque envelopes. Participants were randomly assigned to either the oxycodone group (Group O) or the control group (Group C) in a 1:1 ratio, both receiving total intravenous anaesthesia. The equivalent

dose converting between sufentanil and oxycodone was 0.001.[9] Group O received intravenous (IV) 0.3 mg/kg oxycodone (Mundipharma [China] Pharmaceutical Co., Ltd., Beijing, China) at induction,[10] with a bolus dose of 0.03 mg/kg as needed for intraoperative analgesia.[7] Group C received 0.3 μg/kg sufentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) IV at induction, followed by a remifentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) infusion at 0.1–0.3 μg/kg/min. Adjunctive anaesthesia medications were consistent between groups. The principal anaesthesiologist, who was unblinded, opened these envelopes and prepared the medications. Outcome assessors, data collectors, and statisticians were blinded to group allocations and were not involved in the anaesthesia or surgical procedures, nor did they discuss treatment details with participants.

No preoperative medication was given. In the operating room, standard monitoring (non-invasive blood pressure, electrocardiogram, pulse oximetry) and continuous bispectral index (BIS) monitoring were implemented. Central venous access was established with an initial 500-mL infusion of Ringer's lactate solution, followed by a continuous infusion at 10 mL/kg/h. Radial artery cannulation for continuous arterial blood pressure monitoring was performed under local anaesthesia. During induction, patients received IV oxycodone (0.3 mg/kg) or sufentanil (0.3 μg/kg), depending on their group, along with propofol (2–2.5 mg/kg) and rocuronium (0.6 mg/kg). Post intubation, mechanical ventilation was set with a respiratory rate (RR) of 10–15 breaths per minute (bpm), tidal volume of 6–8 mL/kg, inspired oxygen fraction of 60%, and an end-tidal carbon dioxide ($EtCO_2$) pressure of 35–45 mmHg. Anaesthesia depth was regulated by continuous propofol infusion to maintain BIS between 40 and 50. Analgesia was managed with IV oxycodone (0.03 mg/kg) as needed or continuous remifentanil infusion (0.1–0.3 μg/kg/min), with heart rate (HR) and blood pressure (BP) fluctuations kept within 20% of baseline values. IV rocuronium (0.15 mg/kg) was administered intermittently for muscle relaxation. Postoperative nausea and vomiting (PONV) was prevented with IV palonosetron (0.25 mg) with dexamethasone (5 mg). The multi-modal analgesia regimen included IV parecoxib (40 mg). At surgery completion, bilateral transversus abdominis plane (TAP) blocks were performed under ultrasound guidance with 0.375% ropivacaine (40 mL). A patient-controlled IV analgesia (PCIA) device was set up for 48 h post surgery containing oxycodone (0.5 mg/mL) or sufentanil (0.5 μg/mL) diluted to 100 mL, with a background infusion rate of 1 mL/h, a PCA bolus of 4 mL, a 15-minute lockout, and a maximum dose of 20 mL/h. Residual neuromuscular blockade was reversed with IV neostigmine and atropine as needed. Patients were transferred to the post-anaesthetic care unit (PACU). Trachea was extubated once patients were responsive and met the extubation criteria. A staff anaesthetist, blinded to group assignment, was in charge of pain management. For visual analogue scale (VAS) scores for pain >30 mm, an immediate dose of either IV oxycodone (2 mg) or sufentanil (2 μg) (1 mL, prepared by a non-participating nurse using identically packaged syringes) was administered as needed, with possible repeat dosing every 5 minutes until the VAS score was ≤30 mm. Discharge from the PACU was based on the Steward score. If, PCIA fails to relieve pain in the ward, the surgeon managed it according to their usual practice.

In the PACU, hypotension, hypertension, bradycardia, etc., were managed according to standard protocols. For opioid-induced respiratory depression [respiratory rate (RR) ≤8 breaths/min, pulse oxygen saturation (SpO_2) <90% on room air, or shallow breathing], opioids were discontinued, the patient was stimulated, artificial airway or ventilation was considered, and IV naloxone (0.1–0.2 mg) was administered every 2–3 minutes as needed until adequate respiration (RR >8 breaths/min or SpO_2 > 90% on room air) and consciousness were achieved while minimising discomfort. PONV were treated with IV metoclopramide (10 mg) alongside patient comfort measures. Pruritus was treated with low-dose IV naloxone.

Blood samples (8 mL) were collected at four time-points, namely before anaesthesia induction, at the end of the surgery, and 24 and 48 h postoperatively, divided into two tubes. In one tube, blood was transferred to a 15-mL centrifuge tube, diluted equally with HBSS buffer, and mixed with Ficoll (Ficoll to diluted blood volume ratio = 3:4) to isolate peripheral blood mononuclear cells (PBMCs) using density gradient centrifugation. PBMCs were then adjusted to 10^6 cells/100 μL, incubated with flow cytometry antibodies for 40 minutes, and analysed to determine T lymphocyte subsets, natural killer (NK) cell levels, and $CD4^+$ and $CD8^+$ cell levels, calculating the $CD4^+/CD8^+$ ratio. For the other tube, blood was centrifuged at 3000 rpm for 15 minutes, and the supernatant serum was stored at −80°C for later measurement of IL-6 and IL-10 concentrations using enzyme-linked immunosorbent assay (ELISA).

All collections and analyses were performed by researchers blinded to group assignments.

The primary outcome was the $CD4^+/CD8^+$ ratios at 24 and 48 hours post surgery. Secondary outcomes included NK cell counts, concentrations of IL-6 and IL-10, changes in haemodynamic indexes and SpO_2, time to consciousness recovery (from anaesthetic discontinuation to eye-opening upon verbal stimulus, time to extubation (from surgery completion to tracheal tube removal), sedation scores, pain management outcomes, and recovery quality. HR, mean arterial pressure (MAP), and SpO_2 were recorded upon entering the operating room (baseline), at extubation, 5 and 15 minutes after extubation, and 30 and 60 minutes after surgery. Sedation was evaluated using the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale[11] immediately post awakening and 30 minutes, 1, 4, 24, and 48 h after surgery. The comprehensive pain evaluation encompassed resting and movement-evoked pain from the surgical wound, assessed with VAS scores (0 mm = no pain, 100 mm = unbearable pain) and catheter-related bladder discomfort (CRBD). Resting pain and CRBD were evaluated alongside sedation assessments, with movement-evoked pain assessed at 4, 24, and 48 h post surgery. At 48 h after surgery, patients rated their satisfaction concerning pain management by using a 100-mm VAS scale (the longer the marked length, the higher the satisfaction). Unaware of the grouping, an anaesthetic nurse used a new, unmarked scale for each evaluation. The patients were instructed to use these two types of VAS before beginning the study. Recovery quality was assessed using the 40-item Quality of Recovery questionnaire (QoR-40; maximum score: 200),[12] with scores documented pre-surgery (as baseline) and at 24 and 48 h after surgery. Additionally, the time of the first postoperative flatus and first movement were recorded, along with the incidence of complications such as hypoxemia, PONV, pruritus, and excessive sedation delirium, within 48 h after the operation.

The sample size calculation was performed using PASS 15.0 statistical software (NCSS, LLC., Kaysville, UT, USA). According to the findings by Wan *et al*.,[6] the mean preoperative $CD4^+/CD8^+$ ratio in the oxycodone group was 1.8 (standard deviation (SD): 0.2), which we consider to have statistical significance with a difference of 0.2. With a two-sided α-level of 0.05, a statistical power of 90%, and allowing for a loss to follow-up of 20%, at least 28 participants in each group were calculated.

Statistical analysis was performed using Statistical Package for the Social Sciences SPSS® 26.0 statistical software (International Business Machines Corporation (IBM Corp), Armonk, NY, USA. After a Kolmogorov–Smirnov test assessing the normality of data distribution, data were presented as mean (SD) for normally distributed variables, including $CD4^+$ and $CD8^+$ percentages, $CD4^+/CD8^+$ ratio, MAP, HR, SpO_2, and the times to consciousness recovery, extubation, and leaving bed. Non-normally distributed variables, such as NK cell percentage, IL-6 and IL-10 concentrations, pain VAS, rescue analgesia consumption, total PCIA consumption, analgesia satisfaction VAS, sedation score, time to first flatus, QoR-40, and length of stay, were presented as median (interquartile range (IQR)). Quantitative variables were compared between groups using unpaired Student's *t*-test when data were normally distributed or using the non-parametric Wilcoxon test when data were not normally distributed. Qualitative variables were presented as numbers (%). The Chi-square test or Fisher's exact probability methods were used for between-group comparisons. We considered differences significant at $P < 0.05$.

RESULTS

A total of 56 patients (28 in each group) received either perioperative oxycodone as the sole opioid or conventional opioid regimens and finished the final analysis [Figure 1]. There were no significant differences in the patients' demographic and intraoperative data between the groups [Table 1].

The mean $CD4^+/CD8^+$ ratio at 24 h post surgery was 1.96 (SD: 0.35) in Group O and 2.03 (SD: 0.48) in Group C ($P = 0.545$), and the mean difference between the groups was −0.07 (95% confidence interval (CI): −0.30, 0.16). The ratios at 48 h post surgery were 1.85 (SD: 0.42) in Group O and 1.98 (SD: 0.73) in Group C, and the mean difference between the groups was −0.13 (95% CI: −0.45, 0.19) ($P = 0.423$). No significant differences in the ratios were observed between the groups throughout the study period. However, a slight decrease in the $CD4^+/CD8^+$ ratios was observed at the end of surgery, followed by a recovery trend postoperatively in both groups [Table 2]. No differences in NK cell percentages or concentrations of IL-6 and IL-10 were found between the groups at each time point. However, a notable decrease in NK cell percentages and marked increases in IL-6 and IL-10 were observed in both groups at 24 and 48 h post surgery [Table 2].

Table 1: Demographic and operative data

Variables	Group O (*n*=28)	Group C (*n*=28)	*P*
Age (years)	49.1 (8.2)	48.5 (7.2)	0.782
Height (cm)	159.8 (4.9)	160.3 (4.7)	0.677
Weight (kg)	59.3 (6.4)	60.8 (5.7)	0.359
Body mass index (kg/m^2)	23.2 (2.2)	23.7 (2.4)	0.434
White blood cell count (10^9/L)	6.22 (1.54)	6.44 (1.82)	0.628
Neutrophil count (10^9/L)	4.02 (1.53)	4.10 (1.39)	0.829
Lymphocyte count (10^9/L)	1.69 (0.55)	1.79 (0.47)	0.490
Surgery duration (min)	181.3 (39.1)	178.7 (49.5)	0.825
Intraoperative total IV fluid used (ml)	2000 (1630–2400)	1700 (1530–2080)	0.068
Intraoperative blood loss (mL)	200 (100–300)	200 (150–200)	0.820
Intraoperative urine volume (mL)	280 (200–300)	200 (110–300)	0.655

Data expressed as mean (standard deviation) or median (interquartile range); O=Oxycodone group, C=Control, IV=Intravenous, *n*=Number of patients

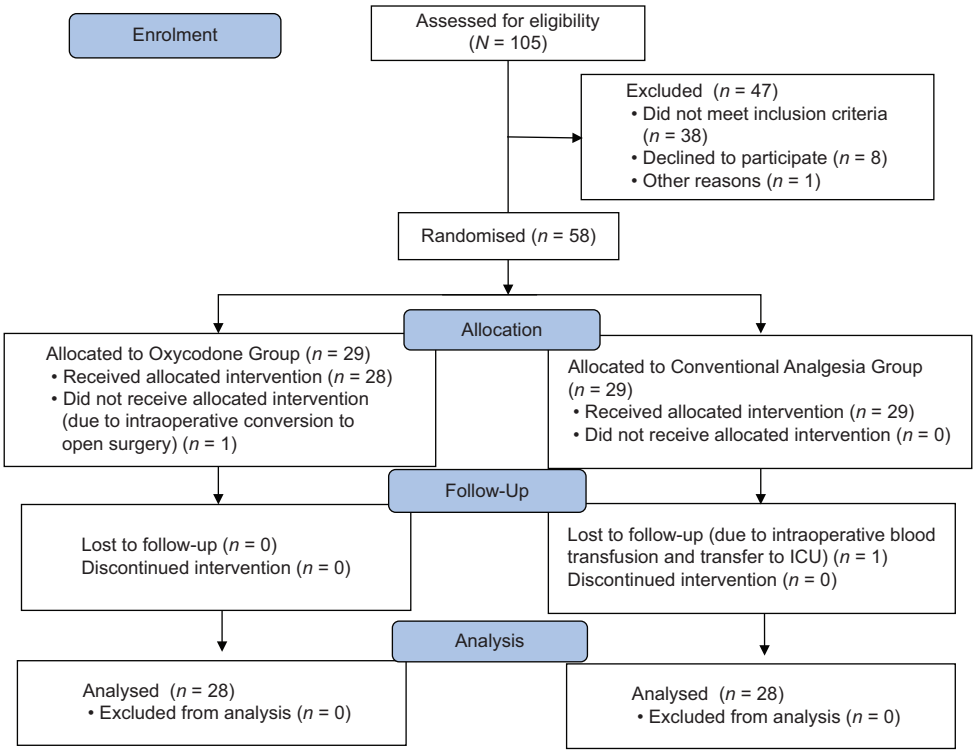

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram

Stable haemodynamic parameters were observed in both groups throughout the surgery. Compared with Group C, the MAPs in Group O were lower within the initial hour postoperatively ($P < 0.001$), all within the normal range. The HRs at extubation and 5 minutes thereafter were significantly lower in Group O than in Group C ($P = 0.001$ and 0.018, respectively) [Table 3].

Both the VAS scores for resting pain and rescue analgesia consumption within the first postoperative hour were notably lower in Group O than in Group C ($P < 0.001$ and $P < 0.001$, respectively). The incidence of CRBD within the first hour postoperatively was significantly reduced in Group O ($P < 0.001$). Over 4, 24, and 48 h postoperatively, the VAS scores for resting and movement-evoked pain, as well as the incidence of CRBD at 4 and 48 h postoperatively, were lower in Group O than in Group C ($P < 0.05$), with fewer PCIA pressing times recorded ($P = 0.045$). The incidence of CRBD within 48 h after surgery was substantially lower in Group O than in Group C ($P = 0.001$). In addition, VAS scores for postoperative analgesia satisfaction were higher in Group O than in Group C ($P = 0.006$) [Table 4].

No significant differences were observed in sedation scores between groups at any time point. However, the times to consciousness recovery and extubation

Table 2: IL-6, IL-10, $CD4^+$, $CD8^+$, and NK cell

Variables	Group O (*n*=28)	Group C (*n*=28)	Mean Difference (95% CI)	*P*
$CD4^+$ (%)				
Baseline	33.72 (5.76)	34.96 (5.22)	−1.25 (−4.19, 1.70)	0.400
At the end of surgery	25.20 (8.13)	26.53 (9.53)	−1.34 (−6.08, 3.41)	0.575
PO 24 h	39.28 (5.45)	38.73 (7.92)	0.55 (−3.10, 4.20)	0.763
PO 48 h	38.09 (5.94)	36.99 (11.16)	1.10 (−3.72, 5.93)	0.647
$CD8^+$ (%)				
Baseline	20.57 (4.57)	20.67 (4.56)	−0.10 (−2.54, 2.35)	0.935
At the end of surgery	18.67 (5.46)	17.69 (5.13)	0.98 (−1.86, 3.82)	0.493
PO 24 h	20.53 (4.09)	19.79 (5.09)	0.74 (−1.73, 3.22)	0.550
PO 48 h	21.16 (3.87)	19.41 (4.70)	1.75 (−0.56, 4.06)	0.135
$CD4^+/CD8^+$				
Baseline	1.69 (0.34)	1.74 (0.30)	−0.05 (−0.22, 0.13)	0.591
At the end of surgery	1.42 (0.47)	1.54 (0.51)	−0.12 (−0.38, 0.15)	0.374
PO 24 h	1.96 (0.35)	2.03 (0.48)	−0.07 (−0.30, 0.16)	0.545
PO 48 h	1.85 (0.42)	1.98 (0.73)	−0.13 (−0.45, 0.19)	0.423
NK cell (%)				
Baseline	13.14 (10.77–15.73)	13.74 (11.56–16.17)	–	0.451
At the end of surgery	13.36 (10.70–20.09)	19.42 (7.65–35.59)	–	0.082
PO 24 h	5.82 (4.19–10.22)	6.57 (4.07–10.16)	–	0.857
PO 48 h	8.26 (5.07–11.92)	7.20 (4.92–13.21)	–	0.857
IL-6 (pg/mL)				
Baseline	5.06 (3.56–7.61)	5.93 (3.96–8.78)	–	0.967
At the end of surgery	5.75 (2.39–11.86)	6.68 (3.44–9.90)	–	0.502
PO 24 h	12.20 (7.59–19.23)	11.17 (8.32–14.89)	–	0.646
PO 48 h	11.26 (5.88–15.56)	13.31 (10.28–16.47)	–	0.156
IL-10 (pg/mL)				
Baseline	442.75 (276.76–638.74)	410.40 (279.80–561.21)	–	0.954
At the end of surgery	525.98 (193.16–826.08)	544.25 (286.38–723.72)	–	0.812
PO 24 h	804.47 (608.21–1405.77)	854.90 (638.26–1335.54)	–	0.948
PO 48 h	812.24 (417.34–1272.11)	955.31 (688.63–1461.53)	–	0.232

Data expressed as mean (standard deviation) or median (interquartile range); O=Oxycodone, C=Control, PO=Postoperative time-point, $CD4^+$=T helper cells, $CD8^+$=Cytotoxic T lymphocytes, NK=Natural killer, *n*=Number of patients, CI=Confidence interval

Table 3: Postoperative haemodynamic indexes and SpO_2

Variables	Group O (*n*=28)	Group C (*n*=28)	Mean Difference (95% CI)	*P*
MAP (mmHg)				
Baseline	92.6 (7.2)	92.3 (9.6)	0.29 (−4.26, 4.83)	0.900
At extubation	83.5 (7.5)	96.9 (10.5)	−13.46 (−18.36, −8.57)	<0.001
5 min after extubation	80.9 (8.0)	93.8 (11.5)	−12.89 (−18.22, −7.57)	<0.001
15 min after extubation	81.8 (7.2)	93.7 (12.0)	−11.86 (−17.18, −6.53)	<0.001
PO 1/2 h post surgery	82.7 (8.2)	93.3 (11.7)	−10.61 (−16.03, −5.18)	<0.001
PO 1 h post surgery	82.9 (7.3)	94.5 (12.0)	−11.61 (−16.94, −6.28)	<0.001
HR (bpm)				
Baseline	75.5 (9.3)	72.0 (11.6)	3.46 (−2.18, 9.10)	0.223
At extubation	72.6 (8.8)	83.3 (13.8)	−10.68 (−16.92, −4.44)	0.001
5 min after extubation	72.7 (8.8)	80.1 (13.3)	−7.36 (−13.42, −1.29)	0.018
15 min after extubation	74.8 (11.6)	79.0 (14.5)	−4.21 (−11.23, 2.80)	0.234
PO 1/2 h	75.0 (11.5)	76.0 (14.1)	−1.04 (−7.93, 5.85)	0.764
PO 1 h	75.0 (11.6)	74.0 (12.1)	0.93 (−5.43, 7.28)	0.771
SpO_2 (%)				
Baseline	98.5 (1.5)	98.4 (1.7)	0.14 (−0.71, 1.00)	0.739
At extubation	99.9 (0.6)	99.6 (1.0)	0.25 (−0.17, 0.67)	0.239
5 min after extubation	99.5 (1.1)	99.6 (0.9)	−0.11 (−0.64, 0.43)	0.689
15 min after extubation	99.5 (1.2)	99.8 (0.4)	−0.36 (−0.84, 0.13)	0.144
PO 1/2 h	99.5 (1.1)	99.8 (0.5)	−0.25 (−0.70, 0.20)	0.270
PO 1 h	99.8 (0.6)	99.9 (0.4)	−0.18 (−0.46, 0.11)	0.213

Data expressed as mean (standard deviation); O=Oxycodone, C=Control, PO=Postoperative time point, MAP=Mean arterial pressure, HR=Heart rate, SpO_2=Pulse oxygen saturation, *n*=Number of patients, CI=Confidence interval

were significantly longer in Group O than in Group C ($P < 0.001$ and < 0.001, respectively). No differences were observed between the times of flatus and mobilisation or the incidence of PONV between groups, with no reports of dizziness, pruritus, or hypoxemia in either group [Table 5].

DISCUSSION

This investigation demonstrated that in laparoscopic cervical cancer surgery, there were no significant differences in the $CD4^+/CD8^+$ ratios, NK cell counts, or IL-6 and IL-10 levels postoperatively between groups receiving oxycodone alone or

Table 4: Postoperative parameters related to pain

Variables	Group O (*n*=28)	Group C (*n*=28)	*P*
Resting pain VAS (mm)			
At awakening	0.0 (0.0–0.0)	48.5 (31.3–72.8)	<0.001
PO 1/2 h	0.0 (0.0–10.0)	27.5 (12.3–38.3)	<0.001
PO 1 h	1.5 (0.0–10.0)	14.5 (5.0–28.8)	<0.001
PO 4 h	9.0 (0.0–10.0)	20.0 (10.0–30.0)	<0.001
PO 24 h	6.0 (0.0–10.0)	18.0 (10.0–23.8)	<0.001
PO 48 h	0.0 (0.0–7.0)	10.0 (0.0–13.3)	0.002
Movement-evoked pain VAS (mm)			
PO 4 h	10.0 (0.0–20.0)	30.0 (20.0–30.0)	<0.001
PO 24 h	10.5 (10.0–20.0)	30.0 (20.0–56.5)	<0.001
PO 48 h	10.0 (4.8–20.0)	20.0 (10.3–29.5)	0.002
Incidence of CRBD	3/28 (10.7)	15/28 (53.6)	0.001
At awakening	0/28 (0)	11/28 (39.3)	<0.001
PO 1/2 h	0/28 (0)	11/28 (39.3)	<0.001
PO 1 h	0/28 (0)	10/28 (35.7)	<0.001
PO 4 h	2/28 (7.1)	12/28 (42.9)	0.002
PO 24 h	3/28 (10.7)	9/28 (32.1)	0.051
PO 48 h	3/28 (10.7)	10/28 (35.7)	0.027
Rescue analgesia consumption PO 1 h (mg/μg)	0 (0–0)	5 (2–8)	<0.001
PCIA pressing times	1.0 (0.0–3.0)	2.5 (1.0–5.0)	0.045
Total postoperative analgesia consumption in PCIA (mg or μg)	29.0 (24.0–31.5)	29.0 (26.0–34.0)	0.358
Extra analgesia requirement in the ward	0/28 (0.0)	1/28 (3.6)	>0.999
Postoperative analgesia satisfaction VAS (mm)	95.0 (90.0–99.8)	90.0 (82.0–92.3)	0.006

Data expressed as mean (standard deviation), median (interquartile range) or number (%); O=Oxycodone, C=Control group, VAS=Visual analogue scale, PO=Postoperative time point, CRBD=Catheter-related bladder discomfort, PCIA=Patient-controlled intravenous analgesia, *n*=Number of patients

Table 5: Postoperative parameters related to recovery and adverse events

Variables	Group O (*n*=28)	Group C (*n*=28)	Mean Difference (95% CI)	*P*
Time to consciousness recovery (min)	11.9 (3.8)	8.0 (3.5)	3.86 (1.89, 5.82)	<0.001
Time to extubation (min)	12.5 (3.9)	8.4 (3.7)	4.14 (2.13, 6.16)	<0.001
Sedation score				
At awakening	4.0 (4.0–4.0)	4.0 (3.3–4.0)	–	0.113
PO 1/2 h	5.0 (4.0–5.0)	5.0 (4.0–5.0)	–	0.278
PO 1 h	5.0 (5.0–5.0)	5.0 (5.0–5.0)	–	0.718
Time to leave bed (h)	20.53 (5.44)	20.46 (4.56)	0.07 (−2.62, 2.76)	0.960
Time to first flatus (h)	24.75 (20.70–29.10)	20.85 (19.23–26.80)	–	0.174
QoR-40				
Baseline	194.5 (188.3–198.0)	197.0 (193.3–199.8)	–	0.156
PO 24 h	178.5 (165.0–191.0)	181.0 (168.5–191.5)	–	0.825
PO 48 h	191.0 (178.0–195.8)	190.5 (181.0–195.5)	–	0.837
Length of stay (d)	7.0 (7.0–10.0)	8.0 (6.0–10.8)	–	0.667
Adverse event incidence				
Nausea	6/28 (21.4)	8/28 (28.6)	–	0.537
Vomiting	3/28 (10.7)	7/28 (25.0)	–	0.163
Pruritus	0/28 (0.0)	0/28 (0.0)	–	>0.999
Hypoxemia	0/28 (0.0)	0/28 (0.0)	–	>0.999

Data expressed as mean (standard deviation), median (interquartile range) or number (%); O=Oxycodone, C=Control group, PO=Postoperative time point, QoR-40=40-item Quality of Recovery questionnaire, *n*=Number of patients, CI=Confidence interval

conventional regimens involving sufentanil and remifentanil. However, patients in the oxycodone group experienced more stable early postoperative haemodynamics and enhanced pain management within 48 h postoperatively, particularly with less CRBD.

The perioperative $CD4^+/CD8^+$ ratio and NK cell counts typically decrease by the end of the surgery, with recovery to preoperative levels within 72 h varying depending on surgical methods, anaesthetic-analgesic techniques, and patient factors.[3,13,14] Our study showed postoperative immunosuppression, evidenced by a decrease in the $CD4^+/CD8^+$ ratio at the end of surgery, with gradual recovery at 24 and 48 h postoperatively, alongside reduced NK cell counts, consistent with previous studies. Recent studies have shown that opioid-induced immunosuppression, via interacting with immune cells and activating the hypothalamic-pituitary-adrenal axis and sympathetic nervous system,[15,16] varies by molecule structure: full MOR agonists with hydroxyl groups at both C3 and C6 are more suppressive, while oxycodone, with a C6 carbonyl substitution and a C7-C8 single bond, potentiates analgesia but abolishes immunosuppression, making it advantageous for perioperative management in cervical cancer.[5,6,16-19] However, contrary to expectations, our study found no significant differences in immunity observed between perioperative oxycodone and conventional opioid regimens. Although there were many confounders in the perioperative period, such as pneumoperitoneum,[20] nerve block,[3,21,22] and non-steroidal anti-inflammatory drugs (NSAIDs),[3,13,21] these factors were comparable between groups and were unlikely to interfere with the results, except for the difference in opioids used. Our study did not find any difference in immunity between the two groups, which may be related to the control group's choice of remifentanil for intraoperative analgesia maintenance. Previous studies have shown that low-dose remifentanil has very little effect on immunity compared with morphine and fentanyl.[5,23] In addition, the multi-modal analgesia regimens, including regional blocks and NSAIDs, have an opioid-sparing impact and attenuate postoperative pain and stress, and may also narrow the small differences that may exist between the two groups.

This study illustrated that patients receiving oxycodone reported significantly lower VAS pain scores within 48 h postoperatively, required fewer rescue analgesics within the first postoperative hour, and needed fewer PCIA pressing times than those in the control group. Notably, a marked reduction in the incidence of CRBD was observed in the oxycodone group, consistent with the findings by Xiong *et al*.[24] on its broader therapeutic benefits. Furthermore, patients receiving oxycodone expressed higher satisfaction with postoperative analgesia; unlike sufentanil and remifentanil, which target only MOR, oxycodone with higher KOR affinity offers better visceral pain management. This characteristic may explain the more stable haemodynamics observed during extubation in the oxycodone group. These findings endorse the utilisation of oxycodone as the sole opioid within a multi-modal analgesia framework, providing effective pain relief and maintaining haemodynamic stability in laparoscopic surgery for cervical cancer, consistent with previous studies.[7,8,10,25]

The mean extubation time was longer in the oxycodone group (12.5 minutes) than in the control group (8.4 minutes), aligning with Bao *et al*.[7] No dizziness, pruritus, or hypoxemia was reported in either group, with no significance in PONV. Therefore, using oxycodone as the sole opioid in laparoscopic surgery for cervical cancer is feasible and safe, with no significant adverse events observed.

This study has several limitations. Firstly, the results may not be generalisable to all patients, such as the elderly or those undergoing open abdominal surgery. Given that Kang *et al*.[10] found men require 28% more oxycodone than women to blunt the intubation reaction, further research on male patients is necessary. Secondly, while the sample size was sufficient to assess the impact of experimental drugs on $CD4^+/CD8^+$ ratios, it was too small for a comprehensive evaluation of postoperative recovery quality and adverse reactions. Finally, although the oxycodone dosage used aligns with previous studies, its optimality remains unverified.

CONCLUSIONS

In patients undergoing laparoscopic surgery for cervical cancer, oxycodone administered as the sole opioid within a multi-modal analgesia framework throughout the perioperative period does not yield anticipated benefits in preserving immunity compared to conventional opioid regimens.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared upon request.

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Conflicts of interest

There are no conflicts of interest.

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