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Effect of Intraoperative and Postoperative Infusion of Dexmedetomidine on the Quality of Postoperative Analgesia in Highly Nicotine-Dependent Patients After Thoracic Surgery

A CONSORT-Prospective, Randomized, Controlled Trial

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Abstract: Smoking is one of the most common addictions in the world. Nicotine inhalation could increase the risk of cardiorespiratory diseases. However, the solution that improved postoperative analgesia for highly nicotine-dependent patients undergoing thoracic surgery has not been specifically addressed.

This CONSORT-prospective, randomized, double-blinded, controlled trial investigated the efficacy of combination of dexmedetomidine and sufentanil for highly nicotine (Fagerstrom test of nicotine dependence ≥6)-dependent patients after thoracic surgery.

One hundred seventy-four male patients who underwent thoracic surgery were screened between February 2014 and November 2014, and a total of forty-nine were excluded. One hundred thirty-two highly nicotine-dependent male patients who underwent thoracic surgery and received postoperative patient-controlled intravenous analgesia were divided into 3 groups after surgery in this double-blind, randomized study: sufentanil (0.02 µg/kg/h, Group S), sufentanil plus dexmedetomidine (0.02 µg/kg/h each, Group D1), or sufentanil (0.02 µg/kg/h) plus dexmedetomidine (0.04 µg/kg/h) (Group D2). The patient-controlled analgesia (PCA) program was programmed to deliver a bolus dose of 2 ml, with background infusion of 2 ml/h and a lockout of 5 min, 4-hour limit of 40 ml, as our retrospective study. The primary outcome measure was the cumulative amount of self-administered sufentanil; the secondary outcome measures were pain intensity (numerical rating scale, NRS), level of sedation (LOS), Bruggrmann comfort scale (BCS), functional activity score (FAS), and concerning adverse effects.

The amount of self-administered sufentanil were lower in group D2 compared with S and D1 groups during the 72 hours after surgery ($P < 0.05$), whereas the total dosage and dosage per body weight of sufentanil were significantly lower in D1 group than that of S group only at 4, 8, and 16 hours after surgery ($P < 0.05$). Compared with S group, the NRS scores at rest at 1, 4, and 8 hours after surgery and with coughing at 4, 8, 16, and 24 hours after surgery were significantly lower in D2 group ($P < 0.05$). However, compared with D1 group, the NRS scores both at rest and with coughing at 4 and 8 hours after surgery were significantly lower in D2 group ($P < 0.05$). The NRS scores both at rest and with coughing show that there were no significant differences between D1 group and S group at each time point after surgery ($P > 0.05$). LOS of group D2 was higher than S and D1 groups at 1 hour after surgery ($P < 0.05$), BCS of group D2 was higher than S and D1 groups at 4, 8, and 16 hours after surgery ($P < 0.05$), and FAS of group D2 was higher than S and D1 groups at 48 and 72 hours after surgery ($P < 0.05$). The number of rescue analgesia during 72 hours after surgery in D2 group was lower than S and D1 groups ($P < 0.05$). There were no significant differences among the 3 groups in terms of baseline clinical characteristics and postoperative adverse effects except for itching ($P > 0.05$).

Among the tested patient-controlled analgesia options, the addition of dexmedetomidine (0.04 µg/kg/h) and sufentanil (0.02 µg/kg/h) showed better analgesic effect and greater patient satisfaction without other clinically relevant side effects for highly nicotine-dependent patients during the initial 72 hours after thoracic surgery.

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Abbreviations: ASA = American Society of Anesthesiologists, BCS = Bruggrmann comfort scale, BIS = bispectral index, BMI = body mass index, FAS = functional activity score, FTND = Fagerstrom test of nicotine dependence, HR = heart rate, ICU = intensive care unit, LOS = level of sedation, MAP = mean arterial pressure, NRS = numerical rating scale, PACU = postanesthesia care unit, PCA = patient-controlled analgesia, Spo2 = pulse oxygen saturation, SRD = serious respiratory depression.

INTRODUCTION

Smoking is one of the most common addictions worldwide. As patients with tobacco addiction required to stop smoking before thoracic surgery for at least 4 weeks, previous data had been focused on the association between smoking and postoperative outcomes.[1] Nicotine inhalation could increase the risk of cardiorespiratory diseases, which require postoperative intensive care unit (ICU) care or longer admission.[2] However, the solution that improved postoperative analgesia for nicotine-

dependent, especially highly nicotine-dependent, patients undergoing thoracic surgery has not been specifically addressed.

The thoracotomy wound often generates severe postoperative pain, which is considered one of the most severe forms and is difficult to control. It is particularly important to optimize postoperative analgesia in highly nicotine-dependent patients undergoing thoracic surgery. First of all, these patients may be experiencing higher incidence of associated comorbidities and abnormal pulmonary function than nonsmokers because of preexisting long-term smoking before surgery. Second, poor analgesia after surgery usually contributes to further deterioration.[3] Lots of systemic and regional methods of analgesia have been developed for post-thoracotomy pain.[4-6] Dexmedetomidine, a more favorable pharmacokinetic profile than clonidine—$\alpha 2 : \alpha 1$ specificity ratio, 1600:1 versus 200:1; plasmatic half-life $T^{1/2}$, 2–2.5 versus 9–12 hours; protein binding, 94% versus 50%; and lipophilic action, 3.5-fold of that of clonidine—has been used for sedation/analgesia in ICU and during surgery or other procedures such as endoscopy.[7] It also shows superior analgesia and opioid-sparing effects when used as an adjuvant agent after the postoperative period.[8,9]

Our previous study had proved that patients with different levels of nicotine dependence require different amounts of postoperative opioid analgesia.[10] The aim of this prospective, randomized, controlled trial was to evaluate whether dexmedetomidine added to patient controlled analgesia (PCA) sufentanil could afford enhanced analgesic effect, while reducing the adverse effects related to PCA sufentanil administration for highly nicotine-dependent patients during the initial 72 hours after thoracic surgery. At the same time, the adverse effects related to the dexmedetomidine–sufentanil mixture were also investigated.

METHODS

Study Protocol and Patients

This pilot study was designed according to the CONSORT 2010 statement. Ethical approval for this prospective, single-center, double-blinded, randomized controlled trial (No. 2014001) was provided by the Institutional Review Board of Liaocheng People's Hospital, Liaocheng, Shandong Province, P.R. China (Chair person: Professor Guozhang Liu), on January 17, 2014. The study was registered at chictr.org (ChiCTR-TRC-14004191). Informed consent was obtained from all the patients.

Highly nicotine-dependent male patients who underwent thoracic surgery under general anesthesia in our hospital between February 2014 and November 2014 were recruited. Patients were enrolled in this study if they met the following inclusion criteria: age between 35 and 65 years; American Society of Anesthesiologists (ASA) physical classification II or III; intubated L-double-lumen bronchial tube; and received 72 hours PCIA pump after surgery. Exclusion criteria included general anesthesia combined with epidural anesthesia; a long history of opioid analgesic use because of the chronic pain disease, antidepressants, or β-adrenoreceptor blockers preoperatively; obesity (body mass index, BMI >30 kg/m^2); and clinically significant neurologic, cardiovascular, renal, and hepatic diseases; cannot remove the tracheal catheter or correctly use the PCIA pump after surgery. Highly nicotine-dependent male patients were defined as our previous study. (We used the Fagerstrom test of nicotine dependence [FTND] questionnaires to evaluate nicotine dependence of the patients.[11] Highly dependent smokers were stratified by FTND scores ≥ 6.)[10]

Randomization and Masking

A computer-generated randomization table was used to allocate the patients into 3 equal groups (n = 44 each) by an independent anesthetist. After obtaining the patients' and their families' consent, the staff in the Acute Pain Services who was blinded to this study prepared the postoperative patient-controlled intravenous anesthetic agents on the day of surgery, and assessed pain intensity (numerical rating scale, NRS, both at rest and with coughing), the cumulative amount of self-administered sufentanil, level of sedation (LOS), Bruggrmann comfort scale (BCS), concerning adverse effects (nausea and vomiting, itching, shiver, delirium), and serious respiratory depression (SRD) (in those patients, one of the following interventions: physical stimulation of the patient, naloxone administration, or positive pressure ventilation) until 72 hours after surgery.

Anesthesia

Patients underwent L-double-lumen bronchial intubation for general anesthesia using a balanced technique, allowing for reduced dosages of medications. Our regimen consists of midazolam for amnesia, propofol and dexmedetomidine for hypnosis, sufentanil for analgesia, and muscle relaxants for immobilization (the University of Texas, M.D. Anderson Cancer Center).[12]

After arriving at the operating room, all patients were monitored using standard ASA monitoring including continuous 5-lead electrocardiography, pulse oximetry, noninvasive blood pressure, end-tidal CO_2, and temperature by an automated system (Philips IntelliVue MP50; Philips Company, Beijing, China). After an arterial cannula was placed in the left radial artery and the electrodes of the bispectral index (BIS; Aspect Medical System, Newton, MA) were placed on the side of the patient's forehead according to the manufacturer's instruction, supplemental oxygen and intravenous midazolam (0.5–2 mg) were administered. Ten minutes later, a small bolus of dexmedetomidine infusion (0.5 μg/kg) was begun rather than the manufacturer's recommended bolus-loading dose (1 μg/kg) to minimize the adverse effects (eg, hypo/hypertension, bradycardia, and atrial fibrillation) associated with dexmedetomidine loading, and then reduced the infusions of dexmedetomidine (to 0.5 μg/kg/h). Anesthesia was induced by intravenous administration of propofol (1.5–2 mg/kg), sufentanil (TCI 0.2 ng/mL), and cisatracurium (0.2 mg/kg). Anesthesia was maintained with propofol (TCI 2.4–3.0 μg/mL), dexmedetomidine (0.4–0.6 μg/kg/h) and sufentanil (TCI 0.2–0.24 ng/mL), titrated according to BIS (maintained between 40 and 60; BIS monitor, Aspect Medical System, Newton, MA) and hemodynamics. Supplemental dosing of 0.04 mg/kg of cisatracurium was used every hour from induction up to approximately 1 hour prior to the end of surgery. If necessary, intravenous antihypertensives (urapidil [10 mg] or ephedrine [6 mg] when mean arterial pressure [MAP] exceeded 20% of the base value), rather than more anesthesia, may be used in situations wherein sympathetic stimulation was high; yet a sufficient amount of anesthesia was being administered and BIS showed an adequate depth of hypnosis. Atropine (0.2 mg) was used at the time of heart rate (HR) <50 beats/min. The end-tidal carbon dioxide was maintained at 35 to 40 mm Hg. Sufentanil infusion was stopped one and a half hours prior to the end of surgery, whereas at the start of skin closure, propofol was discontinued. The patients were maintained on dexmedetomidine (0.1 μg/kg/h) until extubation in order to impart the cardioprotective benefits of α_2 agonist, namely, stable hemodynamics and rapid awakening/extubation.

Postoperative Analgesia Management

Before the surgery, all patients were instructed with the use of the NRS, which ranged from 0 (no pain) to 10 (worst possible pain) and the intravenous PCA pump (GemStar, Hospira, Lake Forest, IL). After surgery, patients were transferred to the postanesthesia care unit (PACU).

Patients were randomized into 3 groups after entering into PACU, the PCA was programmed to deliver a bolus dose of 2 mL, with background infusion of 2 mL/h and a lockout of 5 min, 4-hour limit of 40 mL, as our retrospective study.[10] The goal of PCA analgesia was to maintain the NRS score no >3 (at rest) in the first 72 hours after surgery. If the NRS was >3 (at rest), the patients were given an additional loading dose of 3 μg sufentanil, or an increased bolus dose to 3 to 4 mL. The 4-hour limit of 40 mL was increased to 50 mL as needed. If the NRS score was >6 (at rest), supplemental rescue boluses of 30 mg intravenous ketorolac was administered. If the rescue analgesia was ineffective 30 min after ketorolac administration, intravenous injection of tramadol (100 mg) was given.

Outcome Measures

The primary outcome measure was the cumulative amount of self-administered sufentanil until 72 hours after the surgery. The secondary outcome measures were the postoperative pain intensity scores both at rest (NRS_r) and with coughing (NRS_c); LOS (recorded on a 5-point scale—0, indicating fully awake; 1, indicating drowsy/closed eyes; 2, indicating asleep/easily aroused with light tactile stimulation or a simple verbal command; 3, indicating asleep/arousable only by strong physical stimulation; and 4, indicating unarousable)[8]; BCS (0, persistent pain; 1, severe pain while deep breathing or coughing; 2, mild pain while deep breathing or coughing; 3, painless while deep breathing; and 4, painless while coughing); FAS (A, no restricted; B, mild-to-moderate restricted; and C, severely restricted), and concerning adverse effects.

HR, MAP, BIS, and pulse oxygen saturation (SpO_2) were recorded at the following time points: arrival at the operating room (T0); before intubation (T1); after intubation (T2); before incision (T3); 30 min after one-lung ventilation (T4); 60 min after one-lung ventilation (T5); and extubation (T6). The cumulative amount of self-administered sufentanil, pain intensity, BCS, LOS, and FAS were recorded at 1, 4, 8, 16, 24, 48, and 72 hours after surgery, respectively. The number of rescue analgesia and the postoperative adverse effects (nausea and vomiting, itching, shiver, delirium, and SRD [any of the following interventions were needed: physical stimulation of the patient, naloxone administration, and positive pressure ventilation]) were also recorded at the end of this study.

Statistical Analysis

The sample size was calculated on the basis of an expected difference of 20% in the cumulative amount of self-administered sufentanil 72 hours after the surgery. For a study power of 80% ($\alpha = 0.05$, $\beta = 0.2$), the required sample size per group was calculated to be 38, a total of 114 patients (PASS 11.0; NCSS Statistical Software, Kaysville, Utah).[8,13] Assuming a dropout rate of 15%, the final sample size was determined to be 44 patients each group. Therefore, a sample size of 132 was chosen for adequate data collection.

Statistical analysis was performed with SPSS for Windows Version 16.0 (SPSS Inc. Chicago, IL). We used the Kolmogorov–Smirnov test to assess distribution of the variables. Homogeneity of variance was determined using Levene tests. Normally distributed data were expressed as mean ± standard deviation, skewed data distribution were expressed using median (interquartile range), and categorical data were expressed as number (n) and percentage (%). Repeated-measures 2-way analysis of variance was used to evaluate the differences at different time points among groups. Bonferroni multiple comparisons were performed for multiple comparisons, and categorical variables were analyzed using χ^2 or Fisher exact tests. Probability (P) values <0.05 were considered statistically significant.
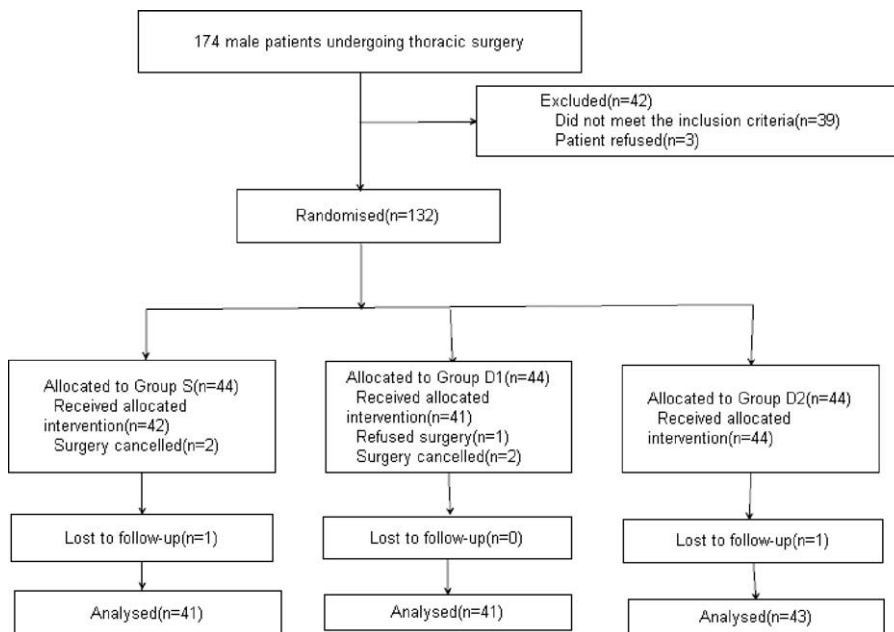

FIGURE 1. Patients enrolment flow diagram. This illustrates the flow of all patients screened, excluded, and randomized.

RESULTS

CONSORT diagram was used during the enrolment of patients (Figure 1); 174 male patients who underwent thoracic surgery were screened, and a total of 125 patients were included in the primary analysis between February 2014 and November 2014. Of the 42 patients, 39 were excluded because of not meeting the inclusion criteria; 3 refused this consent. In addition, 4 patients cancelled surgery (2 from group S, 2 from group D1). One patient refused this surgery (from group D1); 2 patients were excluded after surgery because of incomplete clinical data (1 from group S, 1 from group D2).

Baseline characteristics and demographics of patients in the 3 study arms were comparable (Table 1). There were no significant differences in age, body weight, BMI, ASA grade, and forced vital capacity rate of 1 second/forced vital capacity among the 3 groups ($P > 0.05$; Table 1). No significant differences could be seen among the 3 groups in terms of the intraoperative data and recovery time at PACU ($P > 0.05$; Table 1). The most frequent type of thoracic surgery was radical resection of esophageal carcinoma via single incision, accounting for 85.37%, 82.93%, and 83.72% of all surgeries in S, D1, and D2 groups, respectively. The other type of thoracic surgery was thoracotomy of cardiac cancer, accounting for 14.63%, 17.07%, and 16.28% of all surgeries in S, D1, and D2 groups, respectively. There was no significant difference in the type of surgeries among the 3 groups ($P = 0.954$; Table 1).

The MAP, HR, SpO_2, and BIS did not show any significant difference among the 3 groups during the surgery ($P > 0.05$; Figure 2). The total dosage and dosage per body weight of sufentanil were significantly lower in D2 group than that of S and D1 groups at 1, 4, 8, 16, 24, 48, and 72 hours after surgery ($P < 0.05$; Figure 3), whereas the total dosage and dosage per body weight of sufentanil were significantly lower in D1 group than that of S group only at 4, 8, and 16 hours after surgery ($P < 0.05$; Figure 3). Compared with S group, the NRS scores at rest at 1, 4, and 8 hours after surgery and with coughing at 4, 8, 16, and 24 hours after surgery were significantly lower in D2 group ($P < 0.05$; Figure 4). When compared with the D1 group, the NRS scores both at rest and with coughing at 4 and 8 hours after surgery were significantly lower in D2 group ($P < 0.05$; Figure 4). The NRS scores both at rest and with coughing show that there were no significant differences between D1 group and S group at each time point after surgery ($P > 0.05$; Figure 4).

Table 2 summarized the LOS, BCS, and FAS monitored during 72 hours after surgery. LOS, BCS, and FAS in D2 group were significantly higher at 1 hour ($P = 0.043$); 4, 8, and 16 hours ($P < 0.05$); 48 and 72 hours ($P < 0.05$), respectively, compared with S and D1 groups. At the same time, there were no significant difference between S and D1 group ($P > 0.05$; Table 2). The number of rescue analgesia during 72 hours after surgery in D2 group was significantly lower than S and D1 groups ($P = 0.015$; Table 3). Patients in D2 group had less itching than patients in S and D1 group ($P = 0.014$). Other side effects were no significant differences between the 3 groups ($P > 0.05$; Table 4).

DISCUSSION

This prospective, randomized, controlled trial showed that combination of dexmedetomidine ($0.04\,\mu g/kg/h$) and sufentanil as PCA in highly nicotine-dependent patients undergoing thoracic surgery could decrease both the total dosage and dosage per body weight of sufentanil during the 72 hours after surgery and

TABLE 1. Clinical Characteristics of Patients in S, D1, and D2 Groups

	Group S (n = 41)	Group D1 (n = 41)	Group D2 (n = 43)	P Values
Age, y	59.82 ± 6.38	59.95 ± 5.67	60.59 ± 6.14	0.816
Body weight, kg	68.07 ± 6.09	68.34 ± 5.57	67.48 ± 5.49	0.770
Height, m	1.68 ± 0.05	1.67 ± 0.37	1.67 ± 0.03	0.311
BMI, kg/m^2	24.14 ± 1.67	24.65 ± 1.88	24.11 ± 1.45	0.244
ASA II to III (n)	36/5	35/6	36/7	0.866
FEV$_1$/FVC, %	91.95 ± 5.90	93.36 ± 4.16	93.56 ± 4.09	0.232
Type of surgery, n (%)				
Thoracotomy in esophageal (one incision)	35 (85.37%)	34 (82.93%)	36 (83.72%)	0.954
Thoracotomy in cardiac cancer	6 (14.63%)	7 (17.07%)	7 (16.28%)	
Intraoperative data				
Duration of surgery, min	148.75 ± 14.99	149.77 ± 13.07	150.34 ± 11.28	0.849
Duration of anesthesia, min	187.27 ± 15.11	190.34 ± 14.52	185.50 ± 11.71	0.257
Estimated blood loss, mL	332.50 ± 53.32	345.00 ± 44.12	343.41 ± 27.61	0.336
Fluids, mL	2164.09 ± 191.36	2225.00 ± 191.23	2169.32 ± 143.95	0.206
Urine output, mL	407.95 ± 109.41	439.77 ± 93.12	402.27 ± 75.45	0.133
Sufentanil dosage, $\mu g/kg/h$	0.26 ± 0.05	0.26 ± 0.04	0.27 ± 0.04	0.526
Dexmedetomidine dosage, $\mu g/kg/h$	0.68 ± 0.15	0.68 ± 0.11	0.68 ± 0.11	0.997
Propofol dosage, mg/kg/h	6.88 ± 1.26	7.09 ± 1.20	7.24 ± 1.14	0.378
Number of using vasoactive agent, n (%)	12 (29.27%)	14 (34.15%)	15 (34.88%)	0.787
Cisatracurium dosage, mg/kg/h	0.20 ± 0.03	0.21 ± 0.03	0.20 ± 0.03	0.386
Recovery time at PACU (time)	47.70 ± 8.63	47.16 ± 7.83	48.23 ± 7.50	0.822

Variables presented as mean $\pm$ SD or number of patients n (%). Group S = sufentanil ($0.02\,\mu g/kg/h$); Group D1 = sufentanil plus dexmedetomidine ($0.02\,\mu g/kg/h$, each); Group D2 = sufentanil ($0.02\,\mu g/kg/h$) plus dexmedetomidine ($0.04\,\mu g/kg/h$). None showed any statistical significance ($P > 0.05$). ASA = American Society of Anesthesiologists, BMI = body mass index, FEV$_1$/FVC = forced vital capacity rate of 1 second/forced vital capacity, PACU = postanesthesia care unit, SD = standard deviation.
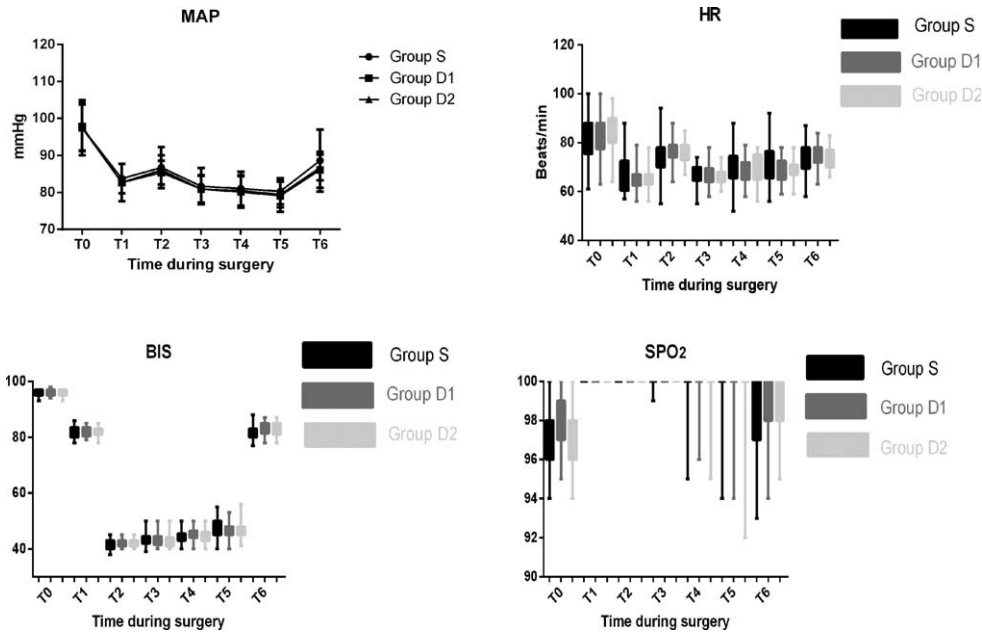
FIGURE 2. Changes in blood pressure, heart rate, Spo_2, and BIS among 3 groups. Continuous variables presented as mean ± standard deviation or median (interquartile range). Group S = sufentanil (0.02 μg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 μg/kg/h, each); and Group D2 = sufentanil (0.02 μg/kg/h) plus dexmedetomidine (0.04 μg/kg/h). None showed any statistical significance ($P > 0.05$). BIS = bispectral index (T0, arrival at the operating room; T1, before intubation; T2, after intubation; T3, before incision; T4, 30 min after one-lung ventilation; T5, 60 min after one-lung ventilation; T6, extubation), HR = heart rate, MAP = mean arterial pressure, Spo_2 = pulse oxygen saturation.
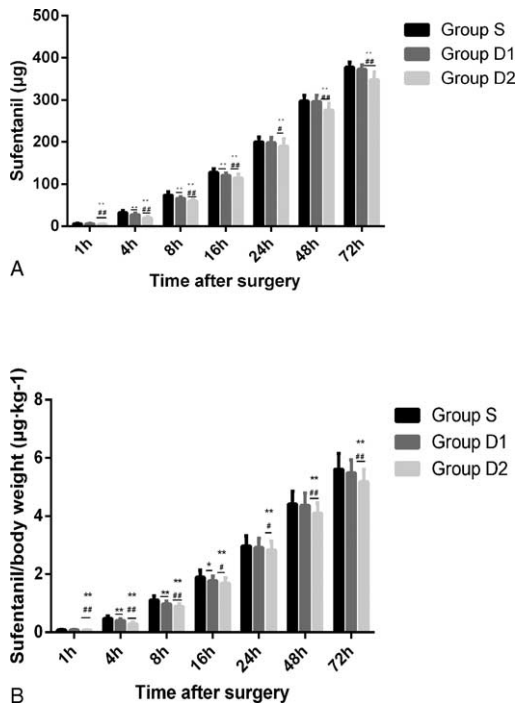

FIGURE 3. Sufentanil dosage during 72 h after surgery in S, D1, and D2 groups. Continuous variables presented as mean ± standard deviation. Group S = sufentanil (0.02 μg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 μg/kg/h, each); and Group D2 = sufentanil (0.02 μg/kg/h) plus dexmedetomidine (0.04 μg/kg/h). *$P < 0.05$ vs Group S; **$P < 0.01$ vs Group S; #$P < 0.05$ vs Group D1; ##$P < 0.01$ vs Group D1.

improve postoperative analgesia during the 24 hours after surgery. We also found that FAS positively improved at 48 and 72 hours after surgery in D2 group, which indicated that patients with high nicotine dependence in D2 group had better functional recovery. No significant differences could be seen among the 3 groups in terms of the baseline clinical characteristics and postoperative adverse effects except for itching ($P > 0.05$).

Regional techniques, such as thoracic epidural analgesia (TEA) paravertebral block, interpleural analgesia, intercostal nerve block, cryointercostal analgesia, transcutaneous electrical nerve stimulation, are very important tools in the treatment of postoperative pain after thoracotomy, especially TEA that is considered to be the gold standard of postthoracotomy analgesia. However, as Kotemane et al[3] have stated that regional technique could occasionally fail as a result of difficult anatomy or poor technique, and was contraindicated in sepsis, coagulation disorders, preexisting neurological disorders, and difficult thoracic vertebral anatomy.[4] In these situations, other methods (such as PCIA) that has few contraindications can offer an attractive alternative. As an important part of the multimodal perioperative analgesic regimen, the options of PCIA must be effective, with minimal side effects and the aim to decrease the potentially harmful consequences of thoracic surgery on the immediate and long-term patient well-being.

In this study, we found that the consumption of sunfentanil was higher than previously reported; this is because we only recruited patients with high nicotine dependence.[13–15] Our previous retrospective study also showed that smokers with high nicotine dependence exhibited more severe postoperative pain and consumed more sufentanil after thoracic surgery compared with those with low nicotine dependence.[10] The mechanisms of increase in postoperative pain associated with
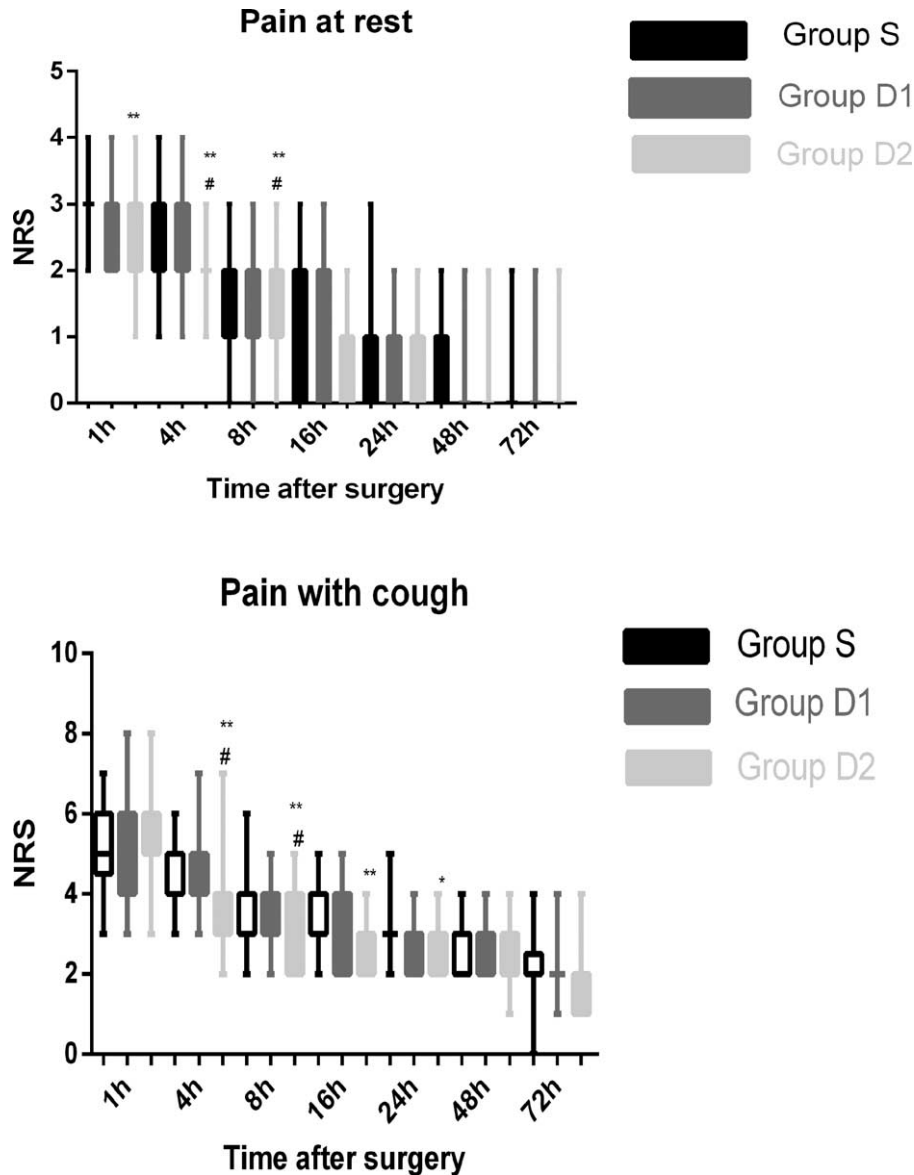
FIGURE 4. Pain score (NRS) during 72 h after surgery in S, D1, and D2 groups. Variables presented as median (interquartile range). Group S = sufentanil (0.02 μg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 μg/kg/h, each); and Group D2 = sufentanil (0.02 μg/kg/h) plus dexmedetomidine (0.04 μg/kg/h). $^{*}P < 0.05$ vs Group S; $^{**}P < 0.01$ vs Group S; $^{#}P < 0.05$ vs Group D1; $^{##}P < 0.01$ vs Group D1. NRS = numerical rating scale, NRSr = pain scores (NRS) at rest, NRSc = pain scores (NRS) with coughing.

smokers have not yet fully elucidated. Paolini and De Biasi[16] showed that nicotine-induced desensitization causes upregulation of nicotinic acetylcholine receptors, which could modulate many major neurotransmitters. Another study found that chronic nicotine inhalation could lead to an alteration in neurotransmission, which in turn result in tobacco abuse.[17] Parkerson et al[18] clarified that patients with high nicotine dependence could activate the hypothalamic–pituitary adrenal axis, and then reduce pain sensitivity. In addition, long-term smoking can induce nicotine resistant to opioid drugs.[19]

The beneficial effects of dexmedetomidine for postoperative pain control have been described in many reviews.[7,8,20] In some studies, intravenous dexmedetomidine during surgery have been found either to have a postoperative opioid-sparing effect or to reduce pain scores.[21–23] In contrast to those reports, we found a reduction in both pain score and opioid consumption in D2 groups, which is in accord with Blaudszun et al.[24] The reasons of this differences may be complex, partly because of the different analgesic mechanism of dexmedetomidine. It is believed that dexmedetomidine exhibits analgesic properties in the brain through the following ways: inhibition of adenylate cyclase activity and subsequent phosphorylation, activation of potassium channels while inhibition of voltage-gated calcium ion channels, hyperpolarization of plasma membrane, and

TABLE 2. LOS, BCS, and FAS During 72 h After Surgery in S, D1, and D2 Groups

		Group S (n = 41)	Group D1 (n = 41)	Group D2 (n = 43)	*P* Values
LOS	1 h	0 (0–1)	0 (0–1)	1 (0–1)[*,#]	0.043
	4 h	0 (0–0)	0 (0–0)	0 (0–0)	0.314
	8 h	0 (0–0)	0 (0–0)	0 (0–0)	1.000
	16 h	0 (0–0)	0 (0–0)	0 (0–0)	1.000
	24 h	0 (0–0)	0 (0–0)	0 (0–0)	1.000
	48 h	0 (0–0)	0 (0–0)	0 (0–0)	1.000
	72 h	0 (0–0)	0 (0–0)	0 (0–0)	1.000
BCS	1 h	1 (1–2)	1 (1–2)	1 (1–2)	0.548
	4 h	2 (1–2)	2 (1–2)	2 (2–3)[**,##]	0.002
	8 h	2 (2–2)	2 (1–2)	2 (2–3)[**,##]	0.001
	16 h	2 (2–3)	2 (2–2)	3 (2–3)[*,##]	0.001
	24 h	3 (2–3)	3 (2–3)	3 (3–3)	0.063
	48 h	3 (3–4)	3 (3–3)	3 (3–4)	0.244
	72 h	4 (3–4)	4 (3–4)	4 (3–4)	0.357
FAS: C/B/A (n)	1 h	36/5/0	37/4/0	39/4/0	0.936
	4 h	32/9/0	35/6/0	37/6/0	0.632
	8 h	15/25/1	22/19/0	24/19/0	0.206
	16 h	11/29/1	14/26/1	17/25/1	0.849
	24 h	6/22/13	5/23/13	3/25/15	0.865
	48 h	3/20/18	2/23/16	0/13/30[*,##]	0.017
	72 h	2/13/26	2/16/23	0/6/37[*,##]	0.018

Variables presented as median (interquartile range) or number of patients, n (%). Group S = sufentanil (0.02 µg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 µg/kg/h, each); and Group D2 = sufentanil (0.02 µg/kg/h) plus dexmedetomidine (0.04 µg/kg/h). BCS = Bruggrmann comfort scale, FAS = functional activity score, LOS = level of sedation.
[*] $P < 0.05$ vs Group S.
[**] $P < 0.01$ vs Group S.
[#] $P < 0.05$ vs Group D1.
[##] $P < 0.01$ vs Group D1.

TABLE 3. Number of Rescue Analgesia During 72 h After Surgery in S, D1, and D2 Groups

	Group S (n = 41)	Group D1 (n = 41)	Group D2 (n = 43)	*P* Values
n (%)	18 (43.90%)	15 (36.59%)	6 (13.95%)[**,#]	0.015

Variables presented as number of patients, n (%). Group S = sufentanil (0.02 µg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 µg/kg/h, each); and Group D2 = sufentanil (0.02 µg/kg/h) plus dexmedetomidine (0.04 µg/kg/h).
[**] $P < 0.01$ vs Group S.
[#] $P < 0.05$ vs Group D1.

TABLE 4. Postoperative Adverse Effects Among 3 Groups

	Group S (n = 41)	Group D1 (n = 41)	Group D2 (n = 43)	*P* Values
Nausea	18 (43.90%)	15 (36.59)	20 (46.51%)	0.656
Vomiting	9 (21.95%)	10 (24.39%)	7 (16.28%)	0.642
Itching	16 (39.02%)	12 (29.27%)	5 (11.63%)[**,#]	0.014
Shiver	8 (19.51%)	6 (14.63%)	6 (13.95%)	0.753
Delirium	12 (29.27%)	8 (19.51%)	5 (11.63%)	0.129
SRD	0	0	0	1.000

Variables presented as number of patients, n (%). Group S = sufentanil (0.02 µg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 µg/kg/h, each); and Group D2 = sufentanil (0.02 µg/kg/h) plus dexmedetomidine (0.04 µg/kg/h). SRD = serious respiratory depression.
[**] $P < 0.01$ vs Group S.
[#] $P < 0.05$ vs Group D1.

reduction of neuronal firing.[25] It is reported that activation of α_2-adrenoceptors by dexmedetomidine could also result in Gs-protein-mediated facilitation of acetylcholine release from the spinal dorsal horn synaptosomes in vitro.[26,27] Further researches are necessary to elucidate the reasons for discrepancies of the effect of dexmedetomidine on pain between movement and rest.

This pilot study addressed the need for adequate postoperative analgesia while at the same time decreased the incidence of itching by reducing opioid use, which is in accord with a meta-analysis of studies.[28] According to Overdyk et al,[29] one of the most dangerous side effects was the respiratory depression and they found respiratory depression rates in postoperative patients with a PCA pump that were higher than previously reported. However, in our study, no patients were found to have SRD (in those patients, one of the following interventions was adopted: physical stimulation, naloxone administration, or positive pressure ventilation). The reasons may be because of ages (patients in our study were younger), option of PCIA drugs (the incidence of RD was less in sufentanil, especially dexmedetomidine, than morphine), sex (only highly nicotine-dependent patients in our study), setting mode of PCA, RD monitoring protocol (may be the main reason for low incidence of RD in our observation), and type of surgery. Dexmedetomidine may increase the risk of stroke and death in patients suffering from bradycardia or using adrenergic antagonists.[30] However, we found no serious complications including stroke and death during our study.

Our study has some limitations. First, dexmedetomidine was administered at a rate of $0.5\,\mu g/kg$ for $10\,min$ before intubation and then at a rate of 0.4 to $0.6\,\mu g/kg/h$ during the operation. The hemodynamic stability may be improved through adjusting the infusion rate according to patient's condition. We did not measure the serum concentration of dexmedetomidine in this study at any time point. Second, we only had investigated highly nicotine-dependent male patients after thoracic surgery, so it remains to be proven whether our findings are also applicable to highly nicotine-dependent female patients after thoracic surgery or highly nicotine-dependent patients undergoing other types of surgery. Finally, this study was performed at a single center. Investigations of more diverse populations from different centers and using various techniques would furnish more conclusive results.

In conclusion, we found that combination of sufentanil and dexmedetomidine ($0.04\,\mu g/kg/h$) was associated with less PCA requirement, better analgesic effect, and patient satisfaction for highly nicotine-dependent patients within the initial 72 hours after thoracotomy compared with combination of sufentanil and a lower dose of dexmedetomidine ($0.02\,\mu g/kg/h$) or sufentanil alone. More studies are still required to determine the optimal dose of dexmedetomidine for reducing postoperative pain and opioid requirements in highly nicotine-dependent patients undergoing other surgeries.

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