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Original Article

Intraoperative and postoperative infusion of dexmedetomidine combined with butorphanol for intravenous patient-controlled analgesia after radical mastectomy: a double-blind, randomized clinical trial

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Abstract: Objective: To evaluate the safety and the analgesic efficacy of a loading dose of dexmedetomidine followed by a continuous infusion as an adjunct to butorphanol patient-controlled intravenous analgesia (PCIA) after radical mastectomy. Methods: In this double-blinded, randomized, controlled study, 60 female patients undergoing elective radical mastectomy under general anesthesia were randomized into two groups (n=30 per group). Group DB received a loading dose of dexmedetomidine (0.5 μg/kg) after anesthesia induction, followed by 300 μg dexmedetomidine plus 10 mg butorphanol via PCIA during the postoperative period. Group B received a volume-matched infusion of placebo after anesthesia induction, followed by 10 mg butorphanol via PCIA. Perioperative hemodynamic variables, the scores of visual analogue scale (VAS), the sedation scores, side effects, the pump-press number, additional analgesics cases and patients' satisfaction were recorded at 24 h after operation. Results: The hemodynamic variables did not show significant difference between two groups during the surgery and 24 hours postoperatively (P>0.05). The VAS scores of group DB was significantly lower than that of group B during postoperative period (P<0.05). The mean total number of button pressing of PCIA in the 24 h postoperatively was significantly decreased in group DB (8.4±4.5 times/each) compared to group B (11.3±5.3 times/each) (P<0.05). Whereas the sedation scores at each observational time point were not significantly different between two groups (P>0.05). Patients in group B displayed more dizziness and postoperative nausea and vomiting (PONV) during the 0-24 h post-surgery (P<0.05). There was no delirium, itch, oversedation, hypotension or bradycardia. The total satisfaction score about postoperative analgesia in group DB was higher than that in group B (P<0.05). Conclusions: For patients after radical mastectomy, a loading dose of dexmedetomidine followed by a continuous infusion as an adjunct to butorphanol PCIA improved the quality of analgesia and also provided an analgesic sparing effect with less adverse effects.

Keywords: Analgesia, patient-controlled, analgesia, postoperative, radical mastectomy, butorphanol, dexmedetomidine

Introduction

Breast cancer that requires frequent surgery was perhaps the most common cancer in women [1]. Radical mastectomy was widely applied in the treatment of operable breast cancer. However, postoperative nausea and vomiting (PONV), pain, and painful restricted movements frequently troubled patients after operation and inadequate analgesia was considered as an independent risk factor [2, 3].

Regional techniques, such as thoracic paravertebral nerve block, were very important tools in the treatment of postoperative pain after radical mastectomy. However, regional techniques were contraindicated in difficult thoracic vertebral anatomy, sepsis, preexisting neurological disorders, and coagulation disorders and occasionally fail because of difficult poor technique or anatomy [4, 5]. In these situations, other methods, such as patient-controlled intravenous analgesia (PCIA), with few contraindications could offer an attractive option. In consideration of multimodal analgesia, opioids combining with an adjunct drug in PCIA had been accepted extensively [6].

Butorphanol, a derivative of morphine with strong weak μ-receptor agonist/antagonist and κ-receptor agonist activity without obvious activity on δ receptors [7], could produce five times greater analgesic effect than that of morphine. It had been frequently used for postoperative analgesia [8]. The advantages of butorphanol PCIA were minimal potential for abuse, fewer side effects and low toxicity [9, 10]. However, its side effects in common with other opioids such as respiratory depression, excess sedation and PONV are obvious [11]. Consequently, it was important to find an adjunct drug producing the effect of multiple analgesia and reducing the dosage and the side effects of butorphanol.

Dexmedetomidine, a highly selective and specific alpha $(\alpha)_2$-adrenergic receptor agonist, had been applied in clinical anesthesia in recent years; it produced a dose-dependent sedation, antisympathetic effect, and analgesia (involving spinal and supraspinal sites) without serious respiratory side effects [12, 13]. Previous research had shown that intraoperative dexmedetomidine appeared to promote the analgesic effect of morphine-based PCIA postoperatively [14]. Dexmedetomidine also showed superior analgesia and opioid-sparing effects when it was used as an adjuvant agent via opioid-based PCIA [15, 16]. Furthermore, dexmedetomidine had been reported to reduce morphine consumption and related side effects in different surgeries [17, 18]. Intraoperative and postoperative dexmedetomidine added to butorphanol PCIA may afford enhanced analgesic.

There were several trials focusing on this strategy, but the dexmedetomidine dose were totally different and conclusion was unclear. This study was conducted to investigate the safety and the analgesic efficacy of a loading dose of dexmedetomidine followed by a continuous infusion as an adjunct to butorphanol PCIA in patients undergoing modified radical mastectomy.

Materials and methods

This prospective, randomized, double-blind clinical study was approved by the Ethical Committee of Yantai Yuhuangding Hospital, Qingdao university. After written informed consent, 60 ASA I-II patients (aged 25-65 years, weighted 50-75 kg) who were scheduled for elective modified radical mastectomy with axillary dissection were allocated into two groups (n=30 each). Those with ASA at least III, obesity (BMI>30), ischaemic heart disease, conduction disturbance, uncontrolled hypertension, history of chronic pain, opioid addiction, alcohol abuse, sedative-hypnotic drug(s), psychiatric disorder, neuropsychiatric diseases, liver or renal impairment and a known allergy to either butorphanol or α_2 adrenergic receptor agonists were excluded from this study. Computer-generated randomization was performed and the patient allocation was delivered in sealed opaque envelopes. A staff anesthesiologist, who was not involved in the management of the patient or the study, opened the envelopes and prepared the drugs according to randomization. The patients and all staff involved in patient management and data collection were blind to the group assignment until the end of the study or an unexpected serious adverse event including circulatory failure, conscious disturbance, and respiratory depression.

Preoperatively, patients were taught the operational use of PCIA and the visual analogue scale (VAS) scores where 0 represented no pain and 10 the worst pain. Upon arrival at the operation room, standard monitoring probes were applied, which included the blood pressure (BP), electrocardiogram (ECG), heart rate (HR), blood oxygen saturation (SpO_2) and the bispectral index (BIS). 0.5 mg penehyclidine hydrochloride was infused intravenously before the initiation of anesthesia. General anesthesia was induced by midazolam 0.05 mg/kg, fentanyl 2-3 μg/kg, propofol 1.5-2.0 mg/kg and cisatracurium 0.15 mg/kg. After laryngeal mask intubation, patients were ventilated to maintain an end-tidal carbon dioxide tension ($P_{ET}CO_2$) at 35 to 45 mmHg. Fentanyl (2-3 μg/kg) was administered before skin incision. Anesthesia was maintained by 3-12 mg/kg/h propofol and 0.06-0.1 μg/kg/min remifentanil; cisatracurium 0.03 mg/kg was given intermittently to maintain muscle relaxant when indicated. During surgery, the respiratory tidal volume, respiratory rate and inspiratory/expiratory ratio was 6-8 ml/kg, 10-14 times, 1:2. Patients' BIS value was maintained 40-60 to insure the anesthetics on the basis of amnesia. Propofol and remifentanil were terminated upon the completion of skin closure.

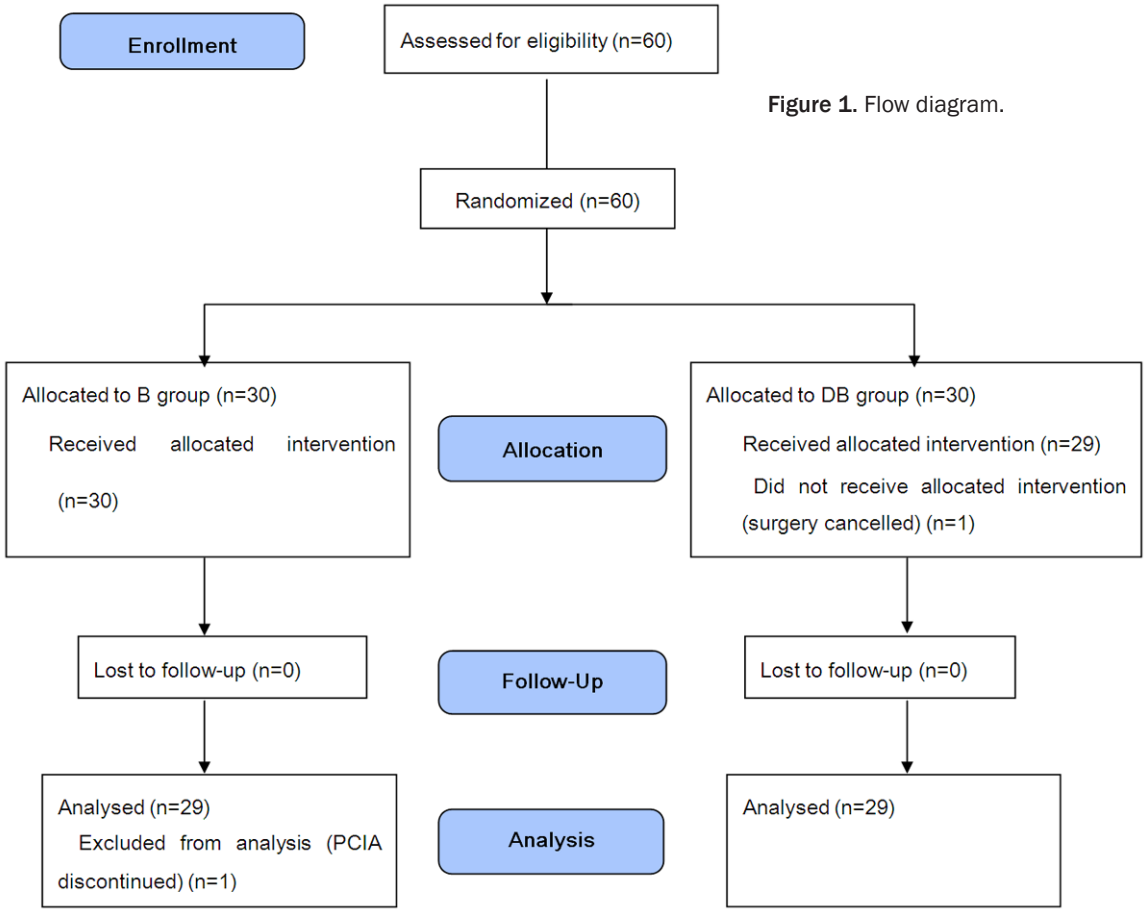

Figure 1. Flow diagram.

In each case, the aim was to maintain mean arterial blood pressure (MBP) within 80-120% of baseline values. MBP rise of more than 20% above baseline was treated with rising of propofol. MBP drop of more than 20% below baseline was treated with reduction of propofol or intravenous boluses of ephedrine 0.1 mg/kg. Bradycardia (HR<50 beats/min) was treated with intravenous atropine 0.01 mg/kg.

Dexmedetomidine were prepared in a 50-ml syringe mixed with normal saline. Immediately after intubation, group DB applied a continuous dexmedetomidine infusion of 0.5 μg/kg by intravenous pumping (not less than 10 minutes). The patients in group B received a volume-matched infusion of normal saline as placebo. Both groups received 0.5 mg butorphanol and 0.25 mg palonosetron at 30 minutes before the end of surgery. The laryngeal mask airway was extubated once spontaneous ventilation of the patient was adequate. The patient was transferred to the PACU for at least 0.5 hour for patient safety, where she received nasal O_2 supplementation and was monitored continuously for vital signs (HR, BP, ECG and SpO_2).

On completion of surgery, both groups were attached to PCIA. In group B, the 100 ml solution in the PCIA reservoir bag contained 10 mg butorphanol in normal saline; in group DB, 10 mg butorphanol plus 300 μg dexmedetomidine in normal saline. Two groups of PCIA pumps were programmed to deliver a patient controlled bolus of 0.5 ml with a lockout time 15 minutes and background infusion of 2 ml/h.

HR, MBP and SpO_2 were recorded at the following time points: arrival at the operating room (baseline, T0); induction (T1); intubation (T2); 25 min after intubation (T3); 60 min after intubation (T4); extubation (T5); 1, 2, 4, 12, 24 h after surgery (T6-T10). The pump-press number and consumption of butorphanol were recorded at T10. VAS at rest (VASR) and during movement (VASM) were assessed at T6-T10. The sedation levels were also recorded at the same

Table 1. Clinical characteristics of patients in the two groups

	Group DB (n=29)	Group B (n=29)	*P* values
Age, y	48±10.8	47±11.5	0.74
ASA I to II, n	20/9	21/8	0.77
Weight, kg	56±7.4	55±6.8	0.59
BMI, kg/m^2	21.08±1.28	21.63±1.41	0.13
Intraoperative data			
Durations of surgery, min	77±6.5	79±7.8	0.29
Duration of anesthesia, min	90±7.6	94±8.9	0.07
Estimated blood loss, mL	18.9±0.3	19.1±0.5	0.06
Fluids, ml	1000±150	1000±200	0.99
Recovery time at PACU, min	46±6	45±4	0.46

time with a five-point scoring scale (0, fully awake; 1, drowsy, closed eyes; 2, asleep, easily aroused with light tactile stimulation or a simple verbal command; 3, asleep, arousable only by strong physical stimulation; and 4, unarousable). VRSR was assessed with the patient lying supine and VRSM was assessed during change from supine to lateral position. If the VAS was >4 or upon patient request, supplemental rescue boluses of 30 mg intravenous ketorolac was administered. PCIA-related bradycardia (HR<50 beats/min), hypotension (BP<90 mmHg/60 mmHg), hyoxemia (SpO_2<90%), somnolence (sedation score ≥3), and respiratory depression (ventilatory frequency <8 bpm lasting for more than 5 min) were considered as severe adverse events. If severe adverse events occurred, the use of PCIA was stopped immediately and the adverse effects were treated with appropriate treatment. Hypotension or bradycardia was treated with intravenous ephedrine 0.1 mg/kg or intravenous atropine 0.01 mg/kg. Respiratory depression was treated with oxygen. Other adverse effects (dizziness, PONV, itching, delirium) were also recorded at T6-T10. According to the experience of postoperative analgesia, patients evaluated the therapeutic measures (very satisfied; satisfied; moderately satisfied; not satisfied) at the first 24 hours post-surgery. In addition, the pain-induced pump press number and additional analgesics cases during postoperative analgesia were also recorded at the same time.

Statistical analysis

All of the data in the present study were analyzed with SPSS for Windows Version 16.0. Data was presented as mean ± SD, number and percentages. After assessing normality, continuous data was compared by using Student's t-test, while the Mann-Whitney test was performed to compare non-continuous and non-normally distributed data. Chi-squared or Fisher' exact test was used to analyze proportions. All data with P<0.05 were considered statistically significant.

Results

Demographic data and basic clinic characteristics

A total of 60 patients were recruited in this study (n=30 in each group). One patient in DB group withdrew because of surgery cancelled; one patient in B group was excluded after surgery because of PCIA discontinued. 58 patients completed this trial (n=29 in each group) (**Figure 1**). The clinical characteristics of patients in the two groups was comparable (**Table 1**). There were no significant differences between two groups in demographic data as regard to age, weight, BMI, intraoperative data (durations of surgery; duration of anesthesia; estimated blood loss; fluids) and recovery time at PACU (*P*>0.05).

The hemodynamic variables did not show significant difference between two groups during the surgery and 24 hours postoperatively in **Figure 2** (*P*>0.05). The MBP and HR showed a significant reduction after anesthesia induction in both groups then returned to baseline level after anesthe sia recovery in both groups. Moreover, there was a trend towards a lower HR and MBP in the DB group after administration of the loading dose of dexmedetomidine, but this failed to reach statistical significance between two groups.

Superior analgesia

Compared with group B, the VAS scores of group DB, either VRSR or VRSM, were significantly lower at 1 h, 2 h, 4 h, 12 h and 24 h after operation (**Figure 3**). No patients received rescue analgesic. Whereas there was no statistically significant difference in levels of sedation between two groups at each observational time point (**Figure 4**). Besides, the mean total num-

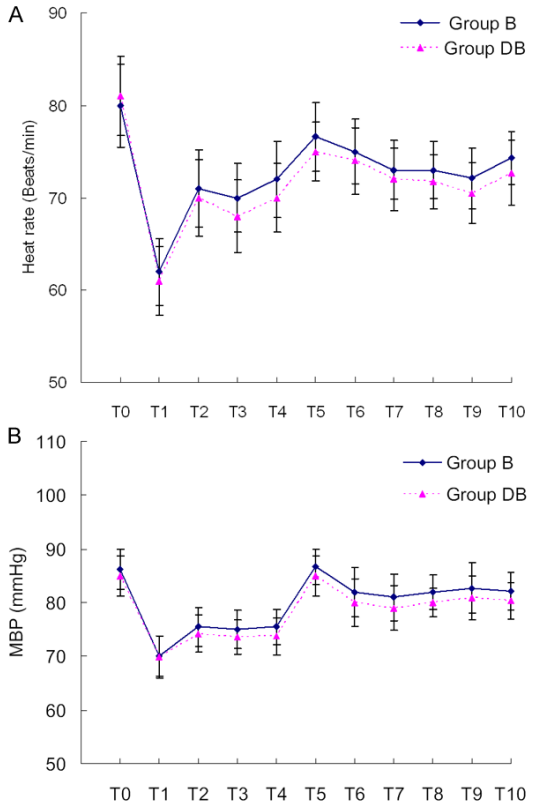

Figure 2. HR, MBP. A. Heart rates at different time points; B. MBP at different time points. T0: Baseline; T1: induction; T2: intubation; T3: 25 minutes after intubation; T4: 60 minutes after intubation; T5: extubation. T6-T10: 1, 2, 4, 12, and 24 h after operation.

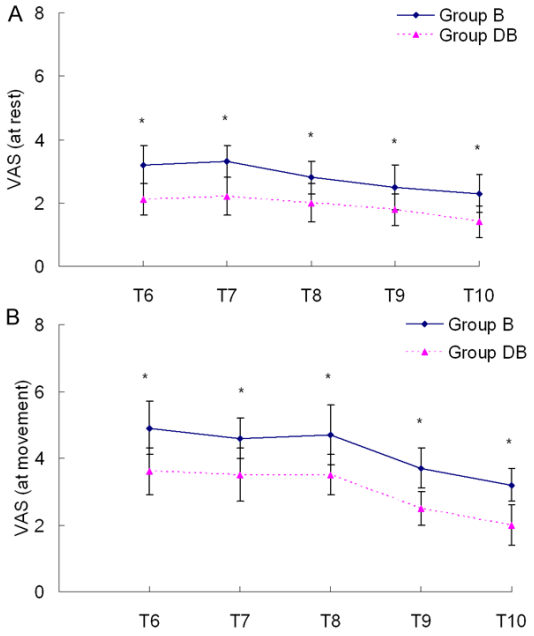

Figure 3. VAS pain scores at different time points in the two groups.

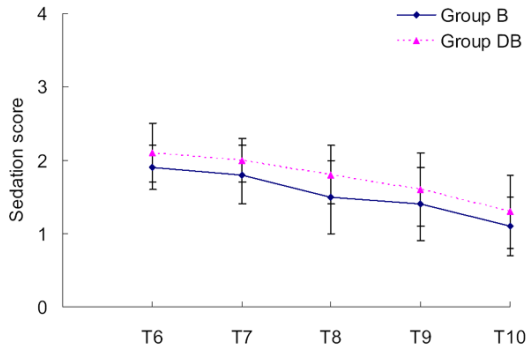

Figure 4. Sedation scores 24 hours after surgery.

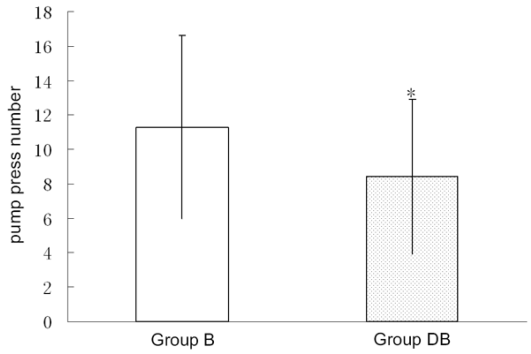

Figure 5. Pump-press numbers 24 hours after surgery. (*P<0.05).

ber of button pressing of PCIA in group DB was also significantly lower than that in group B, which were 8.4±4.5 times/each and 11.3±5.3 times/each respectively (**Figure 5**). In the postoperative period, it means that patients in group DB required 26% less PCIA butorphanol than that in group D. There were 82.8% patients in group DB who were satisfied with the PCIA therapy. By contrast, there were only 58.6% in group B (**Table 2**).

Less postoperative adverse effects

In the postoperative period, there was no instance of serious adverse events (respiratory depression, hypotension, bradycardia, somnolence). The 0-24 h rates of dizziness and PONV in group DB were significantly lower than those in group B (P<0.05). No patients in either group developed itching or delirium (**Table 3**).

Discussion

This trial showed that the dexmedetomidine-butorphanol combination resulted in superior

Table 2. Comparison of patient satisfaction in the Two Groups

	Group DB (n=29)	Group B (n=29)	*P* values
Overall satisfied	24 (82.8%)	17 (58.6%)	0.04
Very satisfied	8 (27.6%)	5 (17.2%)	0.35
Satisfied	8 (27.6%)	6 (20.7%)	0.54
Moderately satisfied	8 (27.6%)	6 (20.7%)	0.54
Not satisfied	5 (17.2)	12 (41.4%)	0.04

Table 3. Postoperative side effects from patients in the two groups

	Group DB (n=29)	Group B (n=29)	*P* values
Nausea			
0-24 h	2 (6.8%)	12 (41.4%)	0.01
0-4 h	1 (3.4%)	6 (20.7%)	0.04
4-24 h	1 (3.4%)	6 (20.7%)	0.04
Vomiting			
0-24 h	2 (6.8%)	12 (41.4%)	0.01
0-4 h	1 (3.4%)	6 (20.7%)	0.04
4-24 h	1 (3.4%)	6 (20.7%)	0.04
Itching (0-24 h)	0	0	1.00
Respiratory depression (0-24 h)	0	0	1.00
Dizziness (0-24 h)	1 (3.4%)	6 (20.7%)	0.04
Bradycardia (0-24 h)	0	0	1.00
hypotension (0-24 h)	0	0	1.00
Over sedation (0-24 h)	0	0	1.00
Delirium (0-24 h)	0	0	1.00

analgesia, significant butorphanol sparing and less side effects without clinically relevant bradycardia, hypotension, oversedation, or respiratory depression.

PCIA, using narcotic analgesics for the treatment of postoperative pain, was one popular way in current clinical practice [19]. Dexmedetomidine approved by the US Food and Drug Administration for sedation of adults for up to 24 h during mechanical ventilation was unlike traditional sedatives, and it could work on the central nervous system at the locus coeruleus to induces sedation similar to natural sleep [20]. The addition of dexmedetomidine to other opioid analgesics, such as sufentanil and morphine, had been shown to enhance the quality of analgesia and also provides an analgesic sparing effect with no serious side effects [15, 21]. Those evidences noted above accordant with the results of the current trial suggested that patients with postoperation pain might benefit from perioperative dexmedetomidine administration. We speculated that dexmedetomidine might act as a ideal candidate in postoperation pain control via butorphanol-based PCIA.

When infused at rates of 0.2-0.7 μg/kg/hr, dexmedetomidine produced clinically effective sedation and reduced the analgesic requirements of ventilated ICU patients [22]. Besides, a loading dose of dexmedetomidine (0.5 μg/kg) was reported to reduce the labour pain [23]. Because of the concern that the use of large loading dose of dexmedetomidine might increase the risk of delayed recovery from anesthesia, we selected a loading dose of dexmedetomidine (0.5 μg/kg). The onset time for dexmedetomidine is approximately 15 minutes, with a longer duration of action (elimination half-life 2-3 hours). Moreover, the duration of operations was relatively short (about 80 minutes) in this study. In relation to those above, dexmedetomidine was adopted this load capacity after anesthesia induction. Because of transient hypertension caused by α_2-agonists at higher doses by activating α_{2B}-adrenoceptor located on smooth muscle cells in the resistance vessels [24], slow intravenous loading over 10 to 20 minutes was recommended [25, 26].

In some studies, intraoperative dexmedetomidine had been found either to have a postoperative opioid-sparing effect or to reduce pain scores [27, 28]. In contrast to those reports, we found a reduction in both pain score and opioid consumption in DB group. The reasons of this differences might be partly because of a continuous infusion as an adjunct to butorphanol PCIA in current trial. That was accorded with previous studies demonstrating opioid-sparing effects by dexmedetomidine. The synergistic analgesic resulting from the different analgesic mechanism of dexmedetomidine and butorphanol was an important reason [29].

It was considered that conscious sedation after surgery was necessary to help patients to reduce postoperative anxiety and improve postoperative recovery. But excessive sedation

was very dangerous. The sedation of dexmedetomidine combined with butorphanol's sedative property might result in the excessive sedation. However, we didn't find excessive sedation during postoperative PCIA and there was also no statistically significant difference in levels of sedation between two groups. This might be due to following four reasons: 1) butorphanol itself has certain calming effect; 2) doses of dexmedetomidine in our study were lower than the recommended maintenance infusion for sedation; 3) the PCIA delivery system could prevent excessive sedation; 4) group DB required less PCIA butorphanol resulting in mitigate the level of sedation.

In this study, the reduction of dizziness and PONV was another benefit of combining dexmedetomidine and butorphanol during the 0-24 h postoperative period. This maybe because dexmedetomidine that can decrease norepinephrine activity and produce a sedative effect may account for this case. Butorphanol-sparing effect of dexmedetomidine which contributed to a reduction in the risk of opioid-related side effects was also an important reason. In addition, pain itself was an important risk factor for PONV [30, 31]. More intense pain may have induced PONV and thus made patients in group B require more PCIA butorphanol which in turn aggravated PONV. Previous study reported that the addition of dexmedetomidine to morphine PCIA without bolus dose could provide superior analgesia, but anti-PONV effects of dexmedetomidine were lessened in the first 4 h after surgery [15]. The current trial avoided the above mentioned situation. The reasons of this differences may be because of an additional intraoperative loading dose of dexmedetomidine in current trial.

Hypotension and bradycardia were the most frequently reported adverse events associated with dexmedetomidine and had limited the clinical applications of dexmedetomidine [32, 33]. However, no such significant hypotension or bradycardia were observed during the first 24 hours post-surgery in current study, which may be due to the low loading dose of intraoperative dexmedetomidine and a relatively lower maintenance dose. Nevertheless, there was a trend towards a lower HR and MBP in the DB group after administration of the loading dose of dexmedetomidine, but none of the patients required treatment.

There were some limitations in the present trial. Firstly, this study was a short-time research and lack of long-term follow-up data. Secondly, we adopted a single dose of dexmedetomidine resulting in failing to evaluate the optimal dose of dexmedetomidine. Finally, this study was performed at single center.

In conclusion, for patients after radical mastectomy, a loading dose of dexmedetomidine (0.5 μg/kg) followed by a continuous infusion as an adjunct to butorphanol PCIA could reduce butorphanol consumption, enhance the analgesic effect and improve patients' satisfaction compared with butorphanol PCIA alone, and was devoid of additional sedation and other relevant adverse effects.

Acknowledgements

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Disclosure of conflict of interest

None.

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