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Original Article

Continuous infusion of intraoperative dexmedetomidine improves chronic pain after thoracotomy via the Toll-like receptor 4/nuclear factor kappa B signaling pathway

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Abstract: Objectives: To explore the role of continuous infusion of intraoperative dexmedetomidine in chronic pain after thoracotomy via the Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) signaling pathway. Methods: Seventy-five patients undergoing thoracotomy were randomized into the control group (CG, n=37) and the observation group (OG, n=38). After induction of anesthesia for 30 min and until the end of surgery, the OG was infused with 0.4 μg/(kg·h) dexmedetomidine, and the CG was infused with the same amount of normal saline. Results: After operation, the OG had lower mean arterial pressure, heart rate, visual analogue scale (VAS) scores, incidence of chronic pain and neuropathic pain, TLR4 and NF-κB expressions, and tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) levels as well as epinephrine and norepinephrine levels than the CG ($P < 0.05$). The number of times the patient pressed the button for pain medication and the dose administered in the OG were less than those in the CG ($P < 0.05$). Conclusion: Continuous infusion of intraoperative dexmedetomidine can maintain perioperative hemodynamic stability in patients undergoing thoracotomy and reduce the stress response, postoperative pain, consumption of analgesic drugs, and the incidence of post-chronic and neuropathic pain, which is closely related to the reduction of inflammation via the TLR4/NF-κB signaling pathway.

Keywords: Thoracotomy, dexmedetomidine, continuous intraoperative infusion, TLR4/NF-κB signaling pathway, chronic pain, inflammatory response

Introduction

Chronic pain (CP) after thoracotomy refers to the pain caused by surgical incision lasting for more than 2 months, manifested as spontaneous pain, referred pain, or hyperalgesia, which may be related to the trauma of thoracotomy, intercostal nerve damage, and an inflammatory response. Surveys show that the incidence rate of CP after thoracotomy is 18%-52% [1]. Currently, acute perioperative pain control is the main method to reduce CP after thoracotomy; for example, gabapentin, parecoxib, and lornoxicam, are given perioperatively. However, the incidence of CP remains high after the completion of a thoracotomy [2-4].

The inflammatory response plays a vital role in CP after thoracotomy. The surgical procedure inevitably involves cutting of tissues, causing tissue and nerve damage, thereby inducing an inflammatory response and the release of a large number of inflammatory factors. Some inflammatory factors stimulate peripheral nociceptors, thereby causing spontaneous pain, while inflammatory mediators stimulate inflammatory cells to release pain-causing substances, resulting in pain.

The Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) signaling pathway is closely related to the inflammatory response. TLR4 activates NF-κB by initiating an intracellular signaling pathway, which in turn stimulates cells to produce tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These inflammatory factors also cause inflammatory cascades and lead to organ damage. Therefore, it is speculated that regulation of the TLR4/NF-κB signaling pathway may inhibit the inflammatory response and contribute to the reduction of CP.

Dexmedetomidine is a commonly used sedative and analgesic drug, and is associated with reduced production of inflammatory cytokines. This study explored the effects of continuous infusion of intraoperative dexmedetomidine on CP after thoracotomy and its relationship with the TLR4/NF-κB signaling pathway.

Materials and methods

Seventy-five patients undergoing thoracotomy in Shanghai Pulmonary Hospital from June 2019 to June 2020 were enrolled. Inclusion criteria were patients (1) undergoing elective thoracotomy; (2) scaled I-II on the American Association of Anesthesiologists (ASA) criteria; (3) receiving general anesthesia combined with thoracic epidural anesthesia; (4) with lung cancer; (5) aged < 70 years; and (6) who were informed and signed the written consent form. Exclusion criteria were patients (1) who had malignant tumors; (2) with CP syndrome; (3) with mental illness; (4) with a history of epilepsy; (5) with liver and kidney insufficiency; (6) with a communication disorder; (7) with systemic acute and chronic infections; (8) with pancreatitis; and (9) with analgesic and tranquilizer use within 48 h. Patients were divided into 37 cases in the control group (CG) and 38 cases in the observation group (OG) according to the random number table. This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital.

Anesthesia details

Intravenous access was established in all patients. Continuous electrocardiogram monitoring was used to monitor blood pressure, heart rate (HR), blood oxygen saturation level, and 3 L/min oxygen consumption. (1) Both groups were given general anesthesia combined with thoracic epidural anesthesia. For thoracic epidural anesthesia, a 25 gauge atraumatic needle was used for epidural puncture at T_{7-8}, and a catheter was inserted. Four milliliters of 1% bupivacaine (Anhui Changjiang Pharmaceutical Co., Ltd., Approval No. H34021983) was injected at a rate of 0.2 mL/h, confirming that the catheter was in the epidural space. Another 4 mL of 1% lidocaine (Xi'an Fenghua Pharmaceutical Co. Ltd., Approval No. H61020861) was injected at T_{4-10}. For anesthesia induction, intravenous (IV) injection of propofol (Hebei Yipin Pharmaceutical Co., Ltd., Approval No. H20093542) (1.5-2.0 mg/kg), sufentanil (Yichang Human0 well Pharmaceutical Co., Ltd., Approval No. H20050580) (4 μg/kg), rocuronium (Yao-Pharma Co., Ltd., Approval No. H20183254) (800 μg/kg), and midazolam (Jiangsu Jiuxu Pharmaceutical Co., Ltd., Approval No. H20-153019) (0.05 mg/kg) was performed. Tracheal intubation was performed through the oral cavity for mechanical ventilation with 6-8 mL/kg tidal volume, respiration rate of 10-12 times/min, respiration ratio of 1:2, and 30-40 mmHg of end-tidal CO_2.

For perioperative maintenance of anesthesia, an IV infusion pump was used to administer propofol [4-6 mg/(kg·h)] and remifentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd., Approval No. H20143315) [0.2-0.4 μg/(kg·h)]. The patient-controlled epidural analgesia pump was used in the epidural space to deliver 300 mL sufentanil (0.5 μg/mL) + 0.2% ropivacaine (Shijiazhuang No. 4 Pharmaceutical Co., Ltd., Approval No. H20203107) for 72 h. The parameter settings were a background infusion rate of 4 mL/h, an initial loading dose of 3 mL, and a lockout interval of 15 min. (2) On this basis, the OG received a loading dose of 0.5 μg/(kg·h) dexmedetomidine (Chengdu Brilliant Pharmaceutical Company, Approval No. H20205002) before anesthesia, followed by a maintenance dose of 0.5 μg/(kg·h) until the end of the operation, while the CG received the same amount of normal saline.

Evaluation criteria

The evaluation criteria were as follows. (1) The mean arterial pressure (MAP) and HR of the two groups were compared before operation, during skin incision, and before and after extubation. (2) After induction of anesthesia, at the end of the operation, and at 1 and 24 h after operation, 5 mL of venous blood was collected. Peripheral blood mononuclear cells (PBMCs) were separated and diluted into a solution with a cell density of 2×10^9 cells. Cell suspension (100 μL) was added to 20 μL CD14-PC5 + 10 μL TLR4 antibody, and incubated overnight at 4°C. After centrifugation, the samples were added to the NF-κB antibody and incubated overnight at 4°C. TLR4 and

Table 1. Comparison of baseline data between two groups ($\bar{x} \pm s$, *n*)

Group	*n*	Gender		Average age (years)	Operation time (min)	Body mass index (kg/m^2)	ASA rating		Clinical staging	
		Male	Female				Grade I	Grade II	Phase I	Phase II
Observation group	38	26	12	58.15±7.31	180.69±32.36	23.91±1.05	10	28	25	13
Control group	37	24	13	59.76±8.06	178.27±35.92	24.13±1.12	11	26	27	10
χ^2/t		0.107		0.907	0.307	0.878	0.108		0.455	
P		0.744		0.368	0.760	0.383	0.742		0.500	

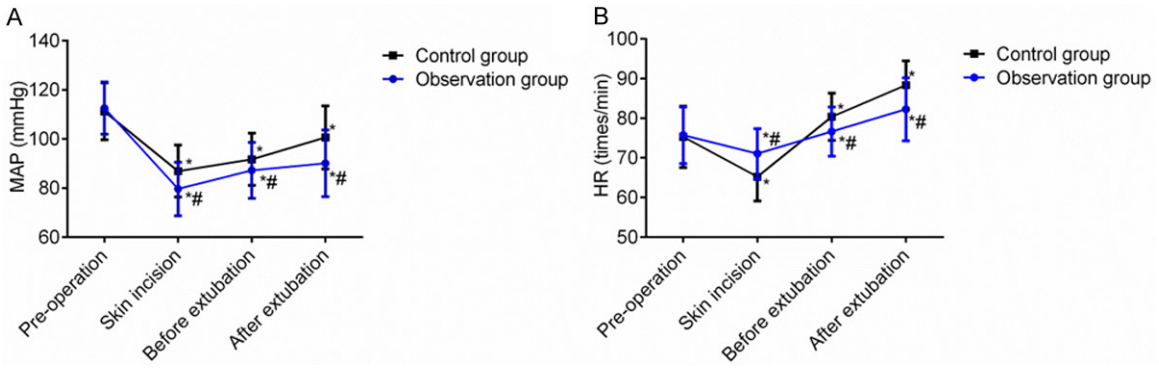

Figure 1. Continuous infusion of intraoperative dexmedetomidine stabilized the perioperative hemodynamic status of patients undergoing thoracotomy. MAP (A) and HR (B) of the observation group during skin incision, before extubation, and after extubation were lower than those of the control group. Note: Compared to the preoperative state, $^*P < 0.05$; compared to the control group at the same time-point, $^\#P < 0.05$.

NF-κB expression was determined using enzyme-linked immunosorbent assay (ELISA). (3) After induction of anesthesia, at the end of the operation, and at 1 and 24 h after operation, 3 mL of venous blood was collected and centrifuged at 3000 r/min for 10 min. TNF-α and IL-1β levels were determined by ELISA. (4) The visual analogue scale (VAS) scores at 6, 12, 24, 48, and 72 h after operation were compared between the two groups, covering 0-10 points. The higher score indicated the more severe pain. (5) Venous blood (3 mL) was collected before and at 24 h after operation to determine serum cortisol (COR), serum epinephrine (E), and norepinephrine (NE) levels. (6) The postoperative patient-controlled analgesia (PCA) usage of the two groups, including the number of times the button was pressed, and the dose administered was determined. (7) The incidence rate of CP was recorded at 15 d, 1, 2, 4, and 6 months after operation. (8) The incidence rate of neuropathic pain was compared between the two groups at 15 d after operation.

Statistical analysis

SPSS 25.0 was used for statistical analyses. Graphpad Prism 8.2 was used as the graphic software. Measurement data were represented by the mean $\bar{x} \pm s$, using a *t*-test. Quantitative data indicated by n (%) were compared using a χ^2 test. $P < 0.05$ indicated a significant difference.

Results

Comparison of baseline data

There was no significant difference between the two groups in gender, age, operation time, body mass index, ASA classification, and clinical staging ($P > 0.05$) (**Table 1**).

Comparison of MAP and HR between the two groups

In contrast to the preoperative state, the MAP and HR of the two groups were first decreased and then increased. The MAP and HR of the OG upon skin incision, before extubation, and after extubation were all lower than those of the CG ($P < 0.05$), suggesting that continuous infusion of intraoperative dexmedetomidine stabilized the perioperative hemodynamic status of patients undergoing thoracotomy (**Figure 1**).

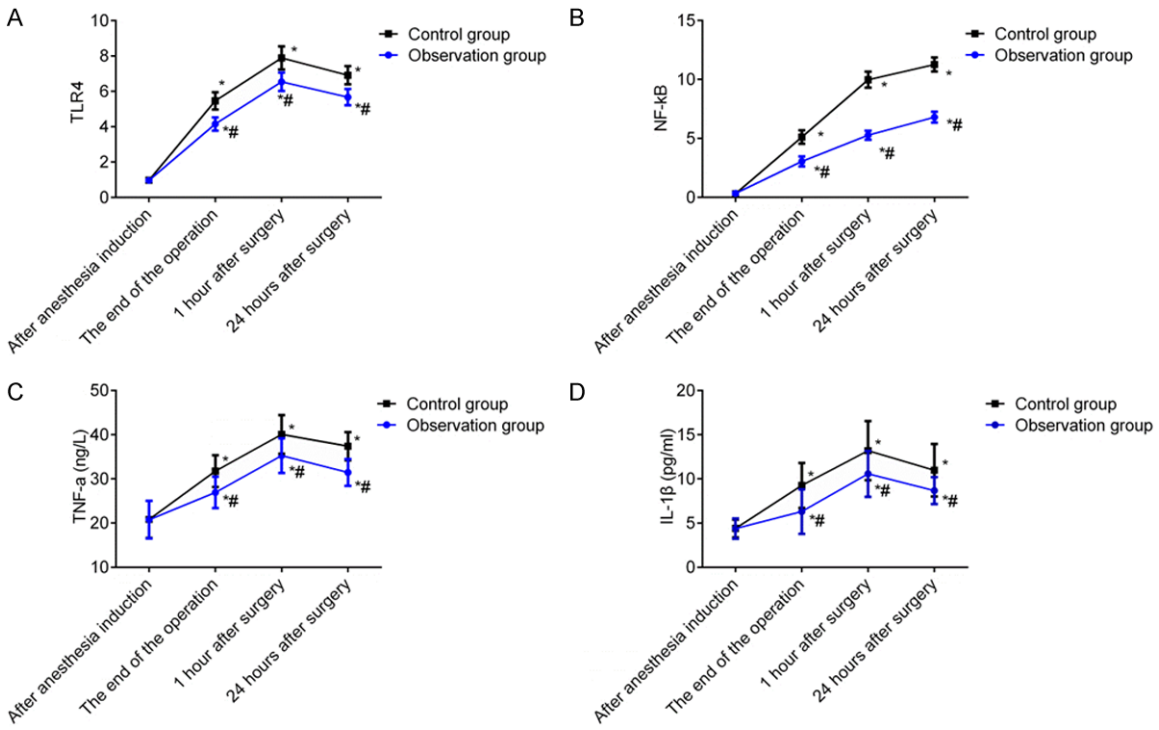

Figure 2. Effect of continuous infusion of intraoperative dexmedetomidine on the expression of TLR4, NF-κB and the levels of TNF-α and IL-1β in patients undergoing thoracotomy (%). At the end of the operation, 1 h and 24 h after operation, the expression of TLR4 (A), NF-κB (B), and the levels of TNF-α (C) and IL-1β (D) in the observation group were higher than those before operation, but were lower than those in the control group. Note: Compared to the preoperative state, $^{*}P < 0.05$; compared to the control group at the same time-point, $^{\#}P < 0.05$.

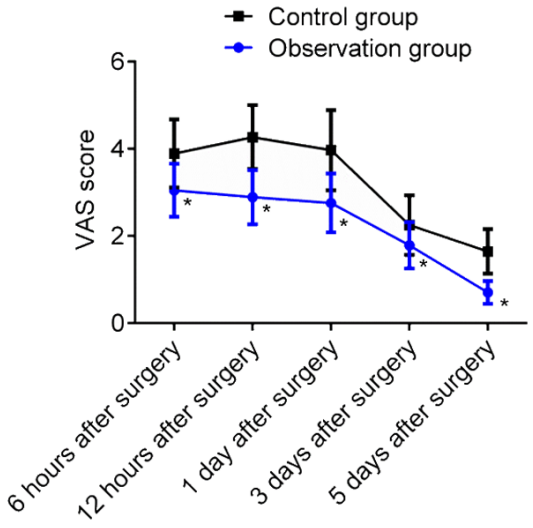

Figure 3. Continuous infusion of intraoperative dexmedetomidine significantly reduced the perioperative pain score (points) of patients undergoing thoracotomy. The VAS scores of the observation group at 6 and 12 h, and 1, 3, and 5 d after operation were lower than those of the control group. Note: Compared to the control group at the same time-point, $^{*}P < 0.05$.

Comparison of TLR4 and NF-κB expression and TNF-α and IL-1β between the two groups

In contrast to those after induction of anesthesia, the expression of TLR4 and NF-κB in the two groups was increased at the end of the operation and at 1 and 24 h after operation, and the OG demonstrated lower levels than the CG, suggesting that continuous infusion of intraoperative dexmedetomidine reduced the expression levels of TLR4 and NF-κB in serum of patients undergoing thoracotomy ($P < 0.05$, **Figure 2A**, **2B**). After induction of anesthesia, expression levels of TNF-α and IL-1β in the two groups were increased at the end of the operation and at 1 and 24 h after operation; however, the OG showed lower levels than the CG ($P < 0.05$, **Figure 2C**, **2D**).

Comparison of VAS scores between the two groups

The VAS scores of the OG at 6 and 12 h, and 1, 3, and 5 d after operation were lower than those of the CG ($P < 0.05$, **Figure 3**).

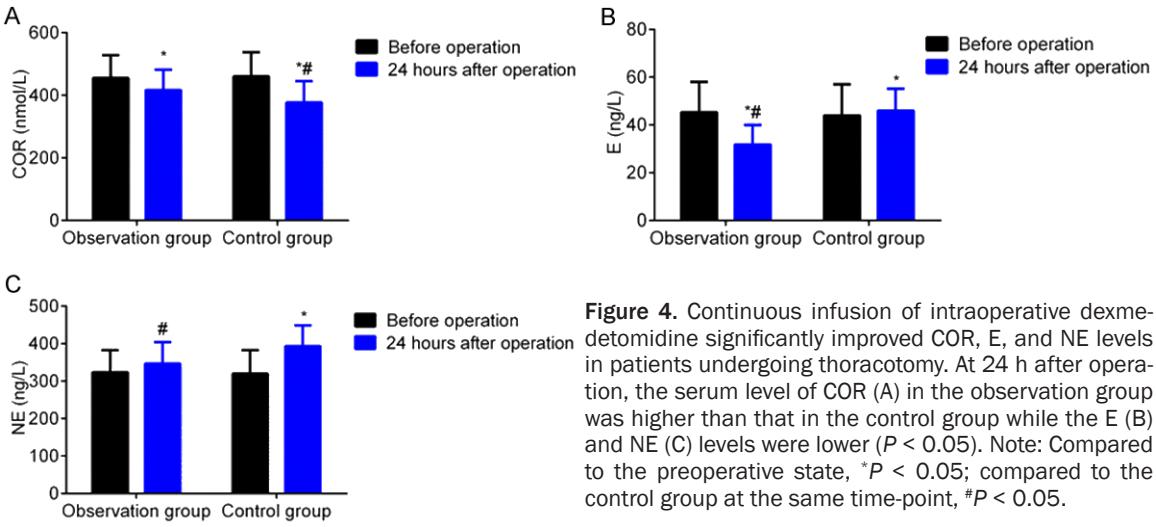

Figure 4. Continuous infusion of intraoperative dexmedetomidine significantly improved COR, E, and NE levels in patients undergoing thoracotomy. At 24 h after operation, the serum level of COR (A) in the observation group was higher than that in the control group while the E (B) and NE (C) levels were lower ($P < 0.05$). Note: Compared to the preoperative state, $^{*}P < 0.05$; compared to the control group at the same time-point, $^{\#}P < 0.05$.

Table 2. Comparison of PCA usage between the two groups ($\bar{x} \pm s$)

Group	*n*	Button Press (times)	Effective number of presses (times)	Number of invalid presses (times)	Given dose (mL)
Observation group	38	4.93±1.55	4.36±1.32	0.57±0.23	37.69±7.22
Control group	37	6.78±1.62	5.53±1.27	1.25±0.35	45.69±6.56
χ^2/t		5.054	3.910	9.969	5.018
P		< 0.001	< 0.001	< 0.001	< 0.001

Table 3. Comparison of postoperative chronic pain between the two groups [n (%)]

Group	*n*	15 d after operation	1 month	2 months	4 months	6 months
Observation group	38	20 (52.63)	16 (42.11)	10 (26.32)	5 (15.79)	2 (7.89)
Control group	37	23 (62.16)	21 (56.76)	19 (51.35)	15 (40.54)	10 (27.03)
χ^2		0.696	1.610	4.955	7.188	6.607
P		0.404	0.205	0.026	0.007	0.010

Comparison of serum COR, E, and NE levels between the two groups

The serum levels of COR and E of the OG were decreased at 24 h after operation, but the NE level showed no significant fluctuations, while the CG exhibited decreased serum levels of COR and increased levels of E and NE. However, at 24 h after operation, the serum level of COR in the OG was higher than that in the CG while the E and NE levels were lower ($P < 0.05$, **Figure 4**).

Comparison of postoperative PCA usage and incidence rate of postoperative CP between the two groups

The number of PCA press, effective press, invalid press and the dose administered in the OG were less than those in the CG ($P < 0.05$, **Table 2**). There was no significant difference in the incidence rate of CP at 15 d and 1 month after operation between the two groups ($P > 0.05$). The OG showed a lower incidence of CP at 2, 4, and 6 months after operation than the CG, suggesting that continuous infusion of intraoperative dexmedetomidine significantly reduced the use frequency of PCA and the incidence of CP ($P < 0.05$, **Table 3**).

Comparison of the incidence rate of neuropathic pain at 15 d after operation

In the frequency of neuropathic pain at 15 d after operation, the frequency of needle pain, burning pain, electric shock, numbness, and pain to touch in the OG was lower than that in the CG ($P < 0.05$, **Figure 5**).

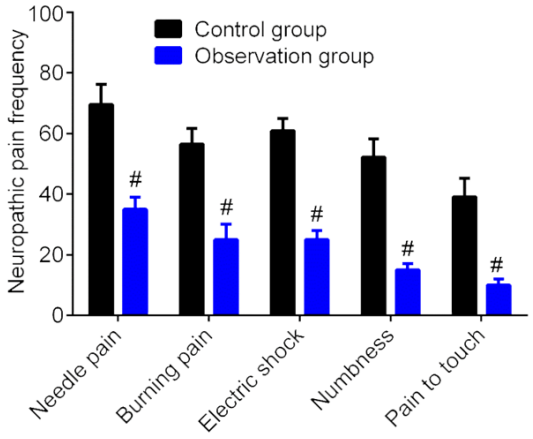

Figure 5. Comparison of the frequency of neuropathic pain between the two groups at 15 d after operation (%). In the frequency of neuropathic pain at 15 d after operation, the frequency of needle pain, burning pain, electric shock, numbness, and pain to touch in the observation group was lower than that in the control group. Note: Compared to the control group, $^{\#}P < 0.05$.

Discussion

Postoperative CP is a common complication in patients undergoing thoracotomy, mainly occurring in the chest and back surrounding the wound, which involves the underarms, shoulders, and upper abdomen. The pain lasts for a long time, up to several months or even years. In patients with CP, approximately 10% experience severe pain, which seriously affects the quality of their postoperative rehabilitation [5]. Therefore, the prevention of CP after thoracotomy has attracted clinical attention, and attempts have been made to prevent and treat it with non-steroidal anti-inflammatory drugs, sedatives, and analgesic drugs, but the effect is unsatisfactory [6-8]. In this study, continuous infusion of intraoperative dexmedetomidine improved CP after thoracotomy. Dexmedetomidine maintained perioperative hemodynamic stability in patients undergoing thoracotomy and reduced stress response, pain in the early stage, consumption of analgesic drugs, as well as the incidence rate of chronic and neuropathic pain.

Dexmedetomidine is a highly selective α-2 agonist with a receptor affinity α_2:α_1 of 1620:1 [9]. Dexmedetomidine has effects of sedation and analgesia, inhibition of sympathetic nerve activity, anti-inflammatory, neuroprotection, maintenance of hemodynamic stability, and inhibition of intraoperative stress responses. Dexmedetomidine has a short half-life (2-3 h vs. 12-24 h for clonidine) and is commercially available and ideal for IV administration [10, 11]. Dexmedetomidine stimulates α_2 receptors located in the locus coeruleus and reduces the excitability of neurons in the locus coeruleus, thereby reducing the release of NE produced by the locus coeruleus to the cerebral cortex and hippocampus, inhibiting sympathetic nerve activity and resulting in a sedative effect. In the meantime, dexmedetomidine was shown to regulate the release of peripheral NE through the negative feedback of presynaptic neuronal receptors, α_2 receptors [12, 13]. Dexmedetomidine might prevent the nociceptive stimulation of the dorsal horn of the spinal cord from entering the central nervous system and has an analgesic effect [14]. Continuous infusion of dexmedetomidine has been reported to reduce the fluctuation of MAP and HR during the extubation process and maintain stable hemodynamics [15]. These observations corroborated the findings of this study, that is, continuous infusion of dexmedetomidine reduced MAP and HR fluctuations upon skin incision, both before and after extubation. Our results demonstrated that continuous infusion of intraoperative dexmedetomidine was beneficial in maintaining hemodynamic stability in patients undergoing thoracotomy.

TLR is an important molecule that regulates the immune response and acute inflammation. TLR4 activates NF-κB and induces cells to produce inflammatory factors, including TNF-α and IL-1β [16, 17]. TNF-α is mainly produced by monocytes and macrophages and initiates an inflammatory response cascade which may cause damage to organs. IL-1β is an initiating factor of the inflammatory cascade and can aggravate the inflammatory response [18]. IL-1β also plays a noxious role in the signal transduction of the central nervous system, causing hyperalgesia [19]. In the event of trauma, IL-1β is upregulated in local peripheral tissues and the central nervous system and participates in the regulation of nociceptive pain [20]. IV injection of 1 μg/kg dexmedetomidine combined with continuous infusion of intraoperative 0.5 μg/(kg·h) dexmedetomidine in elderly diabetic patients undergoing lower extremity surgery inhibits the expression of TLR4 and

NF-κB, as well as the expression of the TLR4/myeloid differentiation primary response 88/NF-κB signaling pathway to improve myocardial damage [21]. Dexmedetomidine inhibits the expression of TLR4 and NF-κB in PBMCs of patients with brain injury, and decreased the serum levels of TNF-α and IL-1β [22]. In this study, the expression of TLR4 and NF-κB in the OG was increased at the end of the operation and at 1 and 24 h after operation but was lower than those of the CG. TNF-α and IL-1β levels in the OG were lower than those in the CG at multiple time-points, which was similar to the results reported above. These data suggested that infusion of dexmedetomidine in patients undergoing thoracotomy inhibited the expression levels of TLR4 and NF-κB, regulating the TLR4/NF-κB signaling pathway, and reducing inflammation.

This study showed that the VAS scores of the OG at 6 h to 5 d after operation were lower than those of the CG, and the number of times that the patient pressed the button for pain medication and the dose administered were less than those of the CG, which suggested that continuous infusion of intraoperative dexmedetomidine relieved acute postoperative pain and reduced postoperative consumption of analgesics.

Additionally, the changes in serum levels of COR, E, and NE in the OG were smaller than those in the CG. The reason may be that dexmedetomidine inhibits the release of catecholamines and NE and a perioperative stress response in patients undergoing thoracotomy [23].

Dexmedetomidine administered on the basis of general anesthesia reduces postoperative CP for patients undergoing breast cancer surgery [24], while paravertebral administration of dexmedetomidine before anesthesia induction combined with postoperative infusion of dexmedetomidine in patients undergoing thoracotomy reduces CP at 3 and 6 months after operation [25]. This study showed that both incidence rate of CP at 2, 4, and 6 months after operation and the frequency of neuropathic pain 15 d after operation were lower in the OG than in the CG, which were similar to the results above. These data demonstrated that continuous infusion of intraoperative dexmedetomidine reduced postoperative CP in patients undergoing thoracotomy.

In summary, continuous infusion of intraoperative dexmedetomidine can maintain perioperative hemodynamic stability in patients undergoing thoracotomy and reduce the stress response, postoperative pain, consumption of analgesic drugs, and the incidence rate of postchronic and neuropathic pain, which is closely related to reducing inflammation via the TLR4/NF-κB signaling pathway. However, further studies should expand the sample size to verify these results.

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Disclosure of conflict of interest

None.

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