Randomized Control Trial

Whole-Course Application of Dexmedetomidine Combined with Ketorolac in Nonnarcotic Postoperative Analgesia for Patients with Lung Cancer Undergoing Thoracoscopic Surgery: A Randomized Control Trial

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Background: Opioid-based postoperative analgesia provides adequate analgesia with much adverse effects and immunosuppression. Dexmedetomidine and ketorolac have properties of opioid-sparing, antiinflammation, and immune protection.

Objectives: To investigate the efficacy and safety of whole-course application of dexmedetomidine combined with ketorolac in nonnarcotic postoperative analgesia and its effect on inflammatory response and immune function in thoracoscopic surgery of lung cancer.

Study Design: Double-blind, randomized control trial.

Setting: The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China.

Methods: Sixty patients scheduled for thoracoscopic surgery were enrolled and randomly divided into 2 groups to receive a combination of intraoperative usage of dexmedetomidine and postoperative patient-controlled intravenous analgesia of dexmedetomidine 0.1 μg/kg/h and ketorolac 3 mg/kg (DEX group) or only postoperative patient-controlled intravenous analgesia of sufentanil 1.5 μg/kg and ketorolac 3 mg/kg (SUF group) for 48 hours. Vital signs, postoperative Visual Analog Scale (VAS) score, Ramsay sedation score, patient-controlled analgesia pressing times, consumption of sufentanil and rescue drug, and complications were compared between the 2 groups. The levels of inflammatory factors and immune function were also compared.

Results: A significant reduction in median blood pressures and heart rates within 48 hours after surgery and perioperative consumption of sufentanil were observed in the DEX group compared with the SUF group ($P < 0.05$). No statistically significant difference was found in VAS scores, patient-controlled analgesia pressing times, and rescue drug consumption between the 2 groups ($P > 0.05$). The incidence of nausea was significantly lower in the DEX group compared with the SUF group ($P < 0.05$). A significant decrease of interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and increased $CD4^+$ and $CD4^+/CD8^+$ were observed in the DEX group compared with the SUF group at 24 and 48 hours after surgery ($P < 0.05$). There was no difference in the levels of $CD8^+$ and natural killer cells between the 2 groups ($P > 0.05$).

Limitations: This study was limited by its sample size.

Conclusions: Whole-course application of dexmedetomidine combined with ketorolac in nonnarcotic postoperative analgesia provided adequate and safe postoperative analgesia, reduced sufentanil consumption, analgesia-related complications, alleviated inflammatory response, and immunosuppression compared with sufentanil-based analgesia in thoracoscopic surgery.

Key words: Dexmedetomidine, ketorolac, sufentanil, thoracoscopic surgery, postoperative analgesic, patient-controlled analgesia, inflammatory response, immune function

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Currently, thoracoscopic surgery (TSS) has become the optimal choice to treat stage I-II nonsmall cell lung carcinoma (NSCLC) (1). However, patients undergoing thoracoscopic or thoracotomy surgery experience moderate to severe postoperative pain resulting in inflammatory reaction and immunosuppression (2). Also, ischemia-reperfusion injury (IRI) caused by one-lung ventilation (OLV) stimulates the inflammatory response and worsens the immune function (3).

Opioids usually result in dose-related complications, moreover immunosuppression leading to postoperative cancer recurrence (4). Nonnarcotic analgesics can reduce opioids consumption to reduce opioid-related complications and immunosuppression (5).

Dexmedetomidine (DEX) is a highly selective alpha-2 adrenergic receptor agonist that has sedative, analgesic, antisympathetic, and anesthetics-sparing properties, perioperative antiinflammatory effect, especially on IRI in lung surgery, and moreover immunoprotective effects (3,6-7).

Ketorolac (KET), a nonsteroidal antiinflammatory drug (NSAID), has been proved to have antiinflammation and opioid-sparing properties with fewer complications (8,9).

This study aims to investigate the efficacy and safety of the whole-course application of DEX combined with KET in postoperative analgesia, and its effect on inflammatory response and immune function of patients undergoing TSS.

Methods

Inclusion and Exclusion Criteria

This study was approved by the ethics committee of the First Affiliated Hospital of Dalian Medical University. The clinical trial registration number is ChiCTR1800019796. Sixty patients with lung cancer (clinical stage I-II NSCLC) who were scheduled for TSS from December 2018 to May 2019 were recruited. Written informed consent was obtained after providing patients with adequate explanations regarding the aims of the study. The inclusion criteria were as follows: American Society of Anesthesiologist (ASA) Physical Status score I to II, ages 18 to 65 years, and body mass index (BMI) < 30 kg/m^2. The exclusion criteria were as follows: history of radiotherapy-chemotherapy, immune disorders, hepatic or renal dysfunction, bradycardia (heart rate [HR] < 45 bpm), gastrointestinal (GI) ulcer or bleeding, and relevant drug allergy.

Randomization

Enrolled patients were randomly assigned according to computer-generated random assignment to receive a combination of intraoperative usage of DEX and postoperative patient-controlled intravenous analgesia (PCIA) of DEX 0.1 μg/kg/h and KET 3 mg/kg (DEX group), or only postoperative PCIA of sufentanil (SUF) 1.5 μg/kg and KET 3 mg/kg (SUF group) for 48 hours. The persons involved in the study, including statisticians, investigators, anesthesiologists, surgeons, and the patients, were blinded to the specific experimental scheme implementation.

Anesthesia Protocol

The vital signs, such as blood pressure, HR, pulse oxygen saturation, respiratory rates, and partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) were recorded. In the DEX group, a bolus intravenously infusion of 1 μg/kg DEX was given over 10 minutes before anesthesia induction, followed by a continuous infusion at a rate of 0.4 μg/kg/h until 30 minutes before the end of the surgery, whereas a placebo infusion of the same amount of normal saline solution was administered in the SUF group. In both groups, anesthesia was induced with 2 mg/kg propofol, 0.3 to 0.5 μg/kg SUF, and 0.2 to 0.3 mg/kg cisatracurium.

Anesthesia was maintained with propofol 2 to 4 mg/kg/h, remifentanil 0.1 to 0.2 μg/kg/min, and cisatracurium 0.1 to 0.15 mg/kg/h to maintain a bispectral index of 45 to 60.

The double-lumen tube was located with a fibrous bronchoscope, and ventilation parameters were modulated to maintain $P_{ET}CO_2$ of 35 to 45 mm Hg. At the end of surgery, the intercostal nerve block was done with 20 mL 0.5% ropivacaine by the same surgeon. After surgery, the patients were extubated and transmitted to the postanesthesia care unit. A dose of 5 μg SUF was administered per time when Visual Analog Scale (VAS) score > 3, until VAS ≤ 3.

Postoperative Analgesia

PCIA protocols within 48 hours after surgery were as follows: in the DEX group, 0.1 μg/kg/h DEX, 3 mg/kg KET, and 0.5 mg palonosetron; in the SUF group, 1.5 μg/kg SUF, 3 mg/kg KET, and 0.5 mg palonosetron were diluted in 100 mL normal saline solution. The infusion rate of 2 mL/h, a bolus dose of 2 mL, and lockout time 20 minutes were set. A rescue analgesic of tramadol was given when VAS score > 4.

Indicators

Hemodynamic Indicators

Mean blood pressures (MAPs) and HRs were recorded before induction (T_0), immediately after surgery (T_1), 4 hours (T_2), 12 hours (T_3), 24 hours (T_4), and 48 hours after surgery (T_5).

Analgesic and Sedative Indices

The resting and coughing VAS (0–10; 0 = no pain, 10 = the worst pain imaginable) and Ramsay sedation score (RSS) (1–6; 1 = anxious and agitated, 2 = cooperative, tranquil, oriented, 3 = responds only to verbal commands, 4 = asleep with brisk response to light stimulation, 5 = asleep without response to light stimulation, 6 = nonresponsive) at T_0-T_5 were recorded. The total and valid PCIA pressing times, the consumption of SUF and tramadol, and analgesia-related complications within 48 hours after surgery were recorded.

Inflammatory and Immune Indicators

A 5 mL sample of peripheral blood were extracted at T_0, T_1, T_4, T_5, and centrifuged at 3000 rpm for 10 minutes at 4°C to obtain the supernatant, which was later preserved at –80°C for detection. Serum concentrations of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α were measured by enzyme-linked immunosorbent assay as described by the manufacturer (R&D Systems, Inc., Minneapolis, MN), and the levels of T lymphocyte subgroups and natural killer (NK) cells were measured through immunofluorescence staining using multitest labeled antibodies.

Statistical Analyses

A pilot study was performed prior to patient recruitment to estimate an appropriate sample size. The pilot study included 20 patients, 10 in each arm. We calculated the primary outcome of the study assessed by $CD4^+/CD8^+$. The sample size of 23 patients in each group provided $\alpha = 0.05$, 90% power, and an allocation ratio = 1.0. Considering potential drop-outs, we decided to enroll 30 patients in each group for the study. The sample calculation was performed with PASS version 11.0 (PASS 11.NCSS, LLC. Kaysville, UT).

Statistical analysis was performed using SPSS 25.0 statistical software (IBM Corporation, Armonk, NY). Data were expressed as mean ± standard deviation or median (interquartile range). The Fisher exact test or the chi-square test was employed to analyze dichotomous data, the Student t-test was used for normally distributed continuous data, and the Mann–Whitney U test was used for nonparametric ordinal data. Analysis of variance for repeated measurements was performed to analyze differences in means between and within the groups. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Sixty patients were recruited by the inclusion criteria. However, 6 patients were subsequently excluded: 3 patients refused to participate, 1 patient changed to thoracic surgery, and 2 in the DEX group were lost to follow-up. Total 26 patients in the DEX group and 28 patients in the SUF group completed the study (Fig. 1). There was no significant difference between groups regarding baseline characteristics ($P > 0.05$); intraoperative profiles, such as surgical type, anesthesia, and operation duration; OLV duration; estimated blood loss; and fluid infusion ($P > 0.05$) (Table 1). SUF dosages in the DEX group was significantly lower than the SUF group (124.23 ± 14.81 μg vs. 234.64 ± 23.37 μg; $P < 0.05$) (Table 1).

Regarding the hemodynamic indicators, MAPs and HRs in the DEX group were relatively lower than in the SUF group at T_1-T_5 ($P < 0.05$) (Fig. 2).

There was no statistical difference in the resting and coughing VAS scores and PCIA pressing times between the 2 groups ($P > 0.05$) (Table 2). RSS in the DEX group was significantly higher at T_1-T_3 than the SUF group ($P < 0.05$) (Table 3). Although the incidence of total analgesic-related complications and nausea in the DEX group were statistically lower than the SUF group ($P < 0.05$) (Table 3). There was one transient hypotension needed to deal with in the DEX group. The incidence of vomiting and pruritus did not differ between the 2 groups, and no respiratory depression or oversedation was observed (Table 3).

The baseline immune function was comparable in the 2 groups ($P > 0.05$). Compared with T_0, the expression levels of $CD4^+$, $CD4^+/CD8^+$, and $CD3^+$ in both groups decreased significantly to the lowest point at T_1 ($P < 0.05$) and began to increase from T_4, which was still significantly lower ($P < 0.05$). Compared with the DEX group, the levels of $CD4^+$, $CD4^+/CD8^+$, and $CD3^+$ in the SUF group were significantly lower at T_4 and T_5 ($P < 0.05$). No significant difference was found in the level of $CD8^+$ between the 2 groups at any time point ($P > 0.05$). The level of NK cells at T_1 was significantly higher

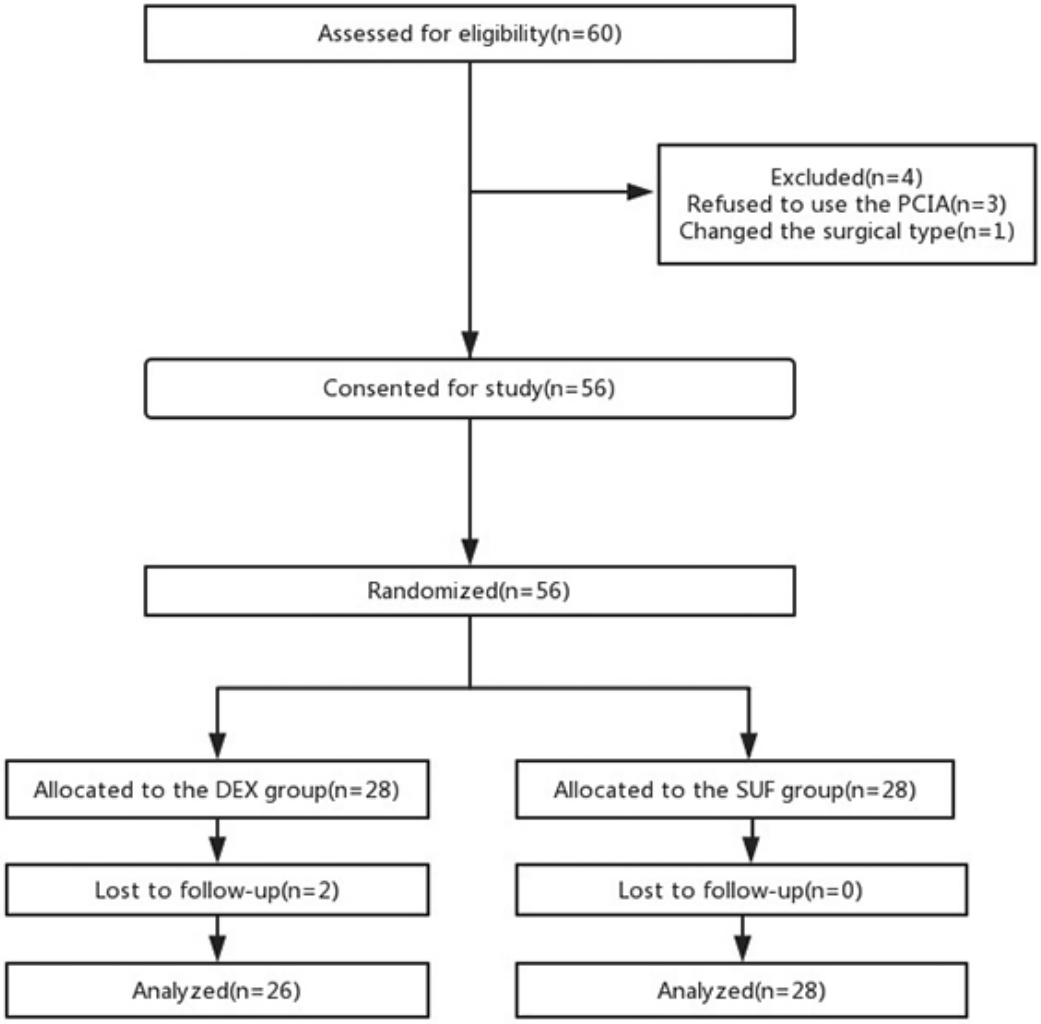

Fig. 1. *Flow chart of study inclusion.*

than at T_0 in the 2 groups ($P < 0.05$), whereas no significant differences were found between the 2 groups at any time point ($P > 0.05$) (Table 4, Fig. 3).

The preoperative inflammatory response was also comparable in the 2 groups ($P > 0.05$). Compared with T_0, the levels of IL-1β, IL-6, and TNF-α were remarkably elevated at T_1, T_4, and T_5, and the amplitude in the SUF group was significantly higher than the DEX group ($P < 0.05$) (Fig. 4).

It is therefore of great benefit for the patients' outcome if surgical trauma is minimized, adequate postoperative analgesia is achieved with a minimum dose of opioids, and inflammatory response caused by OLV is decreased.

Discussion

Patients undergoing TSS usually suffer postoperative immunosuppression, which results from the lung cancer itself, surgical trauma, usage of opioids, and postoperative pain (10). Trauma, pain, and OLV during TSS also induce inflammatory responses, which worsen the immune function (2,3), increase the implantation of surgically disseminated tumor cells and the growth of existing micrometastases (4,11).

Table 1. *Patient characteristics and intraoperative data.*

	SUF group	DEX group	*P* value
Number	28	26	
Demographics			> 0.05
Gender n/N (% female)	11/28 (39)	10/26 (38)	..
Age, years	58 ± 6	54 ± 10	..
BMl kg/m^2	22.8 ± 1.1	22.8 ± 0.9	..
ASA group, n/N(%)			..
Gr oup I	1/28 (4)	2/26 (8)	
Group II	27/28 (96)	23/26 (92)	
lntraoperaive profiles			
Surgical type n/N(% lobectomy)	28/28 (100)	26/26 (100)	1.000
Anesthesia time(min)	172.39 ± 25.05	172.00 ± 20.49	0.950
Operation time(min)	139 .57 ± 24.06	144.42 ± 19 .38	0.420
OLV time(min)	111.29 ± 23.37	118.62 ± 20.71	0.229
Blood loss(mL)	43.04 ± 8.90	46.35 ± 11.06	0.230
Fluid amount(mL)	1250.00 (100 0.00~12 50.00)	1250.00 (10 00.00~1250.00)	0.539
Sufentanil consumption(ug)			
During operation	132.14 ± 13.71	124.23 ±14 .81	0.047
Perioperatlve	234.64 ± 23.37	124.23 ±14.81	0.000

Data are presented as mean ± standard deviatic or mean (interquartile range); n/N is number with the characteristic/total number. BMI, body mass index; ASA, American Society of Anesthesiology physical statues classification system,range 1 (normal) to 5 (moribund); OLV, one-lung ventilation.

Table 2. *VAS scores and PCIA pressing times.*

	SUF group	DEX group
R-VAS		
T_0		
T_1	1 (0-1)	0 (0-1)
T_2	1 (0-2)	0.5 (0-1)
T_3	1 (1-2)	1 (0-2)
T_4	2 (2-3)	2 (1-2.25)
T_5	1 (1-1.75)	1 (0-1)
C-VAS		
T_0	0	0
T_1	2 (1-2)	1 (1-2)
T_2	2 (1-3)	1.5 (1-2)
T_3	2 (2-3)	2 (1-3)
T_4	3 (2-3)	3 (2.75-3.25)
T_5	2 (2-3)	2 (2-2.25)
PCIA pressing times		
Valid times	4 (2-6)	3.5 (1-5.25)
Total times	5 (2-6.75)	4 (1-7)

R-VAS, resting VAS scores; C-VAS, coughing VAS scores; PCIA, patient-controlled intravenous analgesia.

Table 3. *Main adverse events, rescue analgesic requirements and Ramsay scores.*

	SUF group	DEX group
Number	28	26
Adverse events		
Nausea	11 (39)	2 (8)*
Vomit	3 (11)	0
Pruritus	3 (11)	1 (4)
Hypotension	0	1 (4)
Respiratory depression	0	0
Total	17 (61)	4 (15)*
Rescue analgesia	4 (14)	5 (19)
Sedation (1/2/3/4/5/6)		
T_0	9/19/0/0/0/0	8/18/0/0/0/0
T_1	14/10/4/0/0/0	4/8/14/0/0/0*
T_2	0/21/7/0/0/0	0/11/9/6/0/0*
T_3	0/19/7/2/0/0	0/10/10/6/0/0*
T_4	0/19/8/1/0/0	0/15/7/4/0/0
T_5	0/16/11/1/0/0	0/12/9/5/0/0

Data are number of patients or%. * $P < 0.05$, SUF group vs DEX group.

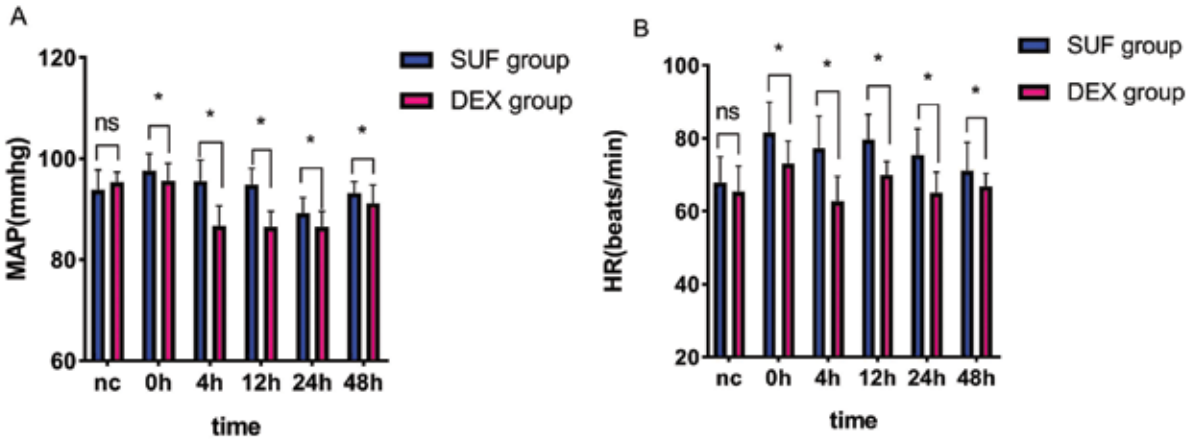

Fig. 2. *Differences in (A) MAP and (B) HR between the 2 groups. *P < 0.05 vs. SUF group. Abbreviation: nc, before induction.*

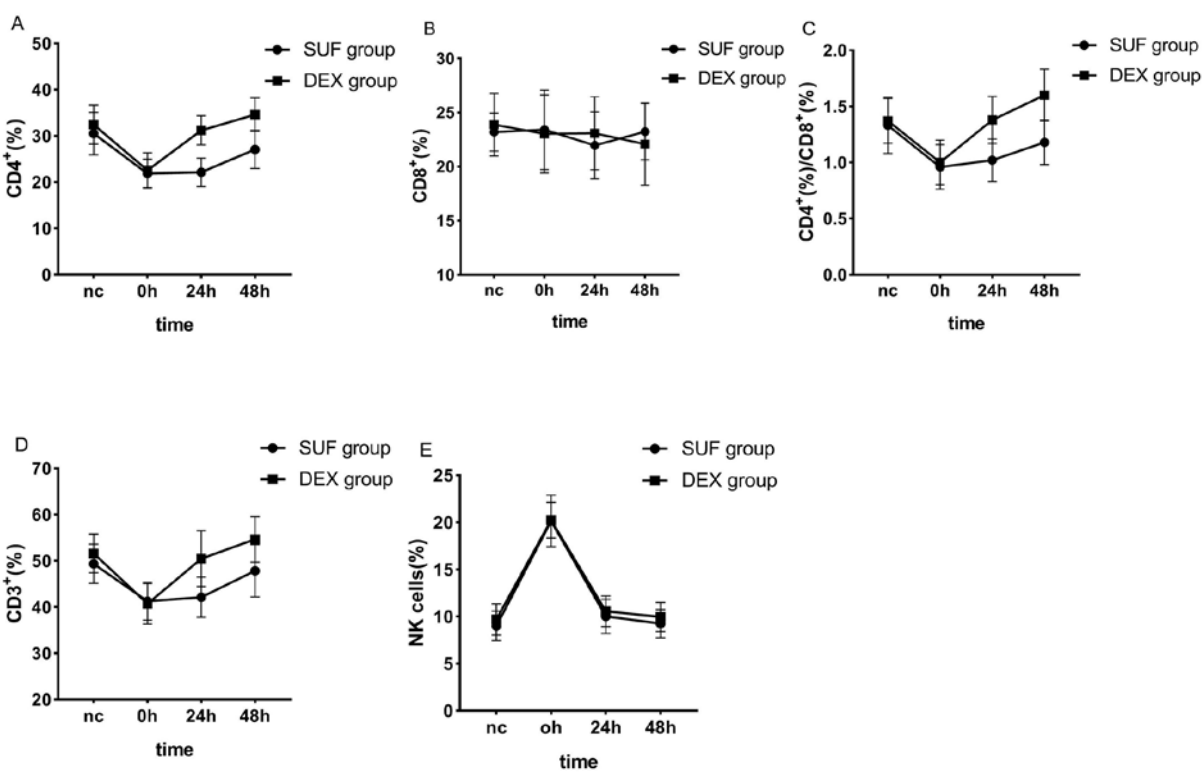

Fig. 3. *Differences in levels of T lymphocyte subsets including (A) $CD4^+$(%), (B) $CD8^+$(%), (C) $CD4^+$(%)/$CD8^+$(%), (D)$CD3^+$ (%), (E) NK cells(%) and NK cells in patients during perioperative period between the 2 groups. Abbreviation: nc, before induction.*

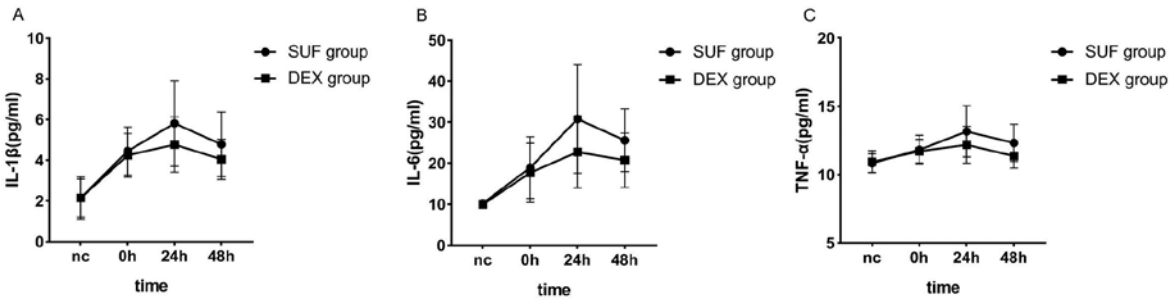

Fig. 4. *Differences in levels of cytokine (A) IL-1β, (B) IL-6, (C) TNF-α in patients during perioperative period between the 2 groups. Abbreviation: nc, before induction.*

Table 4. *Changes in levels of T lymphocyte subsets and NK cells in patients during perioperativeperiod between 2 groups(mean ± SD).*

Group	Time	$CD3^+T$(%)	$CD4^+T$(%)	$CD8^+T$(%)	$CD4^+T/CD8^+T$	NK cells(%)
SUF group	T_0	54.20 ± 9.15	32.47 ± 4.55	24.51 ± 6.16	1.39 ± 0.33	9.02 ± 1.58
	T_1	45.25 ± 7.82[a]	21.85 ± 3.13[a]	23.82 ± 6.73	0.99 ± 0.30[a]	18.81 ± 4.89[a]
	T_4	46.18 ± 10.93[a]	22.13 ± 3.06[a]	23.46 ± 8.29	1.04 ± 0.33[a]	10.03 ± 1.82
	T_5	52.53 ± 8.77	30.90 ± 3.81	24.51 ± 6.50	1.32 ± 0.28	9.27 ± 1.50
DEX group	T_0	56.49 ± 8.51	34.34 ± 4.27	24.52 ± 6.39	1.47 ± 0.34	9.70 ± 1.66
	T_1	44.44 ± 10.60[a]	22.57 ± 3.77[a]	23.40 ± 8.21	1.04 ± 0.29[a]	18.49 ± 3.88[a]
	T_4	51.30 ± 6.93[ab]	28.4 3 ± 3.43[ab]	24.31 ± 4.84	1.21 ± 0.23[ab]	10.57 ± 1.63
	T_5	57.29 ± 7.95[b]	34.61 ± 3.60[b]	24.19 ± 5.67	l.48 ± 0.28[b]	9.97 ± 1.55

[a]compared with that at T_0, $P < 0.05$; [b]compared with that in SUF group, $P < 0.05$.

In this study, multimodal analgesia was employed, using different types of analgesics, such as opioids, NSAIDs, DEX, and tramadol, and intercostal nerve block (12).

DEX, as an adjuvant analgesic, is widely used to improve the patients' pain states, sedation, and sleep quality (13). Recently, DEX was added to opioid-based PCIA and proved to reduce opioids consumption and opioid-related adverse effects, provide stable hemodynamics, and effective postoperative analgesia (14,15). One research studied the optimal dose of DEX combined with SUF in PCIA in patients undergoing spinal surgery. It was realized that 4.33 μg/kg of DEX combined with 3.0 μg/kg of SUF diluted in 250 mL normal saline solution for PCIA at an infusion rate of 4 mL/h provided effective analgesia with no complications, such as bradycardia, hypotension, respiratory depression, or oversedation (16). Similar doses of DEX and SUF were employed in our study.

KET has toxicity effects on the GI, renal, and blood systems, the risk factors of which include usage beyond 5 days, age beyond 65 years, and history of GI bleeding or ulceration (9). In several studies using KET for PCIA, a regimen with fewer complications was recommended (that is a bolus dose of 30 mg followed by continuous infusion of 3.6 mg/h KET) (8,9).

In this study, both regimens provide sufficient analgesia with all the VAS scores < 4 at any time point. There was no statistically significant difference in VAS scores, PCIA pressing times, and consumption of tramadol.

In the DEX group, patients had relatively stable hemodynamics with no severe cardiovascular complications, and the sedation effect was relatively better. DEX produces a similar sleep effect by acting on the alpha-2 receptor of the plaque nucleus and stimulating the endogenous sleep-promoting pathway (13), which makes patients feel more comfortable.

Concerning complications, the incidence of nausea in the DEX group was lower, which may be because of the decreased dosage of SUF and the antiemetic effect

of DEX (16). There was no significant difference in vomiting, oversedation, pruritus, and respiratory depression in both groups.

It is generally believed that IL-1β, IL-6, and TNF-α can influence the severity of inflammation to some extent. TNF-α usually rapidly increases in the early stage of the stress response, such as trauma, OLV, and IRI. It promotes the release of IL-6 and initiates a continuous reaction of inflammation.

DEX can activate the alpha-2 adrenergic receptor and consequently activate cholinergic transmitters to alleviate the stress response, thereby reducing the body's inflammatory response (17,18). Also, DEX has an antiinflammatory effect by affecting immune cells directly or indirectly. Alpha-2 adrenergic stimulation transforms cytokine gene expression from a proinflammatory to an antiinflammatory profile (19). Moreover, DEX can reduce the levels of inflammatory factors such as IL-1β, IL-6, and TNF-α by inhibiting the activation of NF-κB/Toll-like receptor signaling pathway (20).

In this study, the levels of serum IL-1β, IL-6, and TNF-α markedly increased after surgery, and ones in the DEX group were significantly lower than the SUF group at 24 and 48 hours after surgery. That may owe to the antiinflammatory effect of DEX on the recovery of the patients, which is similar to other studies.

NK cells, NKT cells, T lymphocyte helper cells ($CD4^+$), and T cytotoxic lymphocytes ($CD8^+$) are concentrated functional cellular mediators of the immune system and play important roles in tumor cell-mediated immune responses. All mature T cells ($CD3^+$) can be divided into $CD4^+$ and $CD8^+$ cells. $CD4^+$ cells could assist $CD8^+$ to kill tumor cell (21), and $CD8^+$ cells are mainly cytotoxic and inhibiting T cells (22). $CD4^+/CD8^+$ is an important indicator for judging the body's immune function.

Our present data show that surgical trauma and anesthesia induce significant suppression changes in $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ cells, which significantly decreased after surgery (23). The $CD8^+$ levels were stable before and after surgery in both groups, which agreed with other reports (23,24) indicating that the direct killing effect of $CD8^+$ T cells on target cells was not significantly affected. $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ were decreased in the 2 groups at 24 and 48 hour period, but the SUF group decreased significantly. The probable reason was that DEX reduced the degree of immunosuppression by inhibiting the inflammatory response. The previous report shows that cytokines, such as IL-1β, IL-6, and TNF-α, from monocytes/macrophages and lymphocytes activated may stimulate the hypothalamic pituitary adrenal (HPA) (25), whereas the HPA-axis activation suppresses cell-mediated immunity (26,27). Opioids are known to cause immunosuppression (4,28). It has been proven that immune cells, including lymphocytes, NK cells, and macrophages, have opioid receptors on their surface. Immunosuppression either interact directly with opioid receptors on immune cells or receptors within the central nervous system (29,30). Therefore we speculate that opioids consumption reduction to be another important reason for immunosuppression alleviation.

Limitations

The sample size in our study was quite small and only performed at one single center.

Conclusions

Our results suggested that whole-course application of DEX added to SUF or KET could sufficiently relieve pain, reduce opioid consumption, and postoperative nausea, and provide stable hemodynamics in postoperative analgesia. Moreover, the nonnarcotic regimen with DEX and KET could alleviate inflammatory response and immunosuppression in TSS. It is worthy of consideration, but more study is needed to recommend outright.

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