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Effects of Analgesic Adequacy on Perioperative Immune Function and Tumor Microenvironment in Patients Undergoing Gynecological Laparoscopic Malignant Tumor Surgery

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Abstract: *Objective:* To evaluate the effects of adequate perioperative analgesia on immune function, stress-inflammatory responses, tumor microenvironment-related biomarkers, and early recovery after laparoscopic surgery for gynecological malignancies. *Methods:* This prospective study enrolled 116 patients who underwent laparoscopic surgery between June 2023 and November 2024. Patients were randomly assigned to an adequate analgesia group or a conventional analgesia group, with 58 patients in each group. Conventional analgesia was administered on demand, whereas adequate analgesia involved preventive, multimodal, and dynamically adjusted management. Pain scores, rescue analgesia, immune parameters, stress-inflammatory factors, tumor-related biomarkers, and recovery outcomes were compared. *Results:* Numerical rating scale scores at 6, 24, 48, and 72 h were significantly lower in the adequate analgesia group, and the rescue analgesia rate decreased from 50.0% to 15.5% (all $P < 0.001$). Patients receiving adequate analgesia had higher postoperative $CD3^+$ and $CD4^+$ T-cell proportions, $CD4^+/CD8^+$ ratios, natural killer cell activity, IgA, and IgG levels, together with lower $CD8^+$ T-cell proportions. Cortisol, norepinephrine, interleukin-6, C-reactive protein, vascular endothelial growth factor, matrix metalloproteinase-9, and transforming growth factor-β levels were also significantly lower. Moreover, adequate analgesia shortened the time to first ambulation and hospital stay and reduced postoperative adverse events. *Conclusion:* Adequate perioperative analgesia may attenuate stress-inflammatory responses and transient immunosuppression, improve circulating tumor microenvironment-related biomarker profiles, and promote early recovery after laparoscopic surgery for gynecological malignancies.

Keywords: Analgesic adequacy; Gynecological malignant tumors; Laparoscopic surgery; Immune function; Tumor microenvironment

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1. Introduction

Gynecological malignant tumors, including ovarian, endometrial and cervical cancer, remain major threats to women's health. Surgical resection is an essential component of comprehensive treatment. Laparoscopic surgery has been increasingly adopted because it reduces operative trauma and blood loss and facilitates postoperative recovery. Nevertheless, pneumoperitoneum, pelvic tissue manipulation and surgical incisions can still cause substantial postoperative pain.

Surgical trauma and persistent nociceptive input may activate the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, resulting in increased cortisol and catecholamine release and the activation of inflammatory pathways [1, 2]. These neuroendocrine and inflammatory changes may temporarily suppress cellular and humoral immunity, particularly the activity of NK cells and cytotoxic T lymphocytes involved in antitumor immune surveillance [3]. In patients with malignant tumors, perioperative immunosuppression may create conditions that favor the survival of residual tumor cells and circulating tumor cells.

The influence of perioperative anesthetic and analgesic management on immune function and oncological outcomes has consequently attracted increasing attention. Existing evidence suggests that anesthesia-related immunosuppression may be associated with postoperative tumor recurrence and metastasis [4, 5]. Differences in long-term outcomes have also been reported between anesthetic agents used during gynecological cancer surgery [6]. However, clinical evidence remains inconsistent, and it is inappropriate to infer long-term oncological benefit solely from short-term biomarker changes. Analgesic agents may affect immune and inflammatory responses through different pathways. Non-steroidal anti-inflammatory drugs may reduce prostaglandin-mediated inflammation and have potential effects on long-term cancer outcomes [7]. Local anesthetics may influence tumor biology in addition to producing analgesia [8]. Incisional infiltration can reduce postoperative inflammatory cytokine release, while ketamine may exert perioperative immunomodulatory effects [9, 10]. Dexmedetomidine has also demonstrated anti-inflammatory and immune-regulatory properties in experimental and clinical studies involving uterine and ovarian cancer [11, 12]. These findings support the use of balanced multimodal analgesia to improve pain control while limiting excessive opioid exposure and stress activation.

Multimodal analgesia is an important component of enhanced recovery after surgery protocols and has been shown to improve recovery quality after laparoscopic gynecological surgery [13]. However, most previous studies have compared individual drugs or anesthetic techniques. Evidence concerning the overall adequacy of pain control and its relationship with perioperative immune homeostasis and tumor microenvironment-related biomarkers remains limited. The present study therefore investigated whether preventive, multimodal and dynamically adjusted analgesia could improve postoperative immune function, reduce stress-inflammatory responses and alter circulating VEGF, MMP-9 and TGF-β levels in patients undergoing laparoscopic surgery for gynecological malignant tumors.

2. Materials and methods

2.1. Baseline characteristics

This prospective randomized study was conducted at the Gynecological Oncology Center of our hospital between June 2023 and November 2024. A total of 116 patients scheduled for laparoscopic surgery for gynecological malignant tumors were enrolled. A random number table was used to assign patients to an adequate analgesia group and a conventional analgesia group, with 58 patients in each group.

The adequate analgesia group comprised 20 patients with ovarian cancer, 25 with endometrial cancer and 13 with cervical cancer. The conventional analgesia group comprised 22 patients with ovarian cancer, 23 with endometrial cancer and 13 with cervical cancer. Tumor stages were determined according to the International Federation of Gynecology and Obstetrics staging system. Baseline age, body mass index, operative duration, tumor stage and prevalence of hypertension were comparable between the two groups (all $P > 0.05$).

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) age 18–72 years old; (ii) a gynecological malignant tumor confirmed by imaging and pathological examination; (iii) fulfillment of the indications for laparoscopic surgery; (iv) American Society of Anesthesiologists physical status I–II; (v) acceptable preoperative cardiopulmonary, hepatic and renal function; and (vi) provision of written informed consent.

The exclusion criteria were as follows: (i) radiotherapy, chemotherapy, targeted therapy or immunotherapy within 4 weeks before enrollment; (ii) autoimmune disease or regular treatment with glucocorticoids or immunomodulatory agents; (iii) severe cardiac, hepatic or renal dysfunction or coagulation disorders; (iv) a history of another primary malignancy; (v) chronic pain or long-term opioid use; (vi) conversion from laparoscopic to open surgery; or (vii) inability to complete pain assessments and follow-up evaluations.

2.3. Anesthetic and analgesic management

The same gynecological oncology team performed all operations under general anesthesia with endotracheal intubation. Standard perioperative monitoring and clinical pathways were used in both groups.

Patients in the conventional analgesia group received analgesic treatment on demand. Opioid analgesics were administered intermittently during surgery according to the intensity of surgical stimulation. After surgery, intramuscular or intravenous rescue analgesics were administered when patients reported moderate or severe pain, defined as an NRS score of ≥ 4. Preventive analgesia and a fixed postoperative administration schedule were not routinely implemented.

Patients in the adequate analgesia group received preventive and multimodal analgesic management. Incision-site local infiltration analgesia was administered during anesthetic induction, and a stable intraoperative analgesic depth was maintained. Intravenous patient-controlled analgesia was initiated before abdominal closure. Postoperative management included a combination of non-steroidal anti-inflammatory drugs and opioids, with regional nerve block techniques used when appropriate. A pain management team assessed patients twice daily. Drug dosages and administration intervals were adjusted according to pain intensity at rest and during activity, with the aim of maintaining pain within the mild range.

Other perioperative procedures, including fluid management, prophylactic antibiotics, mobilization and postoperative dietary recovery, were consistent between the two groups.

2.4. Outcome measurements

Pain intensity at rest was assessed using the 11-point NRS at 6, 24, 48 and 72 h after surgery. A score of 0 indicated no pain and a score of 10 indicated the most severe pain. The number of patients requiring rescue analgesia was recorded.

Peripheral blood samples were collected 1 day before surgery and on postoperative days 1 and 3. The proportions of $CD3^+$, $CD4^+$ and $CD8^+$ T cells and the $CD4^+/CD8^+$ ratio were determined. NK cell cytotoxic activity was also evaluated.

Humoral immune and stress-inflammatory assessments included serum immunoglobulin A (IgA), immunoglobulin G (IgG), cortisol, norepinephrine, interleukin-6 (IL-6) and C-reactive protein (CRP). Circulating vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9) and transforming growth factor-β (TGF-β) were assessed as tumor microenvironment-related biomarkers.

Early recovery outcomes included time to first ambulation, length of hospital stay, incision infection and adverse events occurring within 1 month after surgery.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 26.0. Normally distributed continuous variables were expressed as the mean ± standard deviation and compared using an independent-samples t-test. Categorical variables were expressed as numbers and percentages and compared using the chi-square test. Repeated-measures analysis of variance was used for variables measured at multiple time points. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

The mean age was 48.7 ± 7.9 years old in the adequate analgesia group and 49.3 ± 8.4 years old in the conventional analgesia group ($P = 0.689$). The corresponding body mass index values were 23.6 ± 2.5 and 23.9 ± 2.7 kg/m² ($P = 0.538$), and operative durations were 124.5 ± 20.6 and 127.8 ± 23.1 min ($P = 0.416$).

The numbers of patients with FIGO stages I, II and III disease were 30, 20 and 8 in the adequate analgesia group and 29, 21 and 8 in the conventional analgesia group, respectively (P = 0.945). Hypertension was present in 11 patients (19.0%) in the adequate analgesia group and 13 patients (22.4%) in the conventional analgesia group (P = 0.652). No significant baseline differences were identified.

3.2. Postoperative pain control

At 6 h after surgery, the NRS score was 3.4 ± 1.0 in the adequate analgesia group and 5.1 ± 1.4 in the conventional analgesia group. At 24 h, the corresponding scores were 2.5 ± 0.8 and 4.3 ± 1.2. At 48 h, they were 1.7 ± 0.6 and 3.1 ± 1.0, while at 72 h they were 1.1 ± 0.5 and 2.2 ± 0.8. Pain scores were significantly lower in the adequate analgesia group at all four time points (all $P < 0.001$). Rescue analgesia was required by 9 patients (15.5%) in the adequate analgesia group and 29 patients (50.0%) in the conventional analgesia group ($P < 0.001$).

3.3. Cellular immune function

No significant preoperative differences in $CD3^+$, $CD4^+$ or $CD8^+$ T cells, $CD4^+/CD8^+$ ratio or NK cell activity were observed between the groups (all $P > 0.05$).

On postoperative day 1, the $CD3^+$ T-cell proportion was 57.8±4.9% in the adequate analgesia group and 50.4 ± 5.3% in the conventional analgesia group. The $CD4^+$ T-cell proportion was 32.3 ± 3.1% and 27.8 ± 3.4%, respectively. The $CD8^+$ T-cell proportion was lower in the adequate analgesia group than in the

conventional analgesia group (29.8 ± 3.4% vs. 32.6 ± 3.8%). The $CD4^+/CD8^+$ ratio was 1.09 ± 0.18 and 0.86 ± 0.16, while NK cell activity was 17.9 ± 2.6% and 13.6 ± 2.8%, respectively. All between-group differences were significant (all $P < 0.001$).

On postoperative day 3, the adequate analgesia group continued to show higher $CD3^+$ T-cell proportions (61.5 ± 4.6% vs. 54.6 ± 5.0%), $CD4^+$ T-cell proportions (35.4 ± 2.9% vs. 30.7 ± 3.2%), $CD4^+/CD8^+$ ratios (1.26 ± 0.19 vs. 0.99 ± 0.17) and NK cell activity (20.9 ± 2.4% vs. 16.3 ± 2.6%). The $CD8^+$ T-cell proportion remained lower in the adequate analgesia group (28.3 ± 3.0% vs. 30.9 ± 3.5%). All differences were statistically significant (all $P < 0.001$).

3.4. Humoral immunity and stress-inflammatory responses

On postoperative day 1, IgA was higher in the adequate analgesia group than in the conventional analgesia group (2.28 ± 0.32 vs. 2.02 ± 0.29 g/L), as was IgG (10.6 ± 1.2 vs. 9.2 ± 1.4 g/L).

Cortisol was significantly lower in the adequate analgesia group than in the conventional analgesia group (405.3 ± 54.6 vs. 528.7 ± 68.5 nmol/L). The adequate analgesia group also had lower norepinephrine (210.4 ± 32.6 vs. 268.9 ± 39.7 pg/mL), IL-6 (43.6 ± 9.2 vs. 66.8 ± 12.7 pg/mL) and CRP levels (17.5 ± 3.9 vs. 25.4 ± 5.3 mg/L). All between-group differences were statistically significant (all $P < 0.001$).

3.5. Tumor microenvironment-related factors and recovery outcomes

VEGF was lower in the adequate analgesia group than in the conventional analgesia group (178.6 ± 26.4 vs. 232.5 ± 33.1 pg/mL). Similar differences were observed for MMP-9 (298.7 ± 39.5 vs. 385.2 ± 48.6 ng/mL) and TGF-β (23.1 ± 3.8 vs. 30.4 ± 5.1 ng/mL). All differences were statistically significant (all $P < 0.001$).

The time to first ambulation was 15.4 ± 3.6 h in the adequate analgesia group and 22.8 ± 4.9 h in the conventional analgesia group ($P < 0.001$). The length of hospital stay was 6.1 ± 1.5 and 8.3 ± 2.1 days, respectively ($P < 0.001$).

Incision infection occurred in 1 patient (1.7%) in the adequate analgesia group and 7 patients (12.1%) in the conventional analgesia group ($P = 0.029$). Adverse events within 1 month after surgery occurred in 4 patients (6.9%) and 14 patients (24.1%), respectively ($P = 0.010$).

4. Discussion

Although laparoscopic surgery causes less tissue injury than open surgery, pneumoperitoneum, pelvic manipulation and incision stimulation can still produce substantial nociceptive input. Inadequately controlled pain activates sympathetic and hypothalamic-pituitary-adrenal responses, leading to the release of cortisol, catecholamines and inflammatory mediators. These alterations may contribute to lymphocyte dysfunction and transient postoperative immunosuppression.

The present study showed that preventive, multimodal and dynamically adjusted analgesia provided more stable pain control than conventional on-demand treatment. Postoperative NRS scores were significantly lower at all assessment points, and the rescue analgesia rate decreased from 50.0% to 15.5%. These findings indicate that a structured analgesic pathway can reduce breakthrough pain during early postoperative recovery.

Surgical and anesthetic factors can influence postoperative cellular immunity [14]. Differences in anesthesia may also affect cytokine release and oxidative stress during abdominal surgery [15]. In the present

study, the adequate analgesia group showed less pronounced postoperative reductions in $CD3^+$ and $CD4^+$ T cells, $CD4^+/CD8^+$ ratio and NK cell activity. Recovery of these parameters was also faster by postoperative day 3. A possible explanation is that reduced nociceptive signaling limits neuroendocrine activation and inflammatory injury to immune cells.

$CD3^+$ T cells reflect overall cellular immune status, whereas $CD4^+$ T cells participate in immune regulation and antitumor responses. NK cells recognize and eliminate malignant cells without prior antigen sensitization. Preservation of these cell populations may therefore be particularly relevant in the perioperative management of patients with malignant tumors. Nevertheless, short-term changes in circulating lymphocyte subsets cannot establish an effect on tumor recurrence or survival.

Patients receiving adequate analgesia also had lower postoperative cortisol, norepinephrine, IL-6 and CRP levels. Perioperative inflammatory dysregulation is closely related to corticosteroid and stress pathway activation [16]. The simultaneous reduction in stress hormones and inflammatory mediators suggests that improved pain control may interrupt the interaction between nociception, neuroendocrine activation and inflammation. Higher postoperative IgA and IgG concentrations further indicate that adequate analgesia may help preserve humoral immune function.

The levels of VEGF, MMP-9 and TGF-β were significantly lower in the adequate analgesia group. VEGF promotes angiogenesis, MMP-9 participates in extracellular matrix degradation and tumor invasion, and TGF-β is involved in immune suppression and tumor immune escape. Inflammatory factors and T-cell subset abnormalities have also been associated with recurrence-related changes in epithelial ovarian cancer [17]. The reductions observed in the present study suggest a potential relationship between analgesic adequacy and circulating tumor microenvironment-related biomarkers.

However, VEGF, MMP-9 and TGF-β were measured in peripheral blood and cannot directly represent the local tumor microenvironment. The findings should therefore be interpreted as changes in systemic biomarker profiles rather than evidence that adequate analgesia prevents recurrence or metastasis. Although different anesthetic techniques, including epidural anesthesia, have been investigated in relation to ovarian cancer prognosis [18], the long-term oncological effects of perioperative analgesia remain uncertain.

Adequate analgesia also shortened the time to first ambulation and hospital stay and reduced incision infection and short-term adverse events. Effective pain control may facilitate mobilization, respiratory activity, sleep and participation in postoperative rehabilitation. Nevertheless, the study was conducted at a single center with a relatively small sample, and the included patients had different tumor types and stages. The follow-up duration was also insufficient to evaluate disease-free or overall survival. Future multicenter studies should standardize analgesic drug doses, measure local tumor tissue biomarkers and include long-term recurrence and survival outcomes.

5. Conclusion

In conclusion, preventive, multimodal and dynamically adjusted analgesia improved postoperative pain control, attenuated stress-inflammatory responses, reduced transient immune suppression and was associated with lower circulating VEGF, MMP-9 and TGF-β levels. Adequate analgesia may therefore represent a valuable component of perioperative care for patients undergoing laparoscopic surgery for gynecological malignant tumors, although its long-term oncological benefits require further investigation.

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Disclosure statement

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