Effects of dexmedetomidine and ketorolac applied for patient-controlled analgesia on the balance of Th1/Th2 and level of VEGF in patients undergoing laparoscopic surgery for cervical cancer: A randomized controlled trial

LI AO[1,2], JINLIN SHI[3], JIANHUI GAN[3], WENLI YU[4*] and HONGYIN DU[4*]

[1]Department of Anesthesiology, The First Central Clinical School, Tianjin Medical University, Tianjin 300192, P.R. China; [2]Department of Anesthesiology, Tangshan Maternity and Child Healthcare Hospital, Tangshan, Hebei 063000, P.R. China; [3]Department of Anesthesiology, Tangshan People's Hospital and Tangshan Cancer Hospital, North China University of Science and Technology, Tangshan, Hebei 063000, P.R. China; [4]Department of Anesthesiology, Tianjin First Central Hospital, Tianjin 300192, P.R. China

Received January 30, 2024; Accepted May 16, 2024

DOI: 10.3892/ol.2024.14512

Abstract. The aim of the present study was to explore the effects of dexmedetomidine (DEX) combined with ketorolac on postoperative patient-controlled analgesia (PCA), the balance of Th1/Th2 and the level of vascular endothelial growth factor (VEGF) in patients with cervical cancer following laparoscopic radical surgery. A total of 70 women with cervical cancer undergoing laparoscopic radical hysterectomy were enrolled in the study to randomly receive postoperative dexmedetomidine combined with ketorolac analgesia (DK group) and postoperative sufentanil analgesia (SUF group). The primary outcomes were the serum levels of interleukin-4 (IL-4), interferon-γ (IFN-γ) and VEGF, and the IFN-γ/IL-4 ratio 30 min before induction (T_0), and 24 and 48 h after surgery. Secondary outcomes included numerical rating scale scores at 0 h (T_0), 4 h (T_1), 12 h (T_2), 24 h (T_3) and 48 h (T_4) postoperatively, cumulative times of rescue analgesia, as well as the incidence of postoperative side effects within 48 h from surgery. Patients in the DK group reported similar analgesic effects as patients in the SUF group at T_2, T_3 and T_4, and the incidence of postoperative nausea and vomiting was significantly lower in the DK group. In the DK group, the serum concentration of IFN-γ and IFN-γ/IL-4 ratio at 24 and 48 h after surgery were higher compared with those in the SUF group. Conversely, the serum concentrations of IL-4 at 24 h after surgery and VEGF at 24 and 48 h after surgery were significantly lower. The results indicated that the combination of DEX and ketorolac for PCA significantly improved postoperative pain and decreased the serum level of VEGF, which are associated with tumor angiogenesis. In addition, it maintained the homeostasis of postoperative immune dysfunction of patients with cervical cancer by shifting the balance between type 1 T helper cells and type 2 T helper cell (Th1/Th2 balance) to Th1 (registration no. ChiCTR1900027979; December 7, 2019).

Correspondence to: Dr Wenli Yu or Dr Hongyin Du, Department of Anesthesiology, Tianjin First Central Hospital, 24 Fukang Road, Nankai, Tianjin 300192, P.R. China
E-mail: yzxyuwenli2003@126.com
E-mail: duhongyin999@yeah.net

*Contributed equally

Key words: dexmedetomidine, ketorolac, cervical cancer, immune, vascular endothelial growth factor, Th1/Th2

Introduction

Cervical cancer is the fourth most common type of cancer in women, with an incidence of 570,000 estimated new cases and 311,000 resultant deaths worldwide in 2018 (1). Currently, laparoscopic radical hysterectomy with pelvic lymph node dissection remains a common treatment option for early cervical cancer. Yet the perioperative period may promote metastasis and recurrence of malignant tumor cells through a variety of mechanisms, such as surgery stress, inhibition of the immune system, modulation of angiogenesis and growth factors (2,3). In addition, perioperative immune dysfunction is associated with the occurrence of postoperative complications, such as infection, delayed wound healing and septic events (4-6). Therefore, perioperative interventions that preserve or enhance immune function during the postoperative period may improve patient outcome. Opioids have long been used in the treatment of perioperative severe acute pain, but it has dose-dependent adverse reactions that contribute to poor patient health outcomes (7). In addition, the opioid-induced immunosuppression should not be ignored. Opioid abuse is widespread and poses a serious threat to public health. Since both pain and opioid analgesics can cause immunosuppression (5), it is important to effectively and safely relieve postoperative pain and avoid immune dysfunction.

As a highly selective α2-adrenoceptor agonist, dexmedetomidine (DEX) has sedative, anti-anxiety and analgesic

effects, while reducing opioid use and alleviating immunosuppression (8). A meta-analysis showed that perioperative administration of DEX as an adjunct to general anesthesia can significantly reduce the levels of inflammatory cytokines, such as interleukin-6 (IL-6), IL-8 and tumor necrosis factor-α (TNF-α) in patients, thus ameliorating the impaired immune function (9). Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and anti-pyretic effects. NSAIDs perform these functions by blocking prostaglandin synthesis through the inhibition of the cyclooxygenase (COX) enzyme (10). Ketorolac may reduce demand of opioid and opioid-related side effects postoperatively (11). Furthermore, postoperative ketorolac analgesia has been shown to contribute to the preservation of natural killer cell cytotoxicity and have a favorable effect on immune function (4).

In addition to immune function, tumor recurrence and metastasis are closely associated with angiogenesis. VEGF levels are closely associated with tumor angiogenesis, tumor proliferation and distant metastasis (12). Studies have shown that opioids may upregulate VEGF and promote angiogenesis (13,14). The μ-opioid receptor antagonist methylnaltrexone has been found to block opioid-induced angiogenesis and exert intracellular effects to inhibit angiogenesis (15).

Although DEX and ketorolac are increasingly common components of multimodal analgesia (16), their effects on perioperative immunity and tumor promotion while controlling postoperative analgesia are rarely studied. Therefore, the present study was conducted to determine the influence of two postoperative analgesic methods on the changes of postoperative serum VEGF levels, T helper cell 1 (Th1) cytokine interferon-γ (IFN-γ) and Th2 cytokine IL-4, as well as to estimate the balance of Th1/Th2 (IFN-γ/IL-4 ratio) (17,18). The potential influence of DEX combined with ketorolac on tumor recurrence and growth following radical cervical cancer resection was also studied.

Materials and methods

Participants. The present study was conducted according to the Declaration of Helsinki and the Guidelines on Good Clinical Practice (19). Approval for the present study was provided by the Ethics Committee of Tangshan Maternity and Child Healthcare Hospital (approval no. 2019-031-01; Tangshan, China). This trial was registered prior to participant enrollment at www.chictr.org.cn (registration no. ChiCTR1900027979). Written informed consent was obtained from each patient from October 2020 to April 2022. The inclusion criteria were as follows: i) Female patients with newly diagnosed cervical cancer; ii) age, 25-65 years; iii) American Society of Anesthesiologists physical status I or II; and iv) scheduled to undergo elective laparoscopic radical hysterectomy with pelvic lymphadenectomy (20). The exclusion criteria were as follows: i) Body mass index >30; ii) history of severe viscera system or immune system diseases, gastrointestinal ulcer or bleeding; iii) history of chemotherapy, radiation or immunosuppressive therapy; iv) history of chronic pain or substance abuse; v) leukocytosis (>10,000/ml) or high level of C-reactive protein; vi) history of allergies to DEX or NSAIDs.

Randomization and blinding. A total of 70 adult female patients were enrolled (age, 25-65 years) and randomly allocated to either the sufentanil (SUF) or the DK group using sequentially-numbered sealed envelopes through a random number generator. The allocation ratio between the two groups was 1:1. An assistant not involved in the study prepared and distributed the envelopes. One anesthesiologist blinded to the allocation status was responsible for administering anesthesia and perioperative care. Based on the randomized sequence, the postoperative patient-controlled analgesia (PCA) pumps were prepared on the day of surgery by an independent nurse anesthetist. PCA pumps were sealed and then transferred to the intraoperative anesthesiologist blinded to their contents. Similarly, each surgery was performed by the same group of surgeons. The anesthesia follow-ups were conducted by another anesthesiologist, who was also blinded to the treatment regimen and not allowed to be involved in data analysis.

Anesthesia and pain management. Upon arrival at the operating room, each patient was monitored using electrocardiography and blood pressure, pulse oxygen saturation, pressure of end-tidal carbon dioxide ($P_{ET}CO_2$), and bispectral index (BIS) measurements were taken. Patients were administered 0.5 mg penehyclidine and 1-2 mg midazolam intravenously (IV) prior to the induction of anesthesia. Anesthesia was induced with 2-3 mg/kg propofol, 0.3-0.5 μg/kg sufentanil and 0.2 mg/kg cisatracurium. Propofol and remifentanil were administered to the patients through a target-controlled infusion during surgery to maintain hemodynamic stability intraoperatively. Mechanical ventilation was performed with 8 ml/kg tidal volume, and ventilator frequency was adjusted to maintain $P_{ET}CO_2$ at 35-40 mmHg. According to surgical requirements, cisatracurium was administered intermittently to promote muscle relaxation. The depth of anesthesia was also monitored using a BIS monitor (Aspect Medical System, Inc.), which was maintained at a value of 40-60. A total of 10 min before the end of surgery, each group was administered 6 ml of the corresponding PCA pump drug. PCA in each group was initiated at the end of the surgery and maintained for up to 48 h postoperatively.

Both groups of participants were treated with an IV PCA pump for postoperative pain management. The SUF group received SUF via IV PCA. The SUF PCA was composed of 1.5 μg/kg SUF mixed with normal saline to a total volume of 100 ml. The DK group received DEX and ketorolac through IV PCA, which was composed of 2 μg/kg DEX and 3 mg/kg ketorolac mixed with normal saline to a total volume of 100 ml. The bolus dose was set to 0.5 ml at a basal infusion rate of 2 ml/h, with a lockout interval of 15 min. At the end of the surgery, residual muscle relaxation was antagonized with 1 mg neostigmine and 0.5 mg atropine. Following extubation, the patient was sent to the post-anesthesia care unit for further monitoring.

Observation indexes. An 11-point numerical rating scale (NRS; range, 0-10, 0 indicating no pain and 10 indicating the worst pain imaginable) was performed to assess the pain intensity at rest and while coughing 30 min before induction (T_0), 4 h after surgery (T_1), 12 h after surgery (T_2), 24 h after surgery (T_3) and 48 h after surgery (T_4). To ensure the accuracy of the assessment,

Table I. Clinical characteristics of patients between two groups.

Variables	SUF	DK	P-value
Average age, years	46.2±9.3	48.0±9.2	0.453
Body mass index, kg/m^2	23.8±3.4	24.0±3.8	0.768
ASA physical status, I/II	20/12	19/15	0.585
Anesthesia duration, min	253.1±39.2	244.3±35.4	0.342
Operation duration, min	215.7±37.8	210.6±32.3	0.557
Blood loss, ml	215.4±58.0	205.7±57.8	0.499
Infusion volume, ml	1564.2±260.2	1532.8±210.9	0.591
Urine output, ml	301.5±51.8	313.5±56.7	0.371

Values are presented as mean ± standard deviation or numbers. ASA, American Society of Anesthesiologists.

the use of the NRS was explained in detail to each patient. The participants were advised to press the PCA bolus when NRS >3. The valid PCA pressing times and total consumption of the PCA pump within 48 h from surgery were recorded. Furthermore, main postoperative side effects and complications, such as post-operative nausea and vomiting (PONV), pruritus, respiratory depression and dizziness were observed.

A total of 5 ml peripheral venous blood sample of each participant was collected 30 min before induction (T_0), 24 h after surgery and 48 h after surgery for detecting cytokine concentration. To determine cytokine levels, the blood samples were centrifuged at 2,200 x g for 10 min at 4˚C. Next, the supernatant serum was removed and stored at -20˚C for further analysis. Serum concentrations of IFN-γ (cat. no. DIF50C; Human IFN-γ Quantikine ELISA Kit; R&D Systems, Inc.), IL-4 (cat. no. D4050; Human IL4 Quantikine ELISA Kit; R&D Systems, Inc.) and VEGF (cat. no. DVE00; Human VEGF Quantikine ELISA Kit; R&D Systems, Inc.) were measured using ELISA. A Spectra Max 190 microplate reader (Molecular Devices) was used to read the absorbance at 450 nm. To determine the balance of Th1/Th2, the IFN-γ/IL-4 ratio was also calculated. All steps are in accordance with the manufacturer's instructions. All cytokines were detected within 7 days from serum separation, and the procedure was repeated at least 3 times.

Statistical analysis. Statistical analysis was performed using the SPSS statistical software (version 20.0; IBM Corp.). Data were tested for normality using the Shapiro-Wilk test. Continuous variables are presented as the mean ± standard deviation or median (interquartile range), and continuous variables were analyzed using an independent t-test or Mann Whitney U test, where appropriate. The comparisons of cytokine concentrations between groups and within groups were analyzed using a mixed two-way ANOVA followed by Bonferroni correction. Categorical variables were described as numbers or frequencies and analyzed by Fisher's exact test or χ^2 test, where appropriate. P<0.05 was considered to indicate a statistically significant difference.

Results

Participant enrollment. A total of 86 participants were initially recruited. However, 11 participants (12.79%) were excluded due to meeting the exclusion criteria and 5 participants (5.81%) declined to participate. Subsequently, 2 participants (3.49%) in the SUF group and 1 participant (1.16%) in the DK group were lost to follow-up due to refusing to complete blood drawing at any time-point. Consequently, available data from 66 participants (76.74%) were included in the analysis (Fig. 1).

Table II. Pressing times and incidence of adverse events between two groups.

Variables	SUF	DK	P-value
Valid pressing, times	4.3±1.7	4.9±1.6	0.135
Dizziness	6	4	0.505
Pruritis	4	2	0.420
PONV	8	2	0.041[a]
Hypotension	1	1	1.000
Bradycardia	0	2	0.493

[a]P<0.05. Values are presented as mean ± standard deviation or numbers. PONV, postoperative nausea and vomiting.

Demographics and surgery details. No significant differences were observed between the groups regarding the baseline demographic characteristics of patients. The details of surgery and anesthesia, in terms of duration, fluid infusion volume, blood loss and urine output were comparable between the two groups (Table I).

Postoperative analgesia indexes. Compared with T_0, the resting and coughing NRS score of both groups increased at each time point postoperatively. The postoperative resting NRS scores at T_1 in the SUF group were significantly lower compared with those in the DK group (2.1±0.6 vs. 2.5±0.6; P=0.009), but the resting NRS score in both groups at different postoperative time points was <4 (Fig. 2A). There was no difference in the coughing NRS score between the two groups at any times point (Fig. 2B). There was no significant difference in valid PCA pressing times between the two groups (Table II).

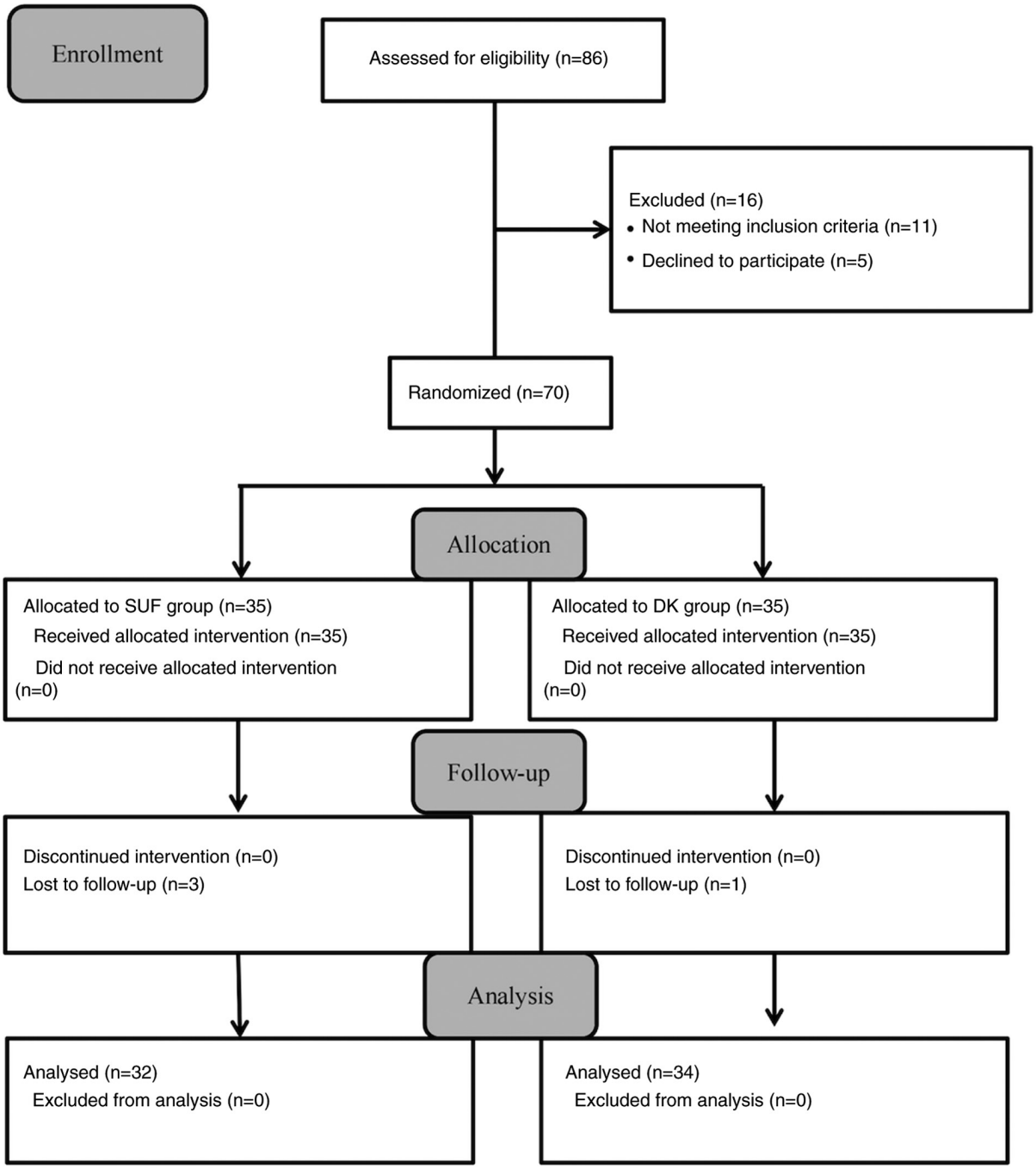

Figure 1. Flow chart of study inclusion and the progress of patients through the trial. SUF, sufentanil; DK, dexmedetomidine combined with ketorolac.

The incidence of PONV was significantly higher in the SUF group compared with the DK group. The incidence of dizziness and pruritus did not differ between the two groups, and no respiratory depression or gastrointestinal hemorrhage was observed. Although there was 1 case of hypotension and 2 cases of bradycardia in the DK group and 1 case of hypotension in the SUF group, there was no statistical difference between the two groups (Table II).

Immunological indexes. Since the pain control effectiveness of the two different pain management strategies were roughly similar, the possible influence of varying pain intensity on postoperative immune function in the two groups could be excluded. The baseline levels of IFN-γ/IL-4 and VEGF at T_0 were similar between the two groups. Compared with baseline levels at T_0, the serum concentration of IFN-γ and the ratio of IFN-γ/IL-4 were significantly decreased at 24 and 48 h after surgery in the SUF group, whereas the serum levels of IL-4 and VEGF were significantly increased at all postoperative time points. Similarly, in the DK group, a lower serum concentration of IFN-γ, a downregulated IFN-γ/IL-4 ratio, and higher serum levels of IL-4 and VEGF were detected at 24 h after surgery compared with T_0. However, the serum level of IFN-γ and the ratio of IFN-γ/IL-4 at 48 h after surgery were similar to those at baseline in the DK group, and the serum levels of IL-4 and VEGF were still upregulated at 48 h after

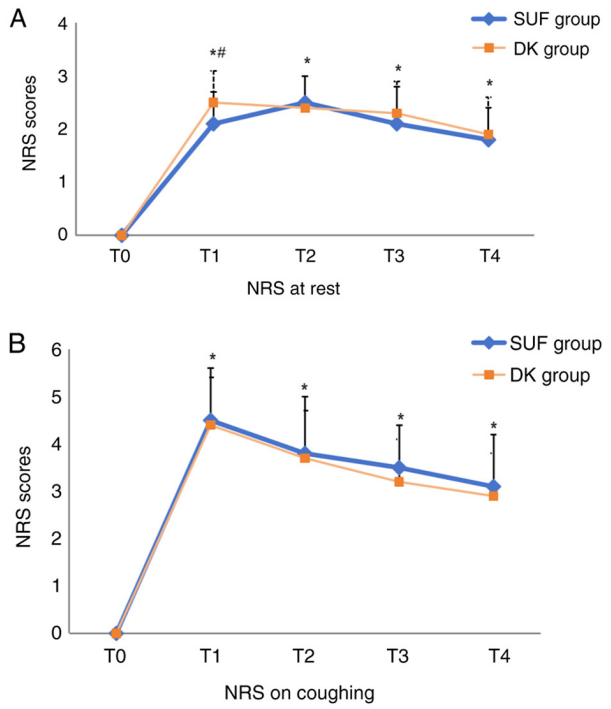

Figure 2. Comparison of NRS scores between two groups. (A) NRS scores at rest; (B) NRS scores on coughing. *P<0.05 vs. T_0; #P<0.05 vs. SUF group. NRS, numerical rating scale; SUF, sufentanil; DK, dexmedetomidine combined with ketorolac.

surgery (Fig. 3). In the DK group, the serum concentrations of IFN-γ and the IFN-γ/IL-4 ratio at 24 and 48 h after surgery were higher compared with the SUF group. Conversely, the serum concentrations of IL-4 at 24 h after surgery and VEGF at 24 and 48 h after surgery were significantly lower (Fig. 3).

Discussion

The present study revealed that the administration of DEX combined with ketorolac for PCA following laparoscopic radical resection of cervical cancer could effectively alleviate postoperative pain intensity, inhibit the perioperative immunosuppressive state by adjusting the inflammatory factor levels and inhibiting Th1/Th2 drift and reduce the expression of VEGF and angiogenesis, which could potentially reduce tumor recurrence.

Cancer surgery and anesthesia can inhibit cellular immune function, release catecholamines and prostaglandin E_2 (PGE_2) and induce the release of a variety of inflammatory cytokines and tumorigenic factors, including TNF-α, IL-1β, IL-6 and VEGF (21,22). Surgical trauma and postoperative acute pain can contribute to the release of inflammatory cytokines, leading to immune dysfunction (4-6). DEX and non-steroidal anti-inflammatory drugs can reduce the consumption of opioids, enhance the analgesic effect, reduce the incidence of adverse drug reactions and improve clinical safety (8,11). In particular, ketorolac can be used to control cancer-related pain and as an analgesic following cancer surgery (23,24). In the present study, within 48 h from laparoscopic radical resection of cervical cancer, DEX combined with ketorolac administered for controlled analgesia had significant analgesic effects with limited adverse reactions, avoiding the related side effects caused by opioid analgesia.

Secondly, in addition to pain management, maintaining immune balance is also important for patient recovery and early discharge following surgery, even for long-term tumor recurrence. Th cells can be differentiated into Th1 or Th2 subtypes. Under normal conditions, Th1 and Th2 cells are in a relative balance state, which is important for maintaining immune balance. Cancer has been shown to disrupt the Th1/Th2 balance, which is called 'balance shifting' (18,25). Since the balance drift from Th1 to Th2 cells seems to be associated with immunosuppression and the progression of cancer (26), Th1/Th2 balance is critical for cancer patients. Cytokines secreted by Th-1 and Th-2 are closely associated with immune response and immune regulation. Th-1 cells promote cell-mediated immune responses and mainly release IL-2, IFN-γ and TNF-β, which are essential for antineoplastic and anti-inflammatory processes (27,28). On the other hand, the pro-inflammatory cytokines secreted by Th-2 cells are mainly composed of IL-4, IL-5, IL-6 and IL-10, facilitating humoral immunity but suppressing particular types of cell-mediated immune responses (29). IFN-γ and IL-4 are key cytokines produced by Th1 and Th2 cells, respectively, so Th1/Th2 balance can be estimated by calculating the IFN-γ/IL-4 ratio (17,18). The implication of the surgery-induced upregulation of Th2 or downregulation of the Th1/Th2 ratio increases susceptibility to infection and tumor progression in the patients with postoperative cellular immunosuppression (30).

The main outcome of the present study was that postoperative DEX combined with ketorolac analgesia significantly alleviated the decrease of the IFN-γ/IL-4 ratio in patients undergoing surgery and anesthesia stress. These results indicated that postoperative DEX combined with ketorolac for PCA may shift the Th1/Th2 balance toward Th1, thereby contributing to immunomodulatory effects. DEX has been shown to reduce the secretion of pro-inflammatory cytokines, thereby modulating harmful inflammatory responses due to surgery, which was consistent with another study in mice with concanavalin A-induced liver injury (31,32). In a randomized controlled trial, the intraoperative administration of DEX could shift the Th1/Th2 imbalance toward Th1 in a dose-dependent manner in patients subjected to surgical and anesthetic stress, exhibiting immunomodulatory effects (33). This is consistent with another study of intraoperative DEX in patients with gastric cancer undergoing gastrectomy, which demonstrated immunomodulatory properties, with a decline in IL-6 and TNF and increase in the Th1/Th2 ratio observed (8). Not only as an analgesic, ketorolac has been shown to improve survival in cancer patients. A retrospective study that included 327 women with breast cancer reported that, compared with other analgesics (SUF, clonidine and ketamine), the intraoperative use of ketorolac reduced the risk of breast cancer relapse (34). Unlike other NSAIDs, ketorolac is a 1:1 racemic mixture of two different independent pharmacological enantiomers (S- and R-ketorolac) (23). S-ketorolac is considered the active component in pain management with selective activity against COX enzymes; while R-ketorolac has an activity as an inhibitor of Ras-related C3 botulinum toxin substrate and cell division control protein 42 GTPases, which are recognized as attractive therapeutic targets in cancer, thereby promoting

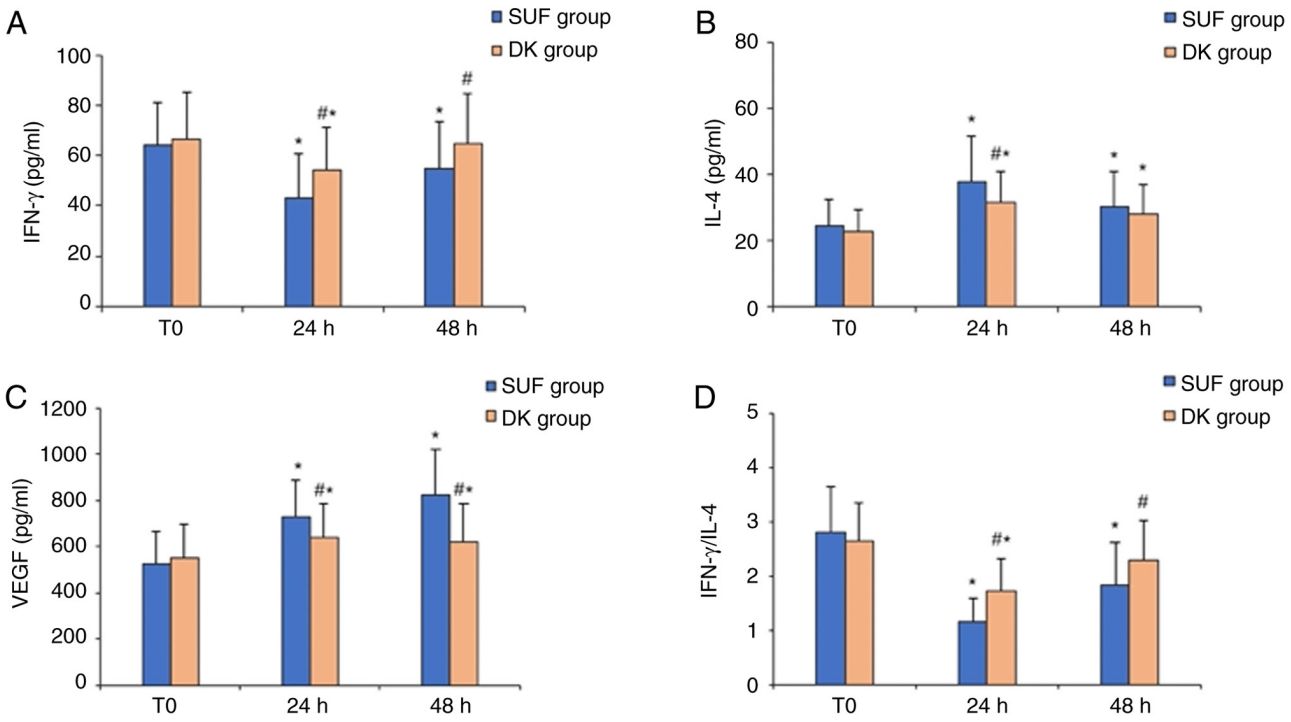

Figure 3. Comparison of serum levels of IFN-γ, IL-4, VEGF and IFN-γ/IL-4 ratio between two groups. (A) IFN-γ; (B) IL-4; (C) VEGF; (D) IFN-γ/IL-4 ratio. *P<0.05 vs. T_0; #P<0.05 vs. SUF group. IFN-γ, interferon-γ; IL-4, interleukin-4; VEGF, vascular endothelial growth factor; SUF, sufentanil; DK, dexmedetomidine combined with ketorolac.

anti-cancer activity (23,35). NSAIDs are well-known immunomodulators. NSAIDs increase mRNA expression and production of cytokines produced by Th1 cells (TNF, IFN-γ and IL-2), but decrease that of IL-4 and IL-6 produced by Th2 cells both at the mRNA and protein levels (36). This regulation may be partially independent of the inhibition of PGE_2 synthesis in T cell clones (36). A recent study has suggested that the combination of DEX and NSAIDs can reduce postoperative IL-2 inhibition, restrain the secretion of serum TNF-α and IL-6 and improve the levels of B and T lymphocytes (37).

Surgery-induced sympathetic nervous system activation and anesthetic-associated cell-mediated immunosuppression may also promote angiogenesis by increasing the release of cytokines such as VEGF (38). VEGF levels are closely associated with tumor angiogenesis, tumor proliferation and distant metastasis (12). Moreover, studies have found that VEGF concentration is associated with clinical stage, tumor size and their role in monitoring the disease process (3,39). VEGF has been found to be overexpressed in cervical cancer cells and the serum levels of VEGF are often elevated in patients with cervical cancer (40,41). Kotowicz *et al* (42) revealed that the elevated serum VEGF concentration in patients with cervical cancer may be an important prognostic factor at the early stage of clinical development. Moreover, the serum VEGF level of patients with cervical cancer was increased, and decreased significantly following successful treatment (43). Therefore, VEGF-mediated angiogenesis has become a new target for anti-cancer therapy in recent years, and different intervention methods have been explored to block tumor angiogenesis (44).

As a monoclonal antibody for VEGF, Bevacizumab has been approved to inhibit tumor angiogenesis and improve overall survival in patients with certain types of tumors (45). Mirzaei *et al* (46) revealed that simvastatin combined with arsenic trioxide inhibits cell proliferation and has antiangiogenesis properties, which may be achieved by downregulating VEGF expression. In addition, a recent study has demonstrated that miR-503-5p inhibits tumorigenesis and angiogenesis in colon cancer by downregulating the expression of VEGF-AA (47).

VEGF has been implicated in tumorigenesis and tumor growth due to its ability to promote angiogenesis, mitotic activity and vascular permeability-enhancing activity (12,40). In addition, PGE_2, the synthesized product of cyclooxygenase-2, can induce tissues to create VEGF, which in turn leads to a gradual increase in VEGF expression (48). NSAIDs inhibit the synthesis of PGE_2 by inhibiting the COX enzyme, showing antitumor and anti-angiogenic properties (49,50). Furthermore, Ji *et al* (48) found that surgeries without any perioperative drugs for analgesia caused marked increases in serum PGE_2 and VEGF in rats, which were inhibited by NSAIDs. A randomized controlled study suggests that the use of COX-2 inhibitors for pain management in cancer patients may decrease the expression of VEGF, thereby reducing the risk of cancer recurrence and metastasis (22). In lung cancer surgery, the administration of DEX can induce the proliferation of monocytic myeloid-derived suppressor cells (MDSCs) which have the ability to promote angiogenesis (51). Treatment with DEX also increases monocytic MDSC in mice and promotes tumor metastasis by increasing VEGF production (51). In the present study, there was a significantly decreased level of VEGF in the DK group compared with the SUF group at 24 and 48 h after surgery, although the VEGF levels were not restored to the preoperative level at 48 h after surgery. The present study showed that DEX and ketorolac patient controlled-analgesia

can effectively inhibit the increase of VEGF serum concentration induced by cervical cancer surgery.

The present study was not without its limitations. First, since it was a single-center study with a strictly defined population, the results may not apply to other institutions, despite the high homogeneity of the two groups. Secondly, it may not be accurate to estimate Th1/Th2 cell balance by detecting serum cytokine concentrations, since not all IFN-γ and IL-4 expression in the sera originates solely from Th1 and Th2 cells. Thirdly, the present study was unable to determine the relationship between changes in cytokine levels and clinical outcomes, such as short-term effects on wound infection or length of hospital stay, and long-term effects on cancer metastasis or recurrence. Finally, it cannot be concluded whether the results were due to the elimination of opioids or the use of COX inhibitors and DEX, and their contribution to the results. Therefore, further studies with larger sample sizes and multiple indicators are warranted to focus on clinical outcomes in terms of perioperative morbidity and long-term metastatic development in patients undergoing cancer surgery.

Briefly, the present prospective, randomized study demonstrated that the combination of DEX and ketorolac for PCA significantly improved postoperative pain following laparoscopic radical resection for cervical cancer, decreased the serum levels of VEGF and enhanced immune function by shifting the Th1/Th2 balance to Th1. The anesthetics decreased the serum VEGF concentration, which may be associated with angiogenesis in cervical cancer. This finding may offer opportunities for postoperative pain management to improve cancer patient outcomes.

Acknowledgements

Not applicable.

Funding

This research was funded by The Tianjin Key Medical Discipline (Specialty) Construction Project (grant no. TJYXZDXK-045A).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LA and JS drafted the manuscript. LA and WY developed the study protocol and LA carried out patient recruitment. JS collected individual data and JG performed statistical analysis. WY and HD contributed to the study conception and reviewed the manuscript. All authors read and approved the final version of the manuscript. LA and WY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Human Research of Tangshan Maternity and Child Healthcare Hospital (approval no. 2019-031-01). The trial was also registered prior to participant enrollment at www.chictr.org.cn (registration no. ChiCTR1900027979). Written informed consent was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
2. Hiller JG, Perry NJ, Poulogiannis G, Riedel B and Sloan EK: Perioperative events influence cancer recurrence risk after surgery. Nat Rev Clin Oncol 2018;15: 205-218, 2018.
3. Manders P, Beex LV, Tjan-Heijnen VC, Span PN and Sweep CG: Vascular endothelial growth factor is associated with the efficacy of endocrine therapy in patients with advanced breast carcinoma. Cancer 98: 2125-2132, 2003.
4. Cho JS, Lee MH, Kim SI, Park S, Park HS, Oh E, Lee JH and Koo BN: The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: A prospective randomized study. Int J Med Sci 14: 970-976, 2017.
5. Snyder GL and Greenberg S: Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth 105: 106-115, 2010.
6. Ogawa K, Hirai M, Katsube T, Murayama M, Hamaguchi K, Shimakawa T, Naritake Y, Hosokawa T and Kajiwara T: Suppression of cellular immunity by surgical stress. Surgery 127: 329-336, 2000.
7. Shafi S, Collinsworth AW, Copeland LA, Ogola GO, Qiu T, Kouznetsova M, Liao IC, Mears N, Pham AT, Wan GJ and Masica AL: Association of opioid-related adverse drug events with clinical and cost outcomes among surgical patients in a large integrated health care delivery system. JAMA Surg 153: 757-763, 2018.
8. Wang Y, Xu X, Liu H and Ji F: Effects of dexmedetomidine on patients undergoing radical gastrectomy. J Surg Res 194: 147-153, 2015.
9. Li B, Li Y, Tian S, Wang H, Wu H, Zhang A and Gao C: Anti-inflammatory effects of perioperative dexmedetomidine administered as an adjunct to general anesthesia: A meta-analysis. Sci Rep 5: 12342, 2015.
10. Rainsford KD: Ibuprofen: Pharmacology, efficacy and safety. Inflammopharmacology 17: 275-342, 2009.
11. Cepeda MS, Carr DB, Miranda N, Diaz A, Silva C and Morales O: Comparison of morphine, ketorolac, and their combination for postoperative pain. Anesthesiology 103: 1225-1232, 2005.
12. Foekens JA, Peters HA, Grebenchtchikov N, Look MP, Meijer-van Gelder ME, Geurts-Moespot A, van der Kwast TH, Sweep CG and Klijn JG: High tumor levels of vascular endothelial growth factor predict poor response to systemic therapy in advanced breast cancer. Cancer Res 61: 5407-5414, 2001.
13. Wang Z, Jiang L, Wang J, Chai Z and Xiong W: Morphine promotes angiogenesis by activating PI3K/Akt/HIF-1α pathway and upregulating VEGF in hepatocellular carcinoma. J Gastrointest Oncol 12: 1761-1772, 2021.
14. Singleton PA and Moss J: Effect of perioperative opioids on cancer recurrence: A hypothesis. Future Oncol 6: 1237-1242, 2010.
15. Singleton PA, Garcia JG and Moss J: Synergistic effects of methylnaltrexone with 5-fluorouracil and bevacizumab on inhibition of vascular endothelial growth factor-induced angiogenesis. Mol Cancer Ther 7: 1669-1679, 2008.
16. Martinez L, Ekman E and Nakhla N: Perioperative opioid-sparing strategies: Utility of Conventional NSAIDs in Adults. Clin Ther 41: 2612-2628, 2019.

17. Adurthi S, Mukherjee G, Krishnamurthy H, Sudhir K, Bafna UD, Umadevi K and Jayshree RS: Functional tumor infiltrating TH1 and TH2 effectors in large early-stage cervical cancer are suppressed by regulatory T cells. Int J Gynecol Cancer 22: 1130-1107, 2012.
18. Ma J, Liu H and Wang X: Effect of ginseng polysaccharides and dendritic cells on the balance of Th1/Th2 T helper cells in patients with non-small cell lung cancer. J Tradit Chin Med 34: 641-645, 2014.
19. Guideline for Good Clinical Practice E6(R1) 1996: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. Accessed May 12, 2015. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
20. American Society of Anesthesiologists: ASA physical status classification system. Accessed November 23, 2018. https://www.asahq.org/resources/American Society of Anesthesiologists.
21. Green JS and Tsui BC: Impact of anesthesia for cancer surgery: Continuing professional development. Can J Anaesth 60: 1248-1269, 2013.
22. Wen Y, Wang M, Yang J, Wang Y, Sun H, Zhao J, Liu W, Zhou Z, Deng H, Castillo-Pedraza C, *et al*: A comparison of fentanyl and flurbiprofen axetil on serum VEGF-C, TNF-α, and IL-1ß concentrations in women undergoing surgery for breast cancer. Pain Practice 15: 530-537, 2015.
23. Hudson LG, Cook LS, Grimes MM, Muller CY, Adams SF and Wandinger-Ness A: Dual actions of ketorolac in metastatic ovarian cancer. Cancers (Basel) 11: 1049, 2019.
24. Butcher B, Hutchings E, Fazekas B, Clark K, Rowett D and Currow D: Opioid-sparing effects of ketorolac in palliative care patients receiving opioids for chronic cancer-related pain: A systematic literature review. Palliat Med 36: 71-80, 2022.
25. Zhang W, Pan Y, Gou P, Zhou C, Ma L, Liu Q, Du Y, Yang J and Wang Q: Effect of xanthohumol on Th1/Th2 balance in a breast cancer mouse model. Oncol Rep 39: 280-288, 2018.
26. Hao CJ, Li J, Liu P, Li XL, Hu YQ, Sun JC and Wei Y: Effects of the balance between type 1 and type 2 T helper cells on ovarian cancer. Genet Mol Res 15 2016.
27. Webster NR and Galley HF: Immunomodulation in the critically ill. Br J Anaesth 103: 70-81, 2009.
28. Liao W, Lin JX and Leonard WJ: IL-2 family cytokines: New insights into the complex roles of IL-2 as a broad regulator of T helper cell differentiation. Curr Opin Immunol 23: 598-604, 2011.
29. Kurosawa S and Kato M: Anesthetics, immune cells, and immune responses. J Anesth 22: 263-277, 2008.
30. Cardinale F, Chinellato I, Caimmi S, Peroni DG, Franceschini F, Miraglia Del Giudice M and Bernardini R: Perioperative Period: Immunological Modifications. Int J Immunopathol Pharmacol 24 (3 Suppl): S3-S12, 2011.
31. Ueki M, Kawasaki T, Habe K, Hamada K, Kawasaki C and Sata T: The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. Anaesthesia 69: 693-700, 2014.
32. Wang H, Hu B, Zou Y, Bo L, Wang J, Li J and Luo Y: Dexmedetomidine premedication attenuates concanavalin A-induced hepatitis in mice. J Toxicol Sci 39: 755-764, 2014.
33. Lee JM, Han HJ, Choi WK, Yoo S, Baek S and Lee J: Immunomodulatory effects of intraoperative dexmedetomidine on T helper 1, T helper 2, T helper 17 and regulatory T cells cytokine levels and their balance: A prospective, randomised, double-blind, dose-response clinical study. BMC Anesthesiol 18: 164, 2018.
34. Forget P, Vandenhende J, Berliere M, MacHiels JP, Nussbaum B, Legrand C and De Kock M: Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. Anesth Analg 110: 1630-1635, 2010.
35. Guo Y, Kenney SR, Muller CY, Adams S, Rutledge T, Romero E, Murray-Krezan C, Prekeris R, Sklar LA, Hudson LG and Wandinger-Ness A: R-Ketorolac Targets Cdc42 and Rac1 and alters ovarian cancer cell behaviors critical for invasion and metastasis. Mol Cancer Ther 14: 2215-2227, 2015.
36. Tsuboi I, Tanaka H, Nakao M, Shichijo S and Itoh K: Nonsteroidal anti-inflammatory drugs differentially regulate cytokine production in human lymphocytes: Up-regulation of TNF, IFN-gamma and IL-2, in contrast to down-regulation of IL-6 production. Cytokine 7: 372-379, 1995.
37. Ma XD, Li BP, Wang DL and Yang WS: Postoperative benefits of dexmedetomidine combined with flurbiprofen axetil after thyroid surgery. Exp Ther Med 14: 2148-2152, 2017.
38. Yang EV, Kim SJ, Donovan EL, Chen M, Gross AC, Webster Marketon JI, Barsky SH and Glaser R: Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: Implications for stress-related enhancement of tumor progression. Brain Behav Immun 23: 267-275, 2009.
39. Gadducci A, Tana R, Cosio S and Genazzani AR: The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up of patients with cervical cancer: A review of the literature. Crit Rev Oncol Hematol 66: 10-20, 2008.
40. Mitsuhashi A, Suzuka K, Yamazawa K, Matsui H, Seki K and Sekiya S: Serum vascular endothelial growth factor (VEGF) and VEGF-C levels as tumor markers in patients with cervical carcinoma. Cancer 103: 724-730, 2005.
41. van Trappen PO, Steele D, Lowe DG, Baithun S, Beasley N, Thiele W, Weich H, Krishnan J, Shepherd JH, Pepper MS, *et al*: Expression of vascular endothelial growth factor (VEGF)-C and VEGF-D, and their receptor VEGFR-3, during different stages of cervical carcinogenesis. J Pathol 201: 544-554, 2003.
42. Kotowicz B, Fuksiewicz M, Jonska-Gmyrek J, Bidzinski M and Kowalska M: The assessment of the prognostic value of tumor markers and cytokines as SCCAg, CYFRA 21.1, IL-6, VEGF and sTNF receptors in patients with squamous cell cervical cancer, particularly with early stage of the disease. Tumour Biol 37: 1271-1278, 2016.
43. Moon HS, Kim SC, Ahn JJ and Woo BH: Concentration of vascular endothelial growth factor (VEGF) and transforming growth factor-beta1 (TGF-beta1) in the serum of patients with cervical cancer: Prediction of response. Int J Gynecol Cancer 10: 151-156, 2000.
44. Mabeta P and Steenkamp V: The VEGF/VEGFR axis revisited: Implications for cance therapy. Int J Mol Sci 23: 15585, 2022.
45. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R and Chinot OL: Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev 86: 102017, 2020.
46. Mirzaei A, Rashedi S, Akbari MR, Khatami F and Aghamir SMK: Combined anticancer effects of simvastatin and arsenic trioxide on prostate cancer cell lines via downregulation of the VEGF and OPN isoforms genes. J Cell Mol Med 26: 2728-2740, 2022.
47. Wei L, Sun C, Zhang Y, Han N and Sun S: miR-503-5p inhibits colon cancer tumorigenesis, angiogenesis, and lymphangiogenesis by directly downregulating VEGF-A. Gene Ther 29: 28-40, 2022.
48. Ji C, Xiong Y, Pan X, Guo X, Li Z, Qian S, Xu C, Yu DH and Liao WQ: Effect of non-steroidal anti-inflammatory drugs on the increasing the incidence of colonic anastomosis in rats. Int J Clin Exp Pathol 8: 6126-6134, 2015.
49. Farooqui M, Li Y, Rogers T, Poonawala T, Griffin RJ, Song CW and Gupta K: COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. Br J Cancer 97: 1523-1531, 2007.
50. Davies G, Martin LA, Sacks N and Dowsett M: Cyclooxygenase-2 (COX-2), aromatase and breast cancer:a possible role for COX-2 inhibitors in breast cancer chemoprevention. Ann Oncol 13: 669-678, 2002.
51. Su X, Fan Y, Yang L, Huang J, Qiao F, Fang Y and Wang J: Dexmedetomidine expands monocytic myeloid-derived suppressor cells and promotes tumour metastasis after lung cancer surgery. J Transl Med 16: 347, 2018.