Randomized Controlled Trial

Anti-nociceptive Effects of Dexmedetomidine Infusion Plus Modified Intercostal Nerve Block During Single-port Thoracoscopic Lobectomy: A Double-blind, Randomized Controlled Trial

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Background: Multimodal general anesthesia based on modified intercostal nerve block (MINB) has been found as a novel method to achieve an intraoperative opioid-sparing effect. However, there is little information about the effective method to inhibit visceral nociceptive stress during single-port thoracoscopic surgery.

Objective: To investigate whether a low-dose dexmedetomidine infusion followed by MINB might be an alternative method to blunt visceral stress effectively.

Study Design: Double-blind, randomized control trial.

Setting: Affiliated hospital from March, 2020 through September, 2020.

Methods: Fifty-four patients were randomized (1:1), 45 patients were included to receive dexmedetomidine with a 0.4 μg/kg bolus followed by 0.4 μg/kg/h infusion (group Dex) or saline placebo (group Con). During the operation, an additional dose of remifentanil 0.05–0.25 μg/kg/min was used to keep mean arterial pressure (MAP) or heart rate (HR) values around 20% below baseline values. The primary outcome was to evaluate remifentanil consumption. Secondary outcomes included intraoperative hemodynamics, the first time to press an analgesia pump, and adverse effects.

Results: Remifentanil consumption during surgery was markedly decreased in the Dex group than in the Con group (0 [0-0] versus 560.0 [337.5-965.0] μg; $P = 0.00$). MAP and HR in the Con group during the first 5 minutes after visceral exploration was significantly higher than in the Dex group ($P < 0.05$). Time to first opioid demand was significantly prolonged ($P = 0.04$) and postoperative length of stay was shortened slightly in the Dex group ($P = 0.05$).

Limitations: This study was limited by the measurement of nociception.

Conclusions: This study demonstrates that low-dose dexmedetomidine infusion combined with MINB might be an effective alternative method to blunt visceral stress in patients undergoing single-port thoracoscopic lobectomy. Furthermore, the analgesic effect of MINB was significantly prolonged after dexmedetomidine infusion.

Key words: Opioid-sparing, nociceptive stress, dexmedetomidine, remifentanil

Trial registration: http://www.chictr.org.cn (ChiCTR2000030959); registered March 19, 2020.

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Although video-assisted thoracic surgery (VATS) is a less invasive treatment, significant surgical stress and postoperative pain remain a common problem (1). The better match for the minimally invasive surgery may be a less invasive analgesia technique (2) and it is now increasingly proposed as an alternative to thoracic epidural analgesia (TEA). The intercostal nerve block is considered a feasible technique for VATS without risk of serious complications, and it is suitable when TEA or paravertebral block have not been performed (3).

Opioids were the definitive analgesia drug to block acute pain, including nociceptive pain from somatic tissue (4) and visceral stress (5). However, concerned by side effects from the amount of opioids, balanced anesthesia called multimodal general anesthesia was a reasonable strategy (6). Our preliminary observation found multimodal general anesthesia based on modified intercostal nerve block (MINB) was a novel method to achieve an intraoperative opioid-sparing effect in minimally invasive lobectomy. MINB was effective to inhibit nociceptive stress arising from peripheral tissue, however, it is unknown about the effective method to inhibit nociceptive stress originated from viscera.

Nociceptive stress during thoracoscopic lobectomy originates from the incision and viscera. Parietal and visceral pleura do not possess the same innervation origin. The first one receives its main innervation by the intercostal and the phrenic nerves while the second is innervated by the sympathetic system and the vagus nerve (7). One potential antinociceptive drug, dexmedetomidine (Dex) exerts its antinociceptive effects through decreasing noradrenergic excitatory inputs to the cortex and thalamus (8) or activating inhibitory interneurons that synapse onto projection neurons in the spinal dorsal horn (9). Therefore, we conducted a single-center, randomized, controlled trial to examine whether a low-dose Dex infusion might be an alternative method to blunt visceral stress effectively. This is the first report to explore a potential strategy to inhibit visceral nociceptive stress.

Methods

Trial Design and Patients

This prospective study was nested within a randomized clinical trial which was registered before patient enrollment at http://www.chictr.org.cn (Identifier: ChiCTR2000030959, date of registration: March 19, 2020) and approved by a biomedical ethics committee (approval No. 20200164). After a written informed consent, patients aged 18–75 years, with American Society of Anesthesiologists physical status classification II or III, and scheduled for single-port thoracoscopic surgery between March 20, 2020 and September 30, 2020, were enrolled. Major exclusion criteria were any difficulty with communication, any contraindications to regional techniques (allergy to local anesthetics, infection around the site of the block, and coagulation disorder), history of analgesics dependence, heart rate < 50 beats/minutes or II-III atrioventricular block, allergy to the study drugs, and refusal to participate in the current study. Those transferred to open procedure and those with an estimated blood loss of greater than 500 mL during surgery were subsequently excluded.

Randomization and Double-blinding

Based on random numbers generated by a computer program (IBM SPSS version 21, IBM Corporation, Armonk, NY), patients were randomized (1:1) to receive Dex or saline placebo.

1) Dex group: An initial loading dose (0.4 μg/kg) was given for 15 minutes before the induction of anesthesia, followed by a maintenance infusion of 0.4 μg/kg/h that was stopped 30 minutes before the end of surgery.
2) Control group: An equivalent saline placebo was administered.

Drug masking was performed by a pharmacist. Patients, the investigators, and clinicians were blinded to the treatment allocation.

Anesthesia

Basal blood pressure and heart rate (HR) were recorded after midazolam administration of 0.02 mg/kg. Anesthesia was induced with sufentanil 0.4-0.5 μg/kg and etomidate 0.3 mg/kg, via intravenous (IV) route. An IV bolus of cisatracurium 0.2 mg/kg was given to facilitate double-lumen endotracheal intubation. Anesthesia was maintained with propofol 3-6 mg/kg/h by bispectral index 40-60 and additional bolus doses of remifentanil 0.05–0.25 μg/kg/min to keep mean arterial pressure (MAP) or heart rate values around 20% below baseline values. Sufentanil 0.1-0.2 μg/kg was given in both groups once the chest was closed. Patient-controlled intravenous analgesia (PCIA) with 3 μg/kg sufentanil and flurbiprofen 200 mg diluted to 150 mL was used (with a bolus of 2 mL, a lockout time of 15 minutes and a baseline infusion of 2 mL/h). A bo-

lus dose was given to patients immediately when the visual analog scale (VAS) was ≥ 4 or on patient request. The procedures could be repeated 15 minutes later until the VAS was < 4. If necessary, intravenous tramadol 100 mg every 6 hours was used for additional rescue.

The MAP and HR were continuously measured and recorded before induction (baseline, T0), incision (T1), immediately after entering into the chest (T2), immediately after visceral exploration (T3), one minute after visceral exploration (T4), 3 minutes after visceral exploration (T5), 5 minutes after visceral exploration (T6), immediately after chest closure (T7) and the end of surgery (T8). After induction, we performed a modified intercostal nerve block in all patients and optimized this to a single point injection. After preparing the skin with 2% chlorhexidine solution, we placed a high frequency (5–10 MHz) ultrasound probe (S-Nerve™, SonoSite Inc. Bothell, WA) on the lateral side of the surgical incision. At the fifth intercostal spaces, close to the surgical incision, the ultrasound transducer was placed at the longitudinal rib direction, and using an in-plane technique, the needle was advanced to the inferior border of the rib where 5 mL of ropivacaine 0.35% were injected (Fig. 1).

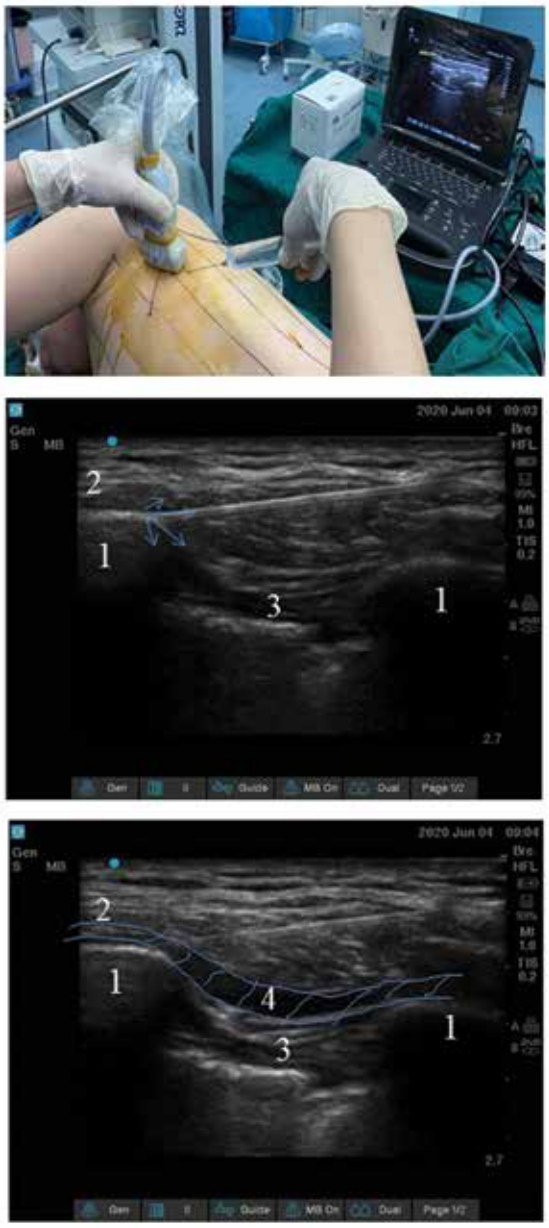

Fig. 1. *Ultrasound view of anterior serratus plane and intercostal level before (A) and after (B) administration of modified intercostal nerve block with 5 mL of ropivacaine 0.35%. 1 ribs, 2 serratus anterior muscle, 3 intercostal muscle, 4 local anesthetic.*

Outcomes

The primary outcome was remifentanil consumption during the operation. Intraoperative hemodynamics, time of tracheal extubation and stay in the postanesthesia care unit (PACU) was recorded. VAS at rest and movement (coughing) were assessed at 3, 6, 12, 24, 36, and 48 hours postoperatively. Time to first analgesic demand and total sufentanil consumption within the 48 hours after surgery was also recorded, as well as the incidence of nausea or vomiting, postoperative delirium, time to pass flatus, and postoperative hospital stay.

Statistical Analysis

The primary endpoint of this study was intraoperative remifentanil consumption. Based on a preliminary study with 10 patients (5 in each group), the mean remifentanil consumption during the operation was 0 versus 1734.0 ± 241.8 μg in group Dex and saline. The sample size calculation was performed with G*Power (Dusseldorf, Germany). With a two-sided α-level of 0.05, a statistical power of 90%, and allowing for a loss to follow-up of 20%, we calculated that a sample total of 40 patients (20 in each group) would be required.

SPSS V.24.0 (IBM Corporation, Armonk, NY) was used to perform the statistical analysis. The normally distributed data between groups were analyzed by Student's t test, while the Mann–Whitney U test was used to analyze the nonnormally distributed and nonparametric data, including intraoperative remifentanil, propofol, and dexmedetomidine consumption; VAS data; time to pass flatus; and total analgesic demands

during 24 and 48 hours. Intraoperative hemodynamic data were analyzed by repeated measures analysis of variance with a Bonferroni correction. Categorical data were analyzed using the χ^2 test. Data are shown as mean ± standard deviation, median (interquartile range), or number of patients (percentage). $P < 0.05$ was considered statistically significant.

Results

A patient flow diagram is shown in Fig. 1. A total of 72 patients were enrolled in this study. Eighteen patients failed to meet the inclusion criteria or declined to participate and met the exclusion criteria; 9 patients discontinued the intervention because of a failure to the prior protocol. Forty-five patients were randomized and were included for analysis (saline group n = 22; Dex group n = 23. Fig. 2).

No significant differences were shown in patient characteristics between groups, including the time of tracheal extubation and stay in the PACU (Table 1). Table 2 shows intraoperative and postoperative opioid consumption. Interestingly, only one patient required supplemental remifentanil in the Dex group. A statistically significant difference was observed in intraoperative remifentanil consumption (0 [0-0] vs. 560.0 [337.5-965.0] μg, $P = 0.00$). Although there was no statistical difference in the total number of PCIA activations and total sufentanil consumption during the first 24 and 48 hours after surgery, the first time to press the analgesia pump in the Dex group was significantly prolonged than that in the saline group ($P = 0.04$). There was a significant reduction in VAS scores 24 hours postoperatively at rest in the Dex group ($P < 0.01$), and also the VAS scores during activity at 12 and 24 hours postoperatively ($P < 0.01$) (Fig. 3). MAP and HR in the saline group at one minute, 3 minutes, and 5 minutes after visceral exploration was significantly higher than that in the Dex group ($P < 0.05$). A similar tendency in MAP and HR before visceral exploration was observed as shown in Fig. 4.

Table 3 shows the incidence of side effects and postoperative outcome. No significant difference was observed in opioid-related side effects such as nausea, vomiting, and the time to pass flatus. However, patients in the Dex group had a minor reduction in postoperative length of stay ($P = 0.05$).

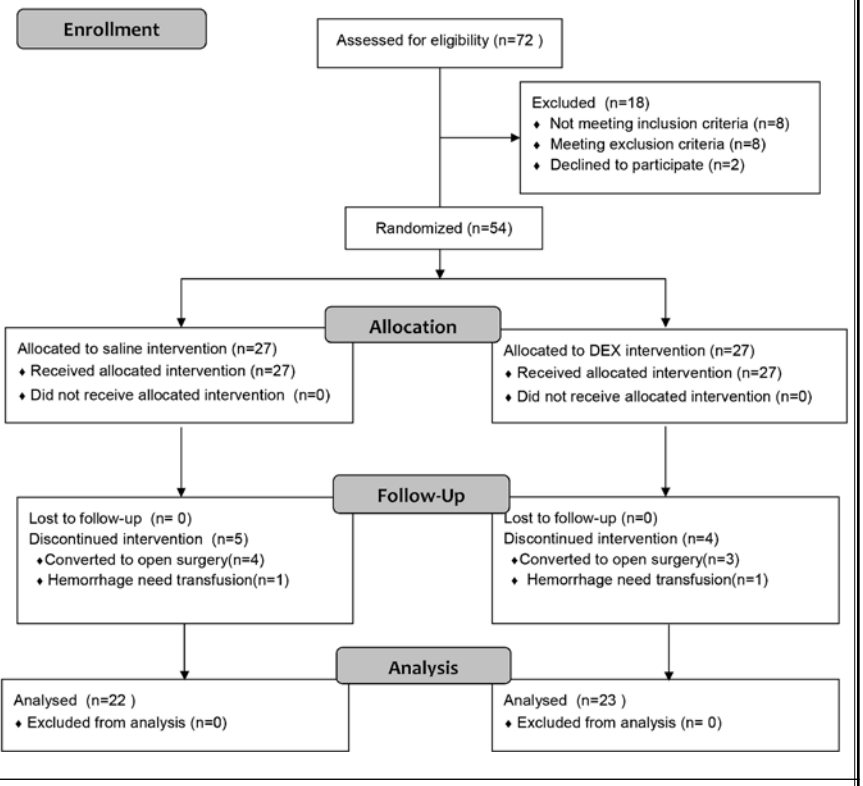

Fig. 2. *Consort flow diagram.*

Discussion

This study first demonstrated the feasibility of intraoperative lower supplementary remifentanil consumption after Dex infusion combined with MINB in patients undergoing single-port thoracoscopic surgery. Meanwhile, the analgesic effect of MINB was significantly prolonged after Dex infusion compared with saline placebo infusion.

The monitoring of the nociceptive–anti-nociceptive balance during anesthesia is still a challenging issue (10). Insufficient analgesia during anesthesia is typically perceived by autonomic reactions such as increases in blood pressure or HR, sweating, increase of the pupil diameter, or lachrymation. Nociceptive transmission from

Table 1. *Demographic data and surgical characteristics.*

Variable	Con (n = 22)	Dex (n=23)	*P* Value
Age, years	52.7±6.5	52.6±11.2	0.97
Male sex, n (%)	8 (36.4%)	9 (39.1%)	1.00
Body-mass index (kg/m²)	23.7±3.1	23.2±3.7	0.66
ASA physical status, n (%)			0.91
II	14 (63.6%)	15 (65.2%)	
III	8 (36.4%)	8 (34.8%)	
Duration of anesthesia (min)	181.8±59.5	182.7±61.2	0.96
Duration of surgery (min)	158.2±57.1	155.6±71.7	0.92
Propofol consumption (mg)	757.0 (533.8-987.5)	600.0 (500.0-910.0)	0.31
Extubation time (min)	5.0 (5.0-10.0)	10.0 (5.0-15.0)	0.08
Time in PACU (min)	35.0 (30.0-45.0)	40.0 (30.0-50.0)	0.67

Data are shown as mean ± SD, median (25th to 75th percentiles), or number of patients (percentage). Dex: dexmedetomidine; Con: saline placebo; ASA: American Society of Anesthesiologists; PACU: postanesthesia care unit.

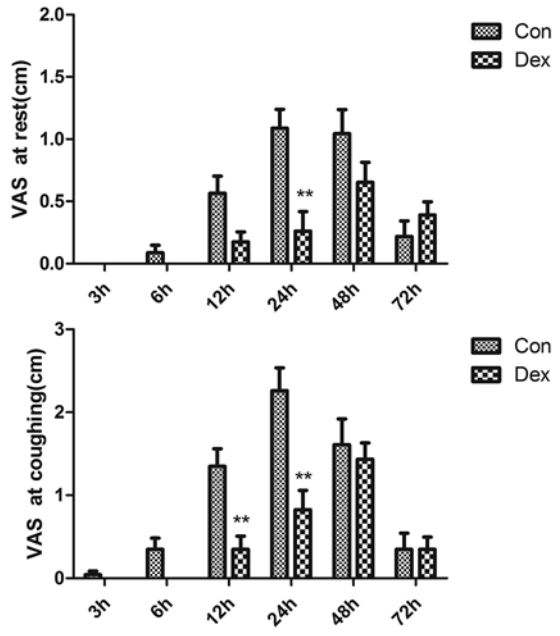

Fig. 3. *Postoperative pain severity VAS score at rest (A) and coughing (B) (in cm) at 3, 6, 12, 24, 48, and 72 hours postoperatively. *P < 0.05 compared with groups GA, Dex: dexmedetomidine; Con: saline placebo.*

Table 2. *Intraoperative and postoperative opioid consumption.*

Variable	Con (n = 22)	Dex (n=23)	*P* Value
Intraoperative remifentanil consumption (μg)	560.0 (337.5-965.0)	0 (0-0)	0.00
Usage of remifentanil, n (%)	22 (100%)	1 (4.3%)	0.00
Time to first opioid demand (h)	14.0 (12.0-32.5)	26.0 (15.0-50.0)	0.04
Total analgesic demands 1 day postop	1.0 (0-4.0)	1.0 (0-1.0)	0.23
Total analgesic demands 2 day postop	3.0 (2.0-7.0)	2.0 (0-5.0)	0.29
Total sufentanil during first 48 h(μg)	131.3 (120.8-143.7)	134.4 (104.0-151.8)	0.64

Data are shown as median (25th to 75th percentiles) or number of patients (percentage). Dex: dexmedetomidine; Con: saline placebo.

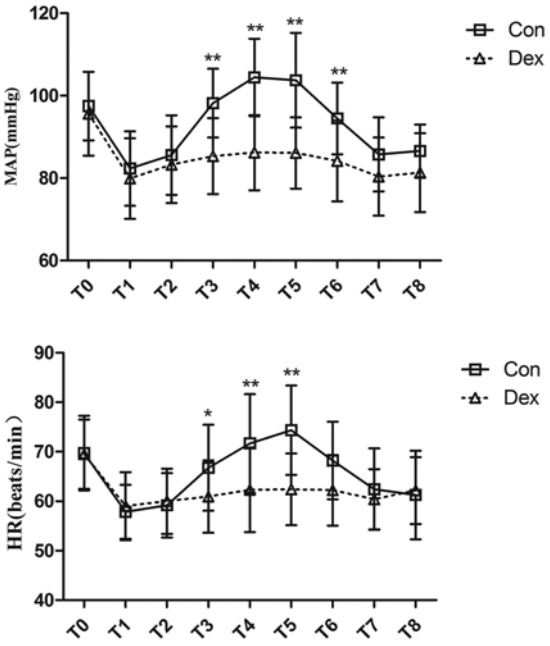

Fig. 4. *Mean arterial pressure and heart rate changes at different times during surgery. Dex: dexmedetomidine; Con: saline placebo; MAP: mean arterial pressure; HR: heart rate; T0: before induction (baseline); T1: incision; T2: immediately after entering into the chest; T3: immediately after visceral exploration; T4: one minute after visceral exploration; T5:3 minutes after visceral exploration; T6:5 minutes after visceral exploration; T7: immediately after chest closure; T8: end of surgery.*

Table 3. *Side effects and postoperative outcome.*

Variable	Con (n = 22)	Dex (n=23)	P Value
Nausea/Vomiting, n (%)	1 (4.5%)	2 (8.7%)	1.00
Pruritus, n (%)	0 (0)	0 (0)	–
Urinary retention, n (%)	1 (4.5%)	0 (0)	0.49
Dizziness, n (%)	2 (9.1%)	2 (8.7%)	1.00
Delirium, n (%)	0 (0)	1 (4.3%)	1.00
Time to flatus (h)	26.7 (18.3-45.0)	23.0 (22.0-37.3)	0.72
Postoperative hospital stays(day)	6.0 (4.0-8.0)	4.0 (4.0-6.0)	0.05

Data are shown as median (25th to 75th percentiles), or number of patients (percentage). Dex: dexmedetomidine; Con: saline placebo.

surgical injury proceeds through C- and A-delta fibers in 3 ways (7): intercostal nerves transmit stimuli from skin, ribs, and muscles; the vagus nerve carries stimuli from the lungs and mediastinum; and phrenic and intercostal nerves innervate the pleura. Therefore, an intercostal nerve block interrupts the flow of afferent pain signals through the intercostal nerve. It does not block visceral pain. Other pain treatment modalities should be added to ensure adequate pain control after thoracotomy (11). In our recent study, MINB has been demonstrated to be effective to blunt the nociceptive stress originating from the incision to the parietal pleura. So, MAP and HR values in the placebo group were below 20% baseline values just before entering into the chest, then, additional remifentanil was used to keep MAP and HR values around 20% below baseline values once visceral exploration began. In contrast, a low-dose Dex (12) infusion before surgery showed an adequate nociceptive control during the operation, which suggested low-dose Dex infusion might be a suitable alternative to additional remifentanil consumption to blunt visceral stress well.

Viscera nociceptors are nonvisceral somatic structures, bare nerve cell endings which are located in the viscera that initiate nociceptive stimulus or pain (13). Opioids, as the primary class of antinociceptive agents, enhance cholinergic input and induce bradycardia, thereby, attenuating the sympathetic nociceptive responses (5). From a conventional point of view, antinociception is usually defined as the dose of opioid analgesics necessary to achieve stable intraoperative blood pressure and HR. However, there are different neurotransmitters and multiple neural circuits in the ascending or descending nociceptive pathways (14). Thus, opioid analgesics could be viewed as necessary, but not sufficient, to handle antinociception. Intraoperative nonopioid drugs such as Dex (15) to blunt increased MAP and HR is used explicitly to maintain antinociceptive effect, although its sedative effects only contribute to unconsciousness implicitly. Dex (16,17) decreased noradrenergic release from the preoptic area of the hypothalamus, and thereby, disinhibited galanergic or GABAergic inhibitory projections to primary arousal nuclei from the pons and midbrain. Animal studies have shown that the systemic administration of Dex exerts pronounced antinociception against acute inflammatory visceral pain (18,19) or colorectal distension-induced visceral pain (20), but no clinical data are available. This was the first study directly examining the responsiveness of this drug to chest-related visceral pain. This observation confirmed the antinociceptive activity of systemic Dex on visceral pain.

Furthermore, a prolonged analgesic effect and decreased length of stay were also observed after intraoperative Dex infusion. A systematic review (21) suggested that perioperative Dex provided better outcomes in elderly patients following noncardiac surgery, yet this came at the cost of an increased incidence of hypotension and bradycardia. Generally, the appropriate dose of Dex for critically ill patients was 0.4-0.7 μg/kg/h (22). In this study, a low-dose Dex was used to avoid hypertension, hypotension, or bradycardia; 0.4 μg/kg/h Dex infusion (23) facilitated a stable hemodynamics response.

There are several strengths to point out. This was the first report to explore an effective method to inhibit visceral nociceptive stress. Visceral stress, innervated by the sympathetic system and the vagus nerve, is rather intricate. As an alternative to remifentanil, intraoperative Dex infusion contributed to inhibiting visceral nociceptive stress. Secondly, thoracic surgical patients are known to require a large amount of opioids to achieve adequate nociception control, and low-dose Dex infusion based on MINB may be one novel strategy for reducing this.

Limitations

This study does have several limitations. First, monitoring sympathetic tone using commercially available devices relies on measures such as blood pressure and HR, which may provide conflicting information on sympathetic tone during anesthesia. The presented evidence for estimation of nociception–antinociception balance is still limited. At present, MAP or HR around 20% below baseline values was used to measure the adrenergic circuit response to nociceptive stimuli (24). Plasma levels

of norepinephrine, epinephrine, and cortisol should be measured further to monitor nociceptive stimuli. Secondly, in China, sufentanil (25-27) is used for anesthesia induction and remifentanil is used for maintenance in thoracoscopic surgery. Although the combination of 2 opioids in this study might make postoperative data difficult to interpret, we primarily focused on intraoperative remifentanil consumption. This factor did not alter several key observations. However, a sole sufentanil or remifentanil administration should be further explored. Lastly, another possible limitation is that our results may have limited external validity, because this was a single-center trial. Therefore, a large-scale randomized controlled trial would be needed to confirm the benefit of Dex infusion.

Conclusion

We demonstrated that a low-dose dexmedetomidine infusion combined with MINB might be an alternative method to blunt visceral stress effectively in patients undergoing single-port thoracoscopic lobectomy. Furthermore, intraoperative dexmedetomidine infusion could prolong the analgesic effect of MINB and shorten the length of stay.

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