

Research Article

# Dexmedetomidine with sufentanil in intravenous patient-controlled analgesia for relief from postoperative pain, inflammation and delirium after esophageal cancer surgery

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**Background and aims:** Postoperative pain can cause serious adverse reactions that severely affect postoperative outcome. The present study evaluated the effect of dexmedetomidine (DEX) added to sufentanil in intravenous patient-controlled analgesia (PCA) on the relief of pain and inflammatory responses during postoperative recovery of patients undergoing a combined thoracoscopic-laparoscopic esophagectomy (TLE). **Methods:** Sixty patients undergoing TLE were randomly allocated to receive 1 µg/ml of sufentanil alone (Group S) or 1 µg/ml of sufentanil plus 2.5 µg/ml of DEX (Group D) for postoperative intravenous (IV) PCA. Postoperative pain relief, cumulative PCA requirements, inflammatory marker levels, delirium and recovery were assessed. **Results:** A joint DEX and sufentanil regimen significantly reduced the area under the curve of numerical rating scores for pain at rest (NRSR) and coughing (NRSC) at 1–48 h postoperatively ( $P = 0.000$ ) that were associated with lower PCA-delivered cumulative sufentanil consumption and less PCA frequency until 48 h postoperatively ( $P < 0.05$  and  $P < 0.0001$ , respectively). The simultaneous administration of DEX and sufentanil significantly reduced plasma IL-6 and TNF- $\alpha$  concentrations and increased IL-10 level ( $P < 0.0001$ ,  $P = 0.0003$  and  $P = 0.0345$ , respectively), accompanied by better postoperative delirium categories and health statuses of patients ( $P = 0.024$  and  $P < 0.05$ , respectively). There was no hypotension, bradycardia, respiratory depression or oversedation in Group D. **Conclusion:** Patients receiving DEX in addition to IV PCA sufentanil for TLE exhibited better postoperative analgesia, fewer inflammatory responses and lower postoperative delirium categories and better health statuses.

## Introduction

Although combined thoracoscopic-laparoscopic esophagectomy (TLE) involves a relatively smaller incision, causes lesser pain and lesser inflammatory responses, and requires lesser recovery times compared with a traditional Ivor-Lewis esophagectomy, postoperative pain and inflammatory responses remain the common problems after esophagectomy, which severely affect patients' postoperative recovery [1–3]. Systemic opioids in intravenous (IV) patient-controlled analgesia (PCA) are widely used; however, their unsatisfactory pain control and apparent side effects limit their application. A combination of an adjunct drug and an opioid in IV PCA is an effective regimen for pain management; it is gaining worldwide popularity in current clinical practices [4]. Dexmedetomidine (DEX) is a highly selective  $\alpha_2$  receptor agonist

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with sedative, analgesic, anxiolytic and sympatholytic properties, and does not result in respiratory depression in clinical practice [5,6]. It has an analgesic-sparing effect, significantly reducing opioid requirements both during the intraoperative and postoperative periods [7,8], and may also decrease postoperative delirium. However, DEX is suggested as a promising option with procedure-specific, multimodal analgesia [9,10]. This may be particularly important in “enhanced recovery after surgery” protocols for patients undergoing TLE, where the reduction in pain and opioid consumption may hasten the recovery of pulmonary function, decrease the incidence of postoperative delirium and improve health status [11]. Thus, DEX in combination with other analgesic (e.g. sufentanil) during IV PCA may reduce the use of opioids and facilitate patients’ postoperative recovery.

However, the clinical use of DEX as an adjunct analgesic with sufentanil in IV PCA for relief of postoperative pain, inflammatory response and delirium during recovery of patients undergoing TLE has not been studied. We therefore conducted this prospective, randomized double-blind study in two tertiary-care hospitals in Hefei and Wuhan, China to explore the efficacy of DEX in addition to IV PCA sufentanil on relief of postoperative pain and inflammatory responses, as well as postoperative delirium categories and recovery following TLE.

## Materials and methods

### Study design

This prospective, randomized, double-blind clinical trial was approved by the Clinical Research Ethics Committees of The First Affiliated Hospital of University of Science and Technology of China and Renmin Hospital of Wuhan University of China and registered at the Chinese Clinical Trial Registry (ChiCTR, <http://www.chictr.org.cn>) by Chao-liang Tang (registration number, ChiCTR-TRC-14004886) on August 4, 2014. Written informed consent was obtained from all patients. Patients of either sex with American Society Anesthesiologists physical status I-III, aged between 18 and 80 years, and undergoing TLE were recruited.

### Exclusion criteria

Exclusion criteria included the following: obstructive or restrictive lung disease with FEV1/FVC% < 70%, and 50% predict  $\leq$  FEV1 < 80% predict; asthma and sleep apnea syndrome; liver or urinary bladder disorders; known allergy to the drugs used in the study; regular use of pain perception-modifying drugs and opioids or sedative medications in the week prior to surgery; known history of second- or third-degree heart block and ischemic heart diseases; difficulties with the use of PCA; known cognitive dysfunction/dementia; and BMI > 35 kg/m<sup>2</sup>.

### Anesthesia procedure

Patients were sent to the surgical room without any premedication 30 min before the surgery. Standard monitoring consisted of five-lead electrocardiography (ECG), oxygen saturation (SpO<sub>2</sub>) and non-invasive blood pressure measurements. The anesthesiologist administering the anesthetic prepared a 50-ml syringe containing 4 µg/ml of DEX. A 20-gauge intravenous cannula was inserted in the dorsum of each patient’s left hand; 0.6 µg/kg of DEX was administered, and was changed to 0.4 µg/kg/h for maintenance after 15 min. Preoxygenation with 100% oxygen was administered before induction, which was delivered through a facial mask for no less than 3 min. After the arterial line was inserted under local anesthesia, general anesthesia was induced with 0.3 mg/kg of etomidate, 0.5 µg/kg of sufentanil and 1.2 mg/kg of rocuronium. Manual facemask ventilation was continued for no less than 4 min until the jaw was relaxed and the Bispectral Index Monitoring (BIS) was less than 50 to allow the double-lumen tube intubation. As the regular thoracoscopy routine was the right in the chest, the left side of double-lumen tube was used. Auscultation and fiberoptic bronchoscopy were used to assess its correct placement. Then, the patients were connected to a mechanical ventilator with a 60% fraction of inspired O<sub>2</sub> (F<sub>i</sub>O<sub>2</sub>) during a 2-lung ventilation, along with 60–100% F<sub>i</sub>O<sub>2</sub> during 1-lung ventilation to maintain end-tidal carbon dioxide pressure (PetCO<sub>2</sub>) in the normal range. One percent sevoflurane was inhaled and the target-controlled anesthesia system (TCI) was used to administer remifentanyl (modified Minto model, Cp 2.0–3.0 ng/ml) and propofol (modified Marsh model, Cp 2.0–3.0 µg/ml) to maintain the BIS between 40 and 60 and to ensure that the mean arterial pressure (MAP) and heart rate (HR) variation did not exceed 20% of the baseline values. Next, a central venous catheter (jugular vein), an indwelling bladder catheter and a gastric tube were inserted. Hypotension (a decrease of >20% of the baseline values) was treated with 5 mg of IV ephedrine or 40 µg of phenylephrine, while bradycardia was treated with 0.5 mg of IV atropine. The same surgical team comprising three thoracic surgeons performed all the surgeries.

A total of 1 mg/kg of tramadol and 10 mg of azasetron were administered intravenously before closing the incision, and then the administration of sevoflurane and DEX was stopped. Before the patient resumed spontaneous breathing and responded to simple commands, assistance was provided with a manual ventilator. Reversal of neuromuscular

blockade was achieved with 50  $\mu\text{g}/\text{kg}$  of neostigmine and 20  $\mu\text{g}/\text{kg}$  of atropine. After meeting the standard extubation criteria, the patient's double-lumen tube was removed [12].

After extubation, patients were transferred to the post anesthesia care unit (PACU) and monitored for a minimum of 1 h postoperatively. A PCA pump (ZZB-IB, Nantong AIPU Medical Inc., China) was connected to the intravenous line and configured to administer the study drug (1 ml demand dose, 10 min lockout, without background infusion). The anesthetist in the PACU, who was unaware of the clinical nature of the study, monitored the patient and prepared a 150 ml solution in the PCA reservoir bag, containing 1  $\mu\text{g}/\text{ml}$  of sufentanil alone (Group S) or 1  $\mu\text{g}/\text{ml}$  of sufentanil plus 2.5  $\mu\text{g}/\text{ml}$  DEX (Group D). If the patient reported an NRS at rest (NRSR) of 5 or higher, the anesthetist in the PACU titrated 2 ml of the PCA solution at 5 min intervals until the Numerical Rating Scale (NRS) was 4 or less. Then, the patients were encouraged to self-administer their own PCA medications. Afterward, all patients were transferred to the intensive care unit (ICU) of the thoracic department for close monitoring over the next 48 h.

## Outcome measures

The Numerical Rating Scale (NRS) (0, no discomfort and no pain; 10, a high level of discomfort and maximum pain) [13] and the quality of recovery (QoR-15) [14], which was scored on a 11-point numerical rating scale (0–10), were explained to the patients and assessed during the preoperative visit. The QoR-15 items included: 1. "Able to breathe easy"; 2. "Been able to enjoy food"; 3. "Feeling rested"; 4. "Have had a good sleep"; 5. "Able to look after personal toilet and hygiene unaided"; 6. "Able to communicate with family or friends"; 7. "Getting support from hospital doctors and nurses"; 8. "Able to return to work or usual home activities"; 9. "Feeling comfortable and in control"; 10. "Having a feeling of general well-being"; 11. "Moderate pain"; 12. "Severe pain"; 13. "Nausea or vomiting"; 14. "Feeling worried or anxious"; 15. "Feeling sad or depressed." Patients were randomly assigned into two study groups, Group S and Group D ( $n = 30$ ), by random number table method, which was prepared by a statistician.

Patients were assessed at 1, 2, 4, 8, 12, 24 and 48 h after surgery. The cumulative PCA requirements and PCA frequency were recorded by the PCA machines. Pain intensity was evaluated with NRSR and NRS during coughing (NRSC). The PCA was used for at least 48 h, during which the patient's respiratory rate, oxygen saturation and sedation score were monitored. The Modified Confusion Assessment Method (CAM)-S scores were used to diagnose postoperative delirium, which consists of four categories: normal, mild, moderate and severe [15]. Changes in the health statuses of the patients on the second day after surgery were also assessed by QoR-15. The anesthetist administering the anesthetic in the operating room, who was blinded to the group assignment, and our analgesia nurses (member of the acute pain service, APS) who did not perform anesthesia and monitoring recorded the date.

## Blood processing and analyses

On the morning of the surgery, upon arrival in the PACU, and on the second day after the surgery, 3 ml of venous blood was collected in tubes without an anticoagulant and maintained perfectly still until serum separation. The serum was precipitated by centrifugation at 4000 rpm at 4°C for 10 min, and then the supernatant was collected and placed in a  $-80^\circ\text{C}$  cryogenic freezer for evaluation of interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels. IL-6, IL-10 and TNF- $\alpha$  levels were measured using Immulite automated chemiluminometer (Siemens Healthcare Diagnostics, Deerfeld, IL).

## Sample size

The power calculation for the study was based on the total postoperative use of sufentanil in the first 48 h, which was our primary outcome. A pilot study involving eight patients at our center found that the mean  $\pm$  standard deviation (SD) of the total postoperative administration of sufentanil in the first 48 h was  $120 \pm 35 \mu\text{g}$ . In a sample size of 52 patients, a clinically significant reduction of 30% in the total postoperative use of sufentanil at a power of 90% was observed, with a two-sided significance level of 0.05. To compensate for the possibility of dropouts, we recruited a total of 60 patients, with 30 patients per group.

## Statistical analysis

The statistical analyses were performed using SPSS Statistics 22.0 software (IBM Corp., Armonk, NY, U.S.A.). All measurement indexes were checked by a normal distribution analysis. Our secondary outcome measurement was postoperative pain relief. The NRS pain scores over the first 48 postoperative hours were expressed as areas under the curve (AUC) using the trapezoid rule and were analyzed by a Mann–Whitney  $U$  test. The demographic characteristics data, cumulative sufentanil consumptions and PCA frequency were evaluated using an unpaired  $t$ -test for

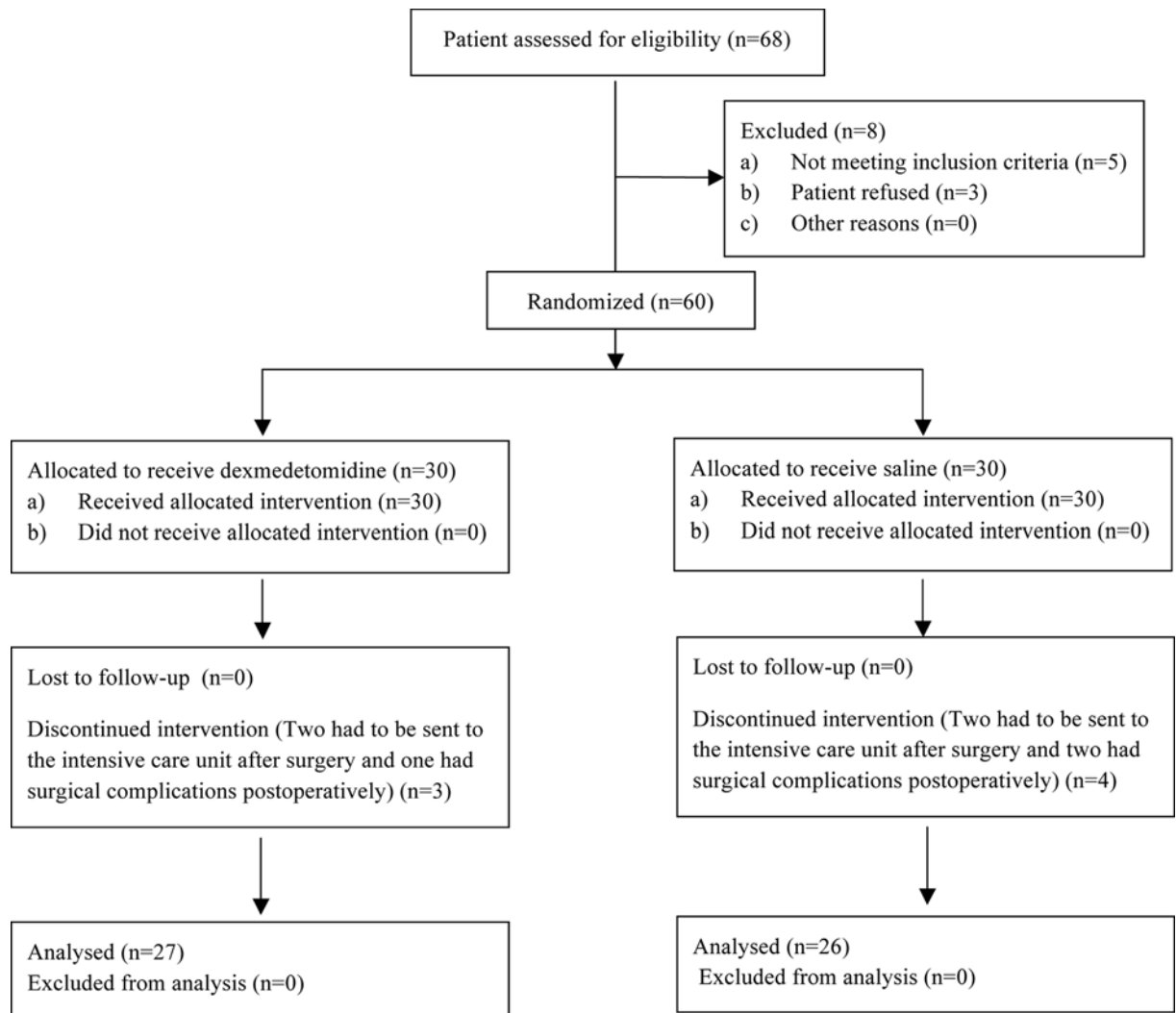


Figure 1. Flow diagram of patient recruitment

between-group comparisons and a paired *t*-test for within group comparisons. The  $\chi^2$  test was used to analyze categorical variables. A Student's *t*-test and a two-way ANOVA test were performed for unpaired quantitative variables. A *P* value < 0.05 was considered significant. For comparisons of three or more pairs, the significance level was adjusted to *P* < 0.01.

## Results

### Quantitative analysis of patients

Sixty patients were recruited from January 2016 to August 2016 and June 2018 to April 2019. Three patients in Group D dropped out of the study, two with sustained hypoxia need breathing support had to be sent to ICU after surgery, and one had postoperative bleeding need reoperation to stop bleeding. Four patients in Group S dropped out of the study, two with sustained hypoxia need breathing support had to be sent to ICU after surgery, and two had postoperative bleeding need reoperation to stop bleeding. Fifty-three patients completed the study: 27 in Group D and 26 in Group S (Figure 1). There were no significant differences in the demographic data, surgical characteristics and intraoperative variables between the two groups (Table 1).

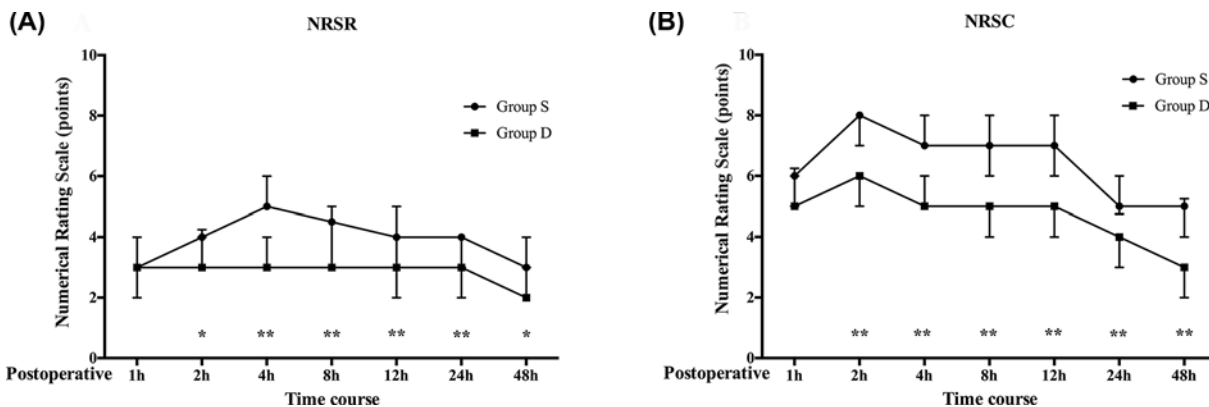
### NRSR and NRSC

NRSR and NRSC at each recorded time point are shown in Figure 2. Pain intensities were similar between groups in

**Table 1 Patient characteristics and intraoperative data**

Characteristic	Treatment groups		P value
	Group S (n = 26)	Group D (n = 27)	
Age (year)	61.1 (8.0)	61.8 (7.5)	0.757
Male	13 (50%)	15 (56%)	0.685
Weight (kg)	66.9 (8.2)	64.7 (10.0)	0.391
Height (cm)	166.4 (9.7)	168.3 (8.9)	0.466
ASA class I/II/III	9/16/1	8/17/2	0.817
<b>Procedures</b>			
Laparoscopy (n)	24 (92%)	24 (89%)	0.670
Maximal laparoscopy pressure (mmHg)	13.0 (0.85)	13.2 (0.74)	0.399
Trocars (n)	3.0 (0.43)	3.0 (0.42)	0.942
Drainage tube (n)	2.2 (0.37)	2.1 (0.32)	0.654
Duration of anesthesia (min)	301.2 (45.6)	297.0 (40.0)	0.726
Duration of surgery (min)	265.8 (46.6)	268.1 (42.0)	0.851
Blood loss (ml)	168.0 (28.1)	165.3 (20.4)	0.687
Fluids (ml)	2142 (496)	2169 (595)	0.857
Urine output (ml)	546 (193)	620 (232)	0.216

Values are mean (SD) or number. All variables were similar between the two groups.



**Figure 2. Numerical rating scores for pain at rest (NRSR) and coughing (NRSC) at 1-48 h postoperatively**

Postoperative numerical rating scale pain scores (A) at rest and (B) during coughing episodes during a 48 h postoperative period. Data are median with error bars showing IQR; \* $P < 0.05$ , \*\* $P < 0.01$ .

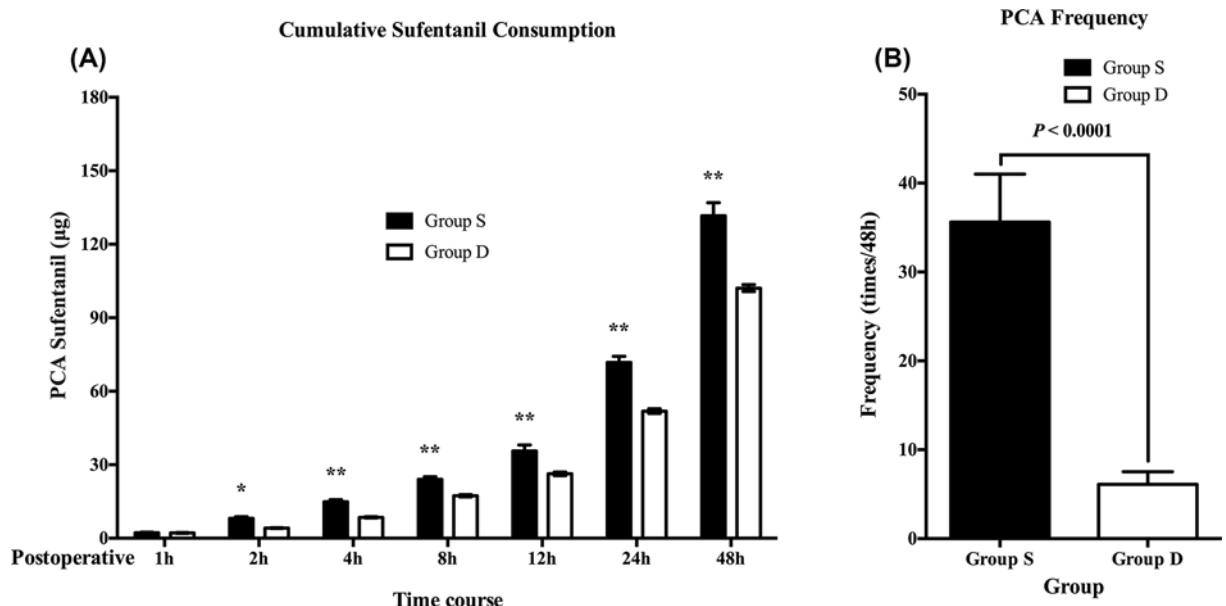
**Table 2 Postoperative area under the curve (AUC) for numerical rating scale (NRS) pain score at rest and during coughing in patients receiving dexmedetomidine or saline**

Characteristic	Treatment groups		P value
	Group S (n = 26)	Group D (n = 27)	
Pain scores at rest			
AUC NRSR 1-60 min	3.0 (0.8)	2.7 (0.7)	0.201
AUC NRSR 1-48 h	174.3 (30.3)	122.6 (21.4)	0.000
Pain scores during coughing			
AUC NRSC 1-48 h	272.1 (42.9)	186.2 (26.3)	0.000

Values are mean (SD).

the first hour following surgery. However, when AUC for NRSR and NRSC pain scores for 1-48 h were compared, the scores were significantly lower in Group D than in Group S ( $P = 0.000$ ) (Table 2).





**Figure 3. The cumulative PCA sufentanil requirements and PCA frequency**

Cumulative intravenous sufentanil consumption ( $\mu\text{g}$ ) delivered by PCA (A) and the PCA frequency (B) during a 48 h postoperative period in patients receiving dexmedetomidine or saline. Values are expressed as means (95% CI); \* $P < 0.05$ , \*\* $P < 0.01$ .

**Table 3 Postoperative delirium categories based on the Confusion Assessment Method (CAM)-S scores**

Groups	Normal	Mild	Moderate	Severe	$\chi^2$	P value
Group S (n = 26)	16	1	5	4	9.399	0.024
Group D (n = 27)	22	4	1	0		

### Cumulative PCA sufentanil and PCA frequency

Patients in Group D required significantly less PCA sufentanil than those in Group S at all times in the study. During the 0–24 h postoperative period, cumulative PCA sufentanil use was 28% more in Group S than in Group D [95% CI of difference was 16.49–23.19,  $P < 0.0001$ ], while 22% more [95% CI of difference was 26.15–32.85,  $P < 0.0001$ ] during the 0–48 h postoperative period. (Figure 3A). The PCA frequency was consistently significantly lesser in Group D than in Group S from the second postoperative hour onwards and throughout the study (Figure 3B). No hypotension or bradycardia was observed after PCA use.

### Postoperative delirium categories

Postoperative delirium categories based on the Confusion Assessment Method (CAM)-S scores are shown in Table 3. More patients from Group S than Group D had serious delirium. Furthermore, postoperative delirium occurred in 10 (38.5%) out of 26 patients receiving saline, and in 5 (19%) out of 27 patients receiving dexmedetomidine ( $P = 0.024$ ).

### Changes in the health statuses

Changes in the health statuses of the patients before surgery (preoperative baseline) and on the second day after surgery (postoperative) are shown in Table 4. Compared with the preoperative statuses, all of the QoR-15 items of Group S, with the exception of the seventh (getting support from hospital), became significantly worse ( $P < 0.05$  or  $P < 0.01$ ), while the incidences of severe pain, nausea or vomiting and mood changes were not significantly different in Group D (Figure 4A,B). The health statuses of the patients before surgery were comparable in both groups (Figure 4C). Compared with Group S, all of the QoR-15 items, with the exception of the seventh (getting support from hospital), were significantly better in Group D ( $P < 0.05$ ) (Figure 4D). No hypotension, or bradycardia and somnolence, or respiratory depression was reported in the present study. None of the adverse events warranted terminating PCA use.

**Table 4** Change in health status of patients before surgery (preoperative baseline) and again on the second day after surgery (postoperative)

QoR-15 Items*	Group S (n = 26)		Group D (n = 27)	
	Preoperative	Postoperative	Preoperative	Postoperative
1. Able to breathe easy	8.73 ± 0.28	6.42 ± 0.20	8.85 ± 0.23	7.78 ± 0.17
2. Been able to enjoy food	6.77 ± 0.34	2.54 ± 0.24	6.59 ± 0.34	3.82 ± 0.25
3. Feeling rested	6.39 ± 0.28	3.73 ± 0.24	6.63 ± 0.27	4.96 ± 0.22
4. Have had a good sleep	5.61 ± 0.29	3.04 ± 0.30	5.93 ± 0.31	4.33 ± 0.25
5. Able to look after personal toilet and hygiene unaided	9.50 ± 0.10	2.65 ± 0.35	9.57 ± 0.10	3.96 ± 0.17
6. Able to communicate with family or friends	9.46 ± 0.11	5.27 ± 0.27	9.52 ± 0.11	6.52 ± 0.23
7. Getting support from hospital doctors and nurses	9.23 ± 0.14	9.04 ± 0.18	9.26 ± 0.13	9.07 ± 0.15
8. Able to return to work or usual home activities	7.12 ± 0.28	1.27 ± 0.09	7.44 ± 0.28	2.37 ± 0.14
9. Feeling comfortable and in control	7.54 ± 0.26	4.65 ± 0.32	7.78 ± 0.27	5.82 ± 0.23
10. Having a feeling of general well-being	7.08 ± 0.32	3.15 ± 0.25	7.15 ± 0.29	4.33 ± 0.25
11. Moderate pain	8.31 ± 0.27	5.92 ± 0.41	8.33 ± 0.28	7.30 ± 0.21
12. Severe pain	9.16 ± 0.15	7.54 ± 0.28	9.19 ± 0.15	8.67 ± 0.14
13. Nausea or vomiting	9.15 ± 0.15	8.00 ± 0.49	9.52 ± 0.14	8.96 ± 0.26
14. Feeling worried or anxious	7.15 ± 0.29	5.50 ± 0.30	7.11 ± 0.28	6.70 ± 0.23
15. Feeling sad or depressed	8.04 ± 0.15	6.80 ± 0.30	8.00 ± 0.14	7.89 ± 0.15
Total	120 ± 1.0	76 ± 1.3	121 ± 1.0	92.5 ± 0.9

Mean ± SEM unless otherwise stated.

\*Each scored on an 11-point numerical rating scale (0–10). QoR = quality of recovery.

## IL-6, IL-10 and TNF- $\alpha$ plasma concentrations

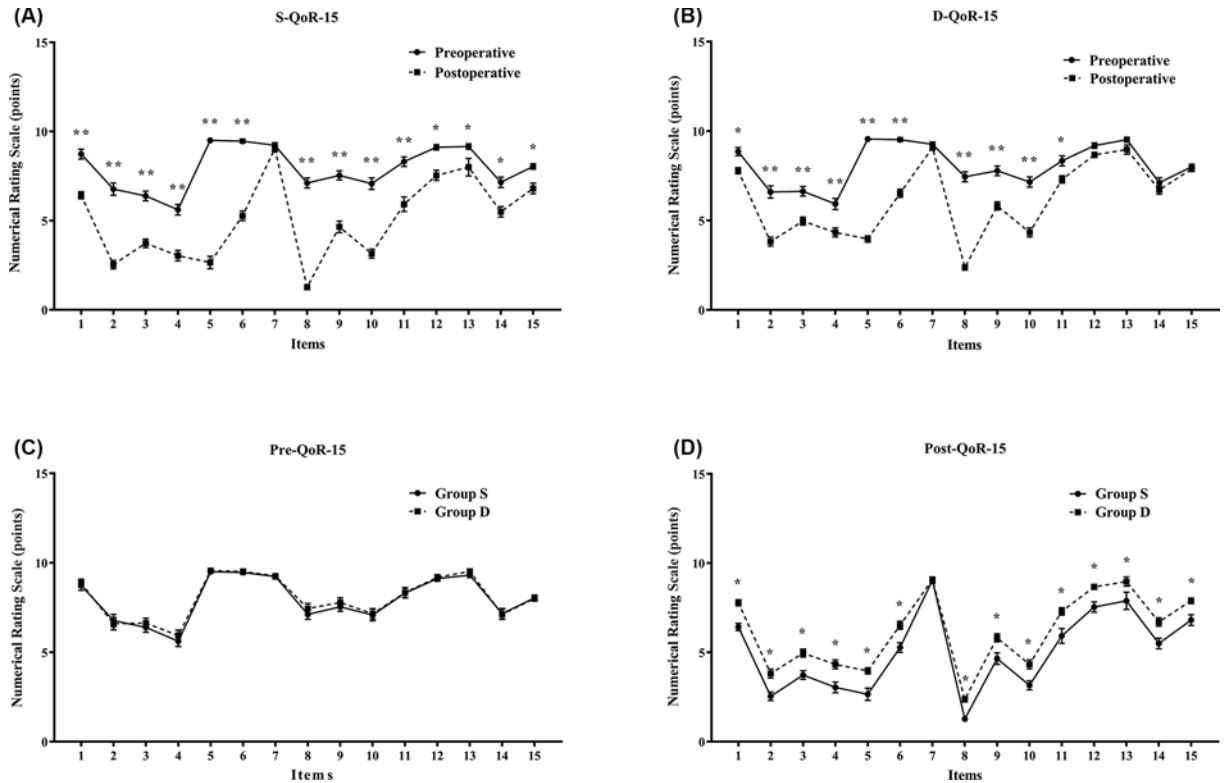
Plasma concentrations of IL-6, IL-10 and TNF- $\alpha$  were not different between the groups during preoperative and 0.5 h postoperative periods, and they all increased in both groups during the postoperative period compared with the preoperative period. IL-6 and TNF- $\alpha$  levels were significantly lower in Group D during the 24 h postoperative period ( $P < 0.0001$  and  $P = 0.0003$ , respectively), while IL-10 was higher in Group D ( $P = 0.0345$ ) (Figure 5).

## Discussion

This randomized, double-blinded comparative study was performed to evaluate the use of DEX in conjunction with sufentanil using IV PCA in TLE. Our principal findings suggest that a DEX-sufentanil mixture significantly reduces postoperative resting and pain due to coughing; enhances the analgesic effect of sufentanil; reduces the PCA sufentanil requirements and the coexisting sufentanil-induced nausea, without inducing clinically relevant bradycardia or hypotension, oversedation or respiratory depression; decreases the incidence of delirium and inflammatory responses after surgery; and improves patient recovery.

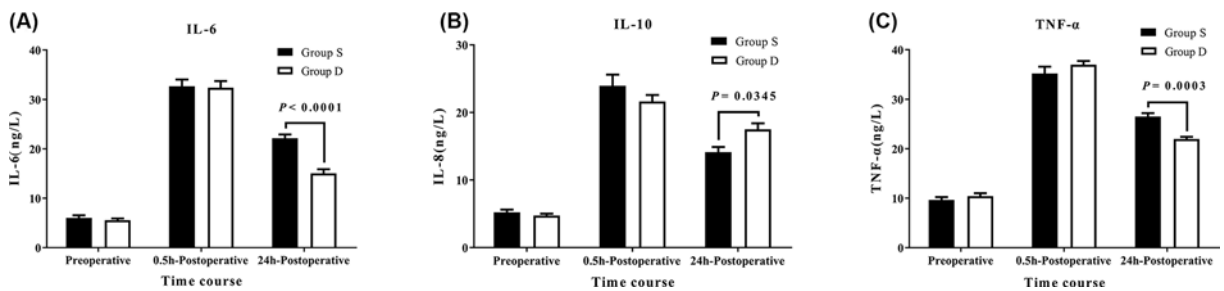
The opioid-sparing effects of DEX have been studied in conscious healthy volunteers and surgical patients [8,13,16,17]. Our finding that patients receiving DEX required 28% less sufentanil via PCA, provided additional evidence for the anesthetic-sparing effect of DEX in clinical practice, which was also associated with reduced postoperative pain in our present study. However, previous studies demonstrated that intravenous DEX has a postoperative opioid-sparing effect but has no impact on the reduction of pain [18]. In the present study, all patients were encouraged to push the PCA button to achieve an equal NRSR  $\leq 4$  between 2 and 48 h after the surgery. Patients receiving a DEX-sufentanil mixture administered via PCA experienced significantly lower AUCs for NRSR and NRSC pain scores during a 1–48 h postoperative period. In the present study, DEX also significantly improved the subjective quality of sleep, while sedation levels were similar between the groups. An analgesic action, rather than a sedative effect, was more likely to correspond for the reduced sufentanil requirements by DEX. The different effects of DEX on postoperative pain between our study and previous studies may be due to different combinations of other anesthetics with DEX, and may also be due to the different doses of DEX used in those studies [19,20].

The main concern related to DEX administered via IV PCA is that it is unnecessary or that it may lead to excessive sedation. Fortunately, there was no evidence of an excessive sedative effect of DEX during the course of PCA used in the present study. This may be because the doses of DEX used in conjunction with sufentanil via PCA were well within a quarter range of the recommended maintenance infusion (0.2–0.7  $\mu\text{g}/\text{kg}/\text{h}$ ) for intensive care sedation [21–23]. These sedative doses of DEX were associated with adverse events, especially hypotension and bradycardia [24]. In



**Figure 4. Quality of recovery by QoR-15 analysis**

Changes in health statuses of patients before surgery (preoperative baseline) and again on the second day after surgery (postoperative). Preoperative versus postoperative health statuses, the QoR-15 items of (A) Group S, (B) Group D; and the QoR-15 items of Group S versus Group D, (C) preoperative health statuses, (D) postoperative health statuses. Values are expressed as means (SEM); \* $P < 0.05$ , \*\* $P < 0.01$ . Quality of recovery (QoR)-15 items included the following (14): 1. 'Able to breathe easy'; 2. 'Able to enjoy food'; 3. 'Feeling rested'; 4. 'Able to sleep well'; 5. 'Able to look after personal toilet and hygiene unaided'; 6. 'Able to communicate with family or friends'; 7. 'Getting support from hospital doctors and nurses'; 8. 'Able to return to work or usual home activities'; 9. 'Feeling comfortable and in control'; 10. 'Having a feeling of general well-being'; 11. 'Moderate pain'; 12. 'Severe pain'; 13. 'Nausea or vomiting'; 14. 'Feeling worried or anxious'; 15. 'Feeling sad or depressed' (each scored on a 11-point numerical rating scale 0–10).



**Figure 5. Plasma IL-6, IL-10 and TNF- $\alpha$  concentrations between the groups**

Changes in plasma (A) interleukin-6 (IL-6), (B) interleukin-10 (IL-10), and (C) tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels in patients receiving dexmedetomidine or saline. Values are expressed as means  $\pm$  SEM.

addition, the reduced cumulative sufentanil requirements administered via PCA may also play an important role in mitigating sedation. In contrast, the PCA-based drug delivery system, which has its own safe individual drug titration, may also help minimize sedation [25].

The pro-inflammatory cytokines (PICs), such as IL-6 and TNF- $\alpha$ , and the anti-inflammatory cytokine, IL-10, are important groups of inflammatory mediators and play an essential role in pain sensitization [26–28]. Systemic or



regional analgesic regimens could prevent both peripheral and central sensitization, thereby attenuating the postoperative amplification of pain sensation [16,29,30]. Significantly increased IL-6, IL-10 and TNF- $\alpha$  serum levels were detected in our patients during the 0.5 h postoperative period in both groups. Group D had lower pro-inflammatory cytokine levels and higher anti-inflammatory cytokine levels compared with Group S during the 24 h postoperative period. This result was consistent with our findings of postoperative NRSR and NRSC pain scores, which indicated that Group D had significantly lower NRSR and NRSC pain scores during the 2–48 h postoperative period than Group S. Our results suggest that a DEX–sufentanil mixture administered via PCA would be effective in reducing an inflammatory response, which would also reduce postoperative pain sensitization.

Postoperative delirium, which is characterized by dysfunction in consciousness, attention and cognition, is always regarded as a reversible cognitive dysfunction syndrome [31]. It is a common complication in elderly patients, especially 1–3 days after a surgery. Excessive and prolonged postoperative delirium may influence a patient's recovery [32–34]. In the present study, we used CAM-S scores, a quite rigorous assessment system, to diagnose postoperative delirium. Furthermore, postoperative delirium occurred in 6 (23%) out of 26 patients receiving saline, similar to previous studies, [35–37] and in 5 (19%) out of 27 patients receiving DEX. Although the incidence of postoperative delirium may not be significant, patients receiving DEX had lower moderate and severe categories of postoperative delirium compared with patients receiving saline (1 and 0 vs 5 and 4). A higher PCA frequency resulted in patients receiving saline also receiving supplemental sufentanil, which might increase the risk of postoperative delirium [38]. The physiopathologic mechanism of how DEX decreases delirium remains unknown. However, its opioid-sparing and anti-inflammatory effects may provide good indications [39,40]. A good number of reasons may explain how DEX decreased postoperative delirium in our study. First, DEX intervention was initiated as soon as patients were transferred to the PACU, which prevented delirium during the early postoperative hours [41]. Second, we used DEX during the 48 h postoperative period, which improved patients' sleep quality in the evening, since a central effect of DEX converges with an endogenous sleep-promoting pathway [42].

A DEX-sufentanil mixture administered via PCA also had a beneficial effect on the recovery of bowel function and ambulation, which may have been associated with lower sufentanil consumption. Large doses of sufentanil may inhibit intestinal motility. A jejunum colostomy indicated that the incidence of nausea or vomiting was directly associated with the discomfort caused by a gastric tube and duodenal feeding tube in both groups. However, patients receiving DEX still showed less nausea or vomiting and fewer side effects from opioids. In addition, the pain caused by chest tubes and ribcage expansion may adversely affect coughing and deep breathing, which may result in respiratory complications and delay recovery [2]. On the contrary, reliable analgesia may facilitate deep breathing, clearance of secretions, promote active participation in physiotherapy and reduce respiratory complications.

There are several limitations in the present study. Although the study had a modest sample size that achieved significant differences in endpoints between the two groups, this sample size was not specifically powered to detect the effects of DEX in postoperative delirium. Furthermore, it has been noted that CAM-S might not be as sensitive as other tools, e.g. 3D-CAM, for delirium assessment, especially for other ethnic groups [43–45]. Although it is stated that in Enhanced recovery programmes (ERP) minimization of opioid administration is key, recently, paravertebral block (PVB) is also recognized as vital to reduce amount of opioids and minimize sedation and constipation in thoracic ERP [2]. And thoracic PVB with the addition of dexmedetomidine could exhibit more improved quality and duration of analgesia, as well as an analgesic sparing effect with no serious side effects [8]. Thus, future studies with larger sample sizes; more sensitive delirium assessment tools and groups with local anesthesia techniques are needed.

## Conclusion

In summary, our study indicates that a DEX–sufentanil mixture administered via PCA after esophageal cancer surgery resulted in a reduction in pain intensities at rest and during coughing episodes. In addition, a decrease in PCA sufentanil requirements resulted in reduced nausea induced by sufentanil. Using a PCA-based drug administration, DEX appears to be a promising and safe adjunct in postoperative pain control in esophageal cancer surgery, since it eliminates unwanted oversedation, attenuates inflammatory responses, implicates positive effects on postoperative delirium, and improves the quality of analgesia and recovery.

## Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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## Author Contribution

C.T. designed and executed the experiments, analyzed data, drafted and proofread the paper. X.C. designed the study and proofread the paper. Y.H. H.W. Q.G. S.S. S.W. and J.W. executed the experiments. Z.Z. and Z.W. analyzed the data.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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## Abbreviations

APS, acute pain service; AUC, area under the curve; BIS, bispectral index monitoring; CAM-S, modified confusion assessment method scores; DEX, dexmedetomidine; ECG, electrocardiography; ERP, enhanced recovery programmers; FiO<sub>2</sub>, fraction of inspired O<sub>2</sub>; HR, heart rate; ICU, intensive care unit; IL, interleukin; IV, intravenous; MAP, mean arterial pressure; NRS, numerical rating scale; NRSC, numerical rating scores for pain at coughing; NRSR, numerical rating scores for pain at rest; PACU, post anesthesia care unit; PCA, patient-controlled analgesia; PetCO<sub>2</sub>, end-tidal carbon dioxide pressure; PICs, pro-inflammatory cytokines; PVB, paravertebral block; QoR, quality of recovery; SD, standard deviation; SpO<sub>2</sub>, oxygen saturation; TCI, target-controlled anesthesia system; TLE, thoracoscopic-laparoscopic esophagectomy; TNF- $\alpha$ , tumor necrosis factor-alpha.

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