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Thoracic epidural anaesthesia and analgesia ameliorates surgery-induced stress response and postoperative pain in patients undergoing radical oesophagectomy

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Abstract

Objective: An acute severe stress response associated with major surgery can adversely affect the inflammatory and hormonal responses. We hypothesised that total intravenous anaesthesia (TIVA) combined with thoracic epidural anaesthesia and analgesia (TEA) attenuates the stress response and postoperative pain in patients undergoing radical oesophagectomy.

Methods: Forty patients scheduled for elective radical oesophagectomy were randomly assigned to one of two groups: TIVA or TIVA+TEA. The plasma levels of stress hormones and cytokines, consumption of fentanyl, postoperative visual analogue scale (VAS) scores within 48 hours, and extubation time were assessed.

Results: The plasma levels of interleukin-6, norepinephrine, cortisol, and adrenocorticotropic hormone at 3 hours after the beginning of surgery were significantly higher in the TIVA group than TIVA+TEA group. The plasma level of interleukin-10 at 3 hours after the beginning of surgery was significantly lower in the TIVA group than TIVA+TEA group. The consumption of fentanyl was significantly greater, VAS scores were significantly higher, and extubation time was significantly longer in the TIVA group than TIVA+TEA group.

Conclusions: The findings suggest that combination of TIVA and TEA may attenuate the intraoperative stress response and postoperative pain in patients undergoing radical oesophagectomy.

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Introduction

With the exposure of the general population to food of questionable safety and severe air pollution, particularly in China, the overall incidence of cancer has dramatically increased. Although the survival rate of patients with cancer is improving because of advances in modern medical technology, cancer is the second most common cause of death after heart disease.[1]

Surgery remains the most effective curative treatment for solid tumours; however, the acute severe stress response associated with major surgery can induce perturbations in the inflammatory, acute-phase, and hormonal responses.[2] The severe stress induced by surgery leads to prolonged damage-associated molecular patterns accompanied by sustained central nervous system stimulation.[3] The main causes of the stress response in surgical patients are related to the neuroendocrine stress exerted through activation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis.[4,5] Classically, upon hypothalamic stimulation, adrenocorticotropic hormone (ACTH) is released from the pituitary in the adrenal cortex, stimulating glucocorticoid synthesis and release. Serova et al.[6] showed that ACTH can have a direct effect on transcription and gene expression of norepinephrine (NE) biosynthetic enzymes even without the contribution of adrenal hormones. ACTH and cortisone (CORT) exert inhibitory effects on immune functions because monocytes, macrophages, and T cells have glucocorticoid receptors.[7] Furthermore, emerging evidence has revealed that NE, the main neurotransmitter of the sympathetic nervous system, regulates a variety of immune functions by binding to adrenergic receptors present on immune cells. Nicholls et al.[8] reported that neutrophil chemotaxis, activation, and phagocytosis can be negatively regulated in an NE-dependent manner. The neuroendocrine system and pro-inflammatory and anti-inflammatory cytokines synergistically increase their suppressive effects on the immune system in the perioperative period. Consequently, this acute stress response, which manifests as activation of the neuroendocrine system and an ensuing cytokine storm, may worsen the long-term clinical outcomes.

The potential effect of anaesthesia on long-term patient outcomes is increasingly being acknowledged.[9] The anaesthetic technique and drug of choice could interact with the cellular immune system and affect the long-term outcomes.[10] Epidural anaesthesia can completely block the sympathetic nerve fibres from level T4 to S5, thereby weakening the stress response induced by activation of the locus coeruleus-sympathetic-adrenal medullary axis and hypothalamic-pituitary-adrenal axis secondary to surgical nociceptive stimulation. Attenuation of the stress response by postoperative thoracic epidural analgesia has demonstrated beneficial effects, including lower pain scores and fewer immunological alterations.[11–14] Hence, additional reduction of perioperative stress using thoracic epidural anaesthesia and analgesia (TEA) may enhance the beneficial effects of TEA.

In the present study, we focused on the impact of TEA on the intraoperative stress response and postoperative pain in patients undergoing radical oesophagectomy. We hypothesised that total intravenous anaesthesia (TIVA) combined with TEA (TIVA+TEA) attenuates the stress response and postoperative pain in patients undergoing radical oesophagectomy. In this study, the entropy index was used to maintain the depth of anaesthesia at a predefined level.

Patients and methods

This prospective, randomised, double-blind study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (Shanghai, China; No. 47-12) on 29 December 2014. Written informed consent was obtained from all participants. The trial was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR 12617000434392).

Study population and study protocol

Patients who were scheduled for elective radical oesophagectomy from May to September 2015 at the Fudan University Shanghai Cancer Center were enrolled. The following patients were excluded from the study: those with an American Society of Anesthesiologists physical status of IV or higher, a contraindication to receiving thoracic epidural anaesthesia, or pre-existing cardiovascular disease; those who underwent preoperative treatment with opioids, nonsteroidal anti-inflammatory drugs, or other immunomodulatory substances; those with an infection or an immune or endocrine system disorder; and those with communication barriers. The patients were randomly divided into two groups (TIVA and TIVA+TEA) using a computer-generated random numbers table. The group allocation was concealed in sealed opaque envelopes, which were opened immediately before the intervention.

The patients in the TIVA+TEA group received 0.375% ropivacaine at 5 mL/hour via a thoracic epidural catheter and intravenous propofol anaesthesia during surgery, followed by patient-controlled epidural analgesia via a pump. A continuous epidural infusion of 0.125% ropivacaine + sufentanil citrate (0.4 μg/mL) + 0.9% physiological saline (200 mL) was initiated at 3 mL/hour after surgery. The patient-controlled epidural analgesia dose was 3 mL, and the lockout time was set to 15 minutes (maximal rate, 15 mL/hour). The patients in the control group (i.e., TIVA group) received intravenous propofol anaesthesia during surgery, followed by patient-controlled intravenous analgesia via a pump. The drugs in the patient-controlled intravenous analgesia pump included sufentanil citrate ($0.03\,\mu g \cdot kg^{-1}$ $hour^{-1}$) + flurbiprofen axetil (100 mg) + ondansetron (8 mg) + 0.9% physiological saline (200 mL). The patient-controlled intravenous analgesia pump parameters were set to a background flow of 3 mL/hour, patient-controlled analgesia dose of 3 mL, and lockout time of 15 minutes (maximal rate, 15 mL/hour). The pumps used in both groups were automatic electronic drug injection pumps (ZZB-II type; Jiangsu Aipeng Medical Equipment Co., Ltd., Jiangsu, China).

An investigator blinded to the group allocation recorded the variables, including the patients' baseline age, height, and weight; preoperative pH, partial pressure of oxygen (PaO_2), and partial pressure of carbon dioxide ($PaCO_2$); surgery duration and blood loss; and mean arterial pressure (MAP) and entropy index every 5 minutes. Blood samples were collected in ethylenediaminetetraacetic acid tubes before the surgery and at 1 and 3 hours after the beginning of surgery. The blood samples were immediately centrifuged after

collection at 3000 rpm for 10 minutes at 4°C. The plasma was thereafter stored at −80°C for future analysis. The plasma levels of interleukin (IL)-6, IL-10, NE, CORT, and ACTH were measured using commercially available quantitative sandwich enzyme-linked immunosorbent assay kits (Quantikine; R&D Systems, Minneapolis, MN, USA).

Another investigator, who acted as the postoperative interviewer, recorded the extubation time, the observer's assessment of alertness/sedation (OAA/S) scores at the time of extubation and after 20 minutes, and the pain scores using a 100-mm visual analogue scale (VAS) at 24 and 48 hours after the operation.

The sample size was calculated based on the following assumptions. The primary outcome measure was the plasma level of stress hormones. The mean postoperative plasma level of CORT was 750 ± 45 ng/mL in patients undergoing radical oesophagectomy under TIVA in our hospital. According to our preliminary study, we assumed that the postoperative plasma level of CORT in the TIVA+TEA group would be reduced by 15% compared with that in the TIVA group. A sample size of 20 patients per group was required for a 2-tailed α of 0.05 and β of 0.10. We thus planned to enrol 40 patients in this study.

Surgery and anaesthesia

After arrival in the operating room, all patients underwent standard examinations including electrocardiography, pulse oxygen saturation, and noninvasive blood pressure monitoring (GE Datex-Ohmeda S/5 Anaesthesia Monitor; GE Healthcare Finland Oy, Helsinki, Finland). An entropy sensor was applied to every patient's forehead and connected to the Datex-Ohmeda S/5 Entropy Module (GE Healthcare Finland Oy). Using the new entropy monitor, two parameters were calculated: state entropy (SE), which reflects the hypnotic level of anaesthesia and is computed using an electroencephalographic range of 0.8 to 32 Hz, and response entropy (RE), which includes an electroencephalographic and forehead muscle electromyographic component and is calculated using a range of 0.8 to 47 Hz. The electromyographic activity during general anaesthesia indicates the patients' arousal and response to pain stimulation.[15] Central venous catheters were inserted before surgery. The patients received a volume preload with hydroxyethyl starch (6% HES 130/0.4) at 10 mL/kg. The ratio of crystal to colloidal fluids was 2:1 during surgery.

In the TIVA+TEA group, a thoracic epidural catheter was introduced into the T6–7 interspace under sterile conditions and advanced 3 cm cephalad by an experienced anaesthetist. A test dose of 5 mL of 1% lidocaine was administered via the catheter 10 minutes later, followed by 5 mL of 0.375% ropivacaine. The neuraxial block was subsequently maintained with 0.375% ropivacaine at 5 mL/hour throughout the surgical procedure.

In both groups, general anaesthesia was induced using an intravenous injection of midazolam (0.03 mg/kg), fentanyl (3–4 μg/kg), and propofol plasma target-controlled infusion [target effect site concentration (Ce) of 3.0–3.5 μg/mL] using a Graseby target-controlled infusion pump (Sims Graseby Limited, Waterford, Hertsfordshire, UK). Tracheal intubation was facilitated with 0.2 to 0.3 mg/kg of cisatracurium when the RE and SE values decreased to <45. The target plasma propofol concentration was adjusted to maintain RE and SE values of 40 to 60 during the surgery. The Ce for propofol was 2.0 to 5.5 μg/mL during the surgery. If the RE and SE values were not within a given range for at least 1 minute or clinical signs of inadequate anaesthesia developed (e.g., patient movement, tearing, coughing, or sweating), we treated the patient by

increasing or decreasing the Ce of propofol in 0.5-μg/mL increments. Neuromuscular blockade was guided by train-of-four monitoring. Cisatracurium was added in 4-mg increments when needed. Interventions for cardiovascular instability were performed if the blood pressure deviated by >30% of its preoperative baseline value for >5 minutes.

Statistical analysis

All statistical analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA). The primary outcome measure was whether TIVA+TEA could attenuate stress-induced immunosuppression in patients undergoing radical oesophagectomy. The patients' age, height, and weight; surgery duration; intraoperative fentanyl consumption; extubation time; and blood loss were analysed using an independent-samples t test. The plasma levels of CORT, ACTH, NE, IL-6, and IL-10; the VAS and OAA/S scores; the RE, SE, and MAP values during the entire operation; and the pH, PaO_2, and $PaCO_2$ were compared using repeated-measures analysis of variance. All data are expressed as mean ± standard deviation, and a p value of <0.05 was considered statistically significant.

Results

From May to September 2015, 40 patients were recruited, all of whom completed the study protocol, and the data from all patients were included in the final analysis. A CONSORT diagram illustrating the patient flow through the study is shown in Figure 1. The patients ranged in age from 20 to 65 years and had an American Society of Anesthesiologists physical status of I to III. The two study groups were similar with regard to the mean age, height, weight, surgery duration, and blood loss (Table 1); RE, SE, and MAP values during the entire operation (Figure 2); and pH, PaO_2, and $PaCO_2$ before and after the operation (Table 2).

The plasma levels of ACTH, CORT, IL-6, and NE were significantly higher 3 hours after the beginning of surgery in the TIVA group than TIVA+TEA group ($p = 0.028$, $p = 0.046$, $p < 0.001$, and $p < 0.001$, respectively) (Figure 3(a)–(d)). The plasma concentration of IL-10 was

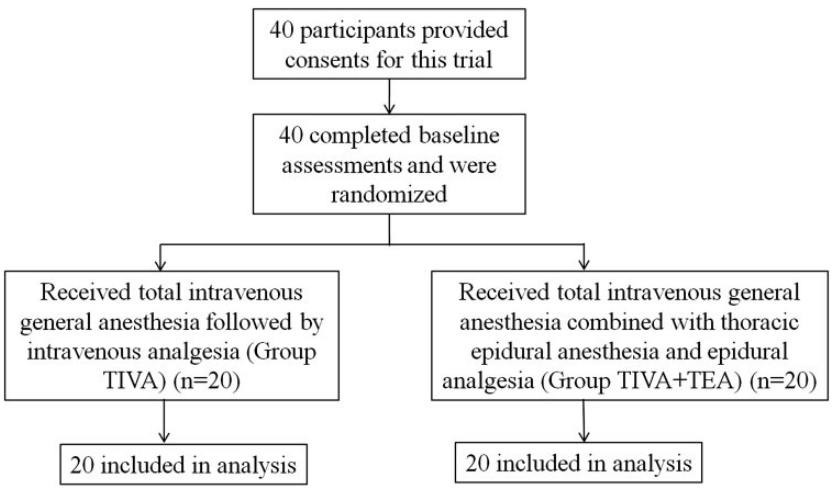

Figure 1. CONSORT diagram illustrating the patient flow in the present study. TEA, thoracic epidural anaesthesia and analgesia; TIVA, total intravenous general anaesthesia.

Table 1. Patients' baseline data.

	TIVA+TEA group $n = 20$	TIVA group $n = 20$	p value
Age (years)	55.7 ± 13.8	55.6 ± 14.2	0.982
Height (cm)	167.9 ± 7.6	165.2 ± 7.5	0.262
Weight (kg)	61.6 ± 10.1	60.0 ± 8.9	0.595
Duration of operation (hours)	3.9 ± 0.4	4.0 ± 0.5	0.745
Extubation time (minutes)	6.4 ± 1.7	10.8 ± 3.0	<0.001*
Blood loss (mL)	457 ± 198	450 ± 127	0.888
Fentanyl (mg)	0.33 ± 0.04	0.51 ± 0.04	<0.001*

Data are presented as mean ± standard deviation. *$p < 0.05$ was considered statistically significant versus TIVA. TIVA, total intravenous general anaesthesia; TEA, thoracic epidural anaesthesia and analgesia.

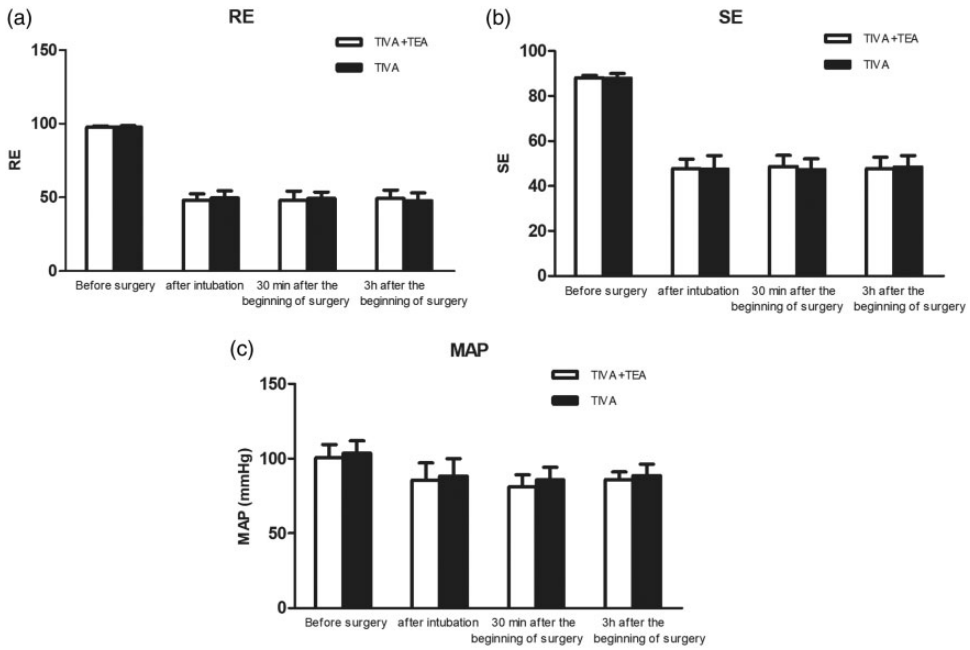

Figure 2. Comparison of the RE, SE, and MAP levels. Comparison of (a) RE, (b) SE, and (c) MAP levels before and during the surgery between the TIVA+TEA group and TIVA group. RE, response entropy; SE, state entropy; MAP, mean arterial pressure; TIVA, total intravenous general anaesthesia; TEA, thoracic epidural anaesthesia and analgesia.

significantly lower at 3 hours after the beginning of surgery in the TIVA group than TIVA+TEA group ($p = 0.039$) (Figure 3(e)). The intraoperative fentanyl consumption and extubation time were significantly higher and longer, respectively, in the TIVA group than TIVA+TEA group ($p < 0.001$) (Table 1). The VAS scores at 24 and 48 hours were significantly higher in the TIVA group than TIVA+TEA group ($p < 0.001$) (Table 2). The OAA/S scores at extubation and after 20 minutes were significantly lower in the TIVA group than TIVA+TEA group ($p < 0.001$) (Table 2).

Table 2. Patients' variables.

	TIVA+TEA group $n = 20$	TIVA group $n = 20$	p value
pH before surgery	7.37 ± 0.02	7.38 ± 0.02	0.328
pH after surgery	7.36 ± 0.04	7.33 ± 0.02	
PaO_2 before surgery (mmHg)	87.4 ± 7.4	89.9 ± 9.8	0.121
PaO_2 after surgery (mmHg)	86.3 ± 6.7	76.7 ± 10.9	
$PaCO_2$ before surgery (mmHg)	34.4 ± 3.9	33.3 ± 3.2	0.798
$PaCO_2$ after surgery (mmHg)	36.7 ± 3.7	38.3 ± 4.5	
OAA/S immediately after extubation	3.5 ± 0.5	2.6 ± 0.5	<0.001*
OAA/S 20 minutes after extubation	4.3 ± 0.5	3.8 ± 0.6	
VAS score 24 hours after surgery (mm)	15.7 ± 5.9	24.7 ± 7.3	<0.001*
VAS score 48hours after surgery (mm)	21.5 ± 4.8	31.5 ± 5.4	

Data are presented as mean ± standard deviation. *$p < 0.05$ was considered statistically significant versus TIVA. OAA/S, observer's assessment of alertness/sedation score; VAS, visual analogue scale; TIVA, total intravenous general anaesthesia; TEA, thoracic epidural anaesthesia and analgesia; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide.

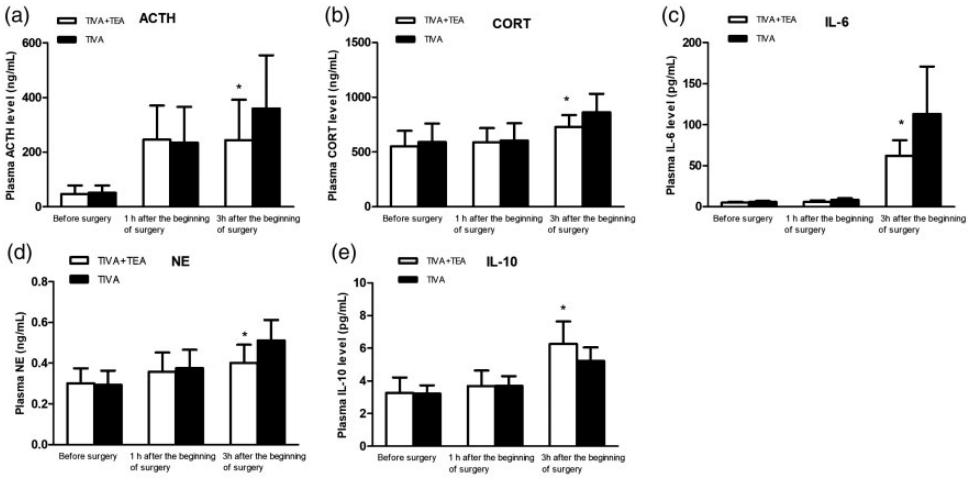

Figure 3. Comparison of ACTH, CORT, IL-6, NE, and IL-10 levels. Plasma (a) ACTH, (b) CORT, (c) IL-6, (d) NE, and (e) IL-10 levels before surgery, 1 hour after the beginning of surgery, and 3 hours after the beginning of surgery were measured between the TIVA+TEA group and TIVA group using enzyme-linked immunosorbent assay. *$p < 0.05$ was considered to be statistically significant versus TIVA. ACTH, adrenocorticotropic hormone; CORT, cortisone; IL, interleukin; NE, norepinephrine; TIVA, total intravenous general anaesthesia; TEA, thoracic epidural anaesthesia and analgesia.

Discussion

The results of the present study confirm that intraoperative thoracic epidural anaesthesia and postoperative epidural analgesia can reduce the stress response during surgery and postoperative pain in patients undergoing radical oesophagectomy by optimising the pain control and fentanyl consumption. These are similar to the findings of previous studies.[16,17] To date, no published prospective human trials have

been designed to investigate whether TEA attenuates the stress response and postoperative pain in patients undergoing radical oesophagectomy using the entropy index to maintain the depth of anaesthesia at a pre-defined level.

Although surgical excision is the most effective treatment, a very small number of tumour cells may remain after curative resection. These tumour cells can be either microscopic deposits at the surgical margins or micrometastases.[18] Studies involving humans have demonstrated that surgery itself can promote the development of metastases by inhibiting natural killer (NK) cell activity.[19] Furthermore, adjuvant oncological treatment (chemotherapy, radiotherapy, or both) is not usually initiated in the immediate postoperative period, leaving a window for possible micrometastases.[10,20,21] Although whether anaesthetic and analgesic techniques can affect cancer recurrence or metastasis remains controversial,[22] many studies have focused on the perioperative factors that may be modified to tip the balance in favour of reduced cancer spread and recurrence.[23–25] Johnson et al.[24] found that lidocaine decreased pulmonary metastasis when combined with sevoflurane anaesthesia, perhaps via anti-inflammatory and anti-angiogenic effects, in a 4T1 murine model of breast cancer. Cho et al.[25] found that propofol anaesthesia with postoperative ketorolac analgesia had a favourable impact on immune function compared with sevoflurane anaesthesia and postoperative fentanyl analgesia in patients undergoing breast cancer surgery.

Surgical stress-induced release of hormones, such as ACTH and CORT, exerts inhibitory effects on immune function. Monocytes, macrophages, and T cells have glucocorticoid receptors that promote cellular signalling to inhibit the production of representative T-helper cell 1 cytokines, such as IL-6, and to produce T-helper cell 2 cytokines, such as IL-10.[7] Stress hormones such as CORT and NE play a key role in stress-induced suppression of the acquired immune system.[8,26,27] Our research revealed that the plasma levels of stress hormones were significantly lower in the patients who received TIVA+TEA than in those who received TIVA alone.

Postoperative pain was shown to facilitate metastatic spread of cancer in a live animal model.[28] Our study indicated that the pain evaluation scores on a 100-mm VAS were significantly higher in the TIVA group than in the TIVA+TEA group at 24 and 48 hours after the operation. Therefore, TEA benefited the patients with reduced VAS scores and less opioid consumption. The effect of regional anaesthesia on human breast cancer cells in vitro has been examined.[29] The beneficial effect of spinal anaesthesia on lung tumour retention in rats undergoing laparotomy was demonstrated in another study.[30] The authors concluded that the surgical stress in rats promoted the development of metastases and that this effect was markedly attenuated by regional anaesthesia.[30] Epidural anaesthesia attenuates stress-induced immunosuppression by blocking the nociceptive stimulation and sympathetic conduction and by the local anaesthetic drug effect because the local anaesthetic drug itself has an anti-inflammatory and anticancer cell growth effect. A previous study revealed that ropivacaine suppresses the in vitro growth of cancer cells in patients with ulcerative colitis.[31]

In the present study, the TIVA+TEA group showed higher OAA/S scores and a shorter emergence time compared with the TIVA group. The combination of TIVA and TEA provided better analgesia. The adequate analgesia and haemodynamic stability in the TIVA+TEA group led to lower doses of propofol and fentanyl. Opioid administration has been shown to suppress cell-mediated and humoral immunity.[32]

This includes NK cell activity, production of immune-stimulating cytokines, phagocytic activity, and antibody production.[33] In addition, opioids suppress postoperative NK-cell cytotoxicity in humans.[34] This opioid effect may be mediated by the neuroendocrine response. Healthy volunteers have also exhibited suppression of components of their cell-mediated immunity, including NK-cell cytotoxicity, by morphine infusion.[35] Therefore, our study revealed that the administration of TIVA+TEA can reduce opioid consumption and postoperative pain scores and improve the comfort and satisfaction of patients with cancer.

The present study had some limitations. First, the follow-up time was limited to 48 hours postoperatively. Longer-term follow-up observations would have yielded more complete, favourable, and persuasive evidence. Second, whether the postoperative pain relief was caused by epidural anaesthesia or epidural analgesia remains unknown. Third, postoperative hormonal changes need further study.

In summary, TIVA+TEA ameliorates the intraoperative inflammatory stress response and postoperative pain in patients undergoing radical oesophagectomy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Supplemental Material

Supplemental material for this article is available online.

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