Efficacy of dexmedetomidine in reducing post-operative pain and improving the quality of recovery in patients with burn wounds undergoing tangential excision skin grafting

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Abstract. Burn-induced acute post-operative pain and the associated stress response may result in prolonged convalescence. The present study investigated the effects of dexmedetomidine (DEX) administration on post-operative pain and the quality of recovery following surgical treatment of moderate-to-severe burn injuries. A total of 60 adult patients undergoing tangential excision skin grafting were randomized into two groups. The DEX group (Group D) received an intravenous (i.v.) single-dose bolus injection of DEX 0.5 μg/kg >10 min prior to induction of anesthesia. Patient-controlled intravenous analgesia (PCIA) was provided to the patients from the end of the surgery, which consisted of 100 μg sufentanil plus 200 μg DEX. The control group (Group C) received an equal volume of normal saline as a pre-operative bolus and post-operative PCIA of 100 μg sufentanil infusion. The Visual Analogue Scale (VAS) score at rest and during movement, the cumulative dose of sufentanil and the 40-item quality of recovery questionnaire (QoR-40) score were assessed at various time-points after the surgery. During the first 24 h post-surgery, patients in Group D exhibited a lower VAS score at rest and during movement, a lower number of PCIA pump presses (29.17±1.91 vs. 34.13±2.73) and lower sufentanil consumption (62.58±0.96 vs. 65.27±1.26) compared with those in Group C ($P<0.05$). Furthermore, the QoR-40 recovery score of patients in Group D at 24 h post-surgery was higher compared with that in Group C ($P<0.01$). In conclusion, the present study indicated that a pre-operative bolus of DEX (0.5 μg/kg) followed by DEX plus sufentanil by PCIA subsequent to surgery improved the quality of analgesia and promoted the quality of recovery at 24 h following tangential excision skin grafting treatment of patients with moderate-to-severe burn injuries compared to PCIA of 100 μg sufentanil only. The present study was retrospectively registered with the trial registration no. ChiCTR1800016646 (date of registration, 14/06/2018).

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Introduction

Acute stress disorder, post-traumatic stress disorder, chronic pain and depression are highly prevalent among survivors of severe burns (1). Anesthetic management may modulate this physiological response and impact post-operative recovery. Maintaining analgesia and appropriate sedation in patients with burns may be highly challenging and typically requires high doses of anxiolytics and analgesics. However, escalating doses of opioids and benzodiazepines provide little additional benefit and may increase the incidence and severity of side effects (2).

Dexmedetomidine (DEX) is a selective α-2 adrenergic agonist that has sympatholytic, analgesic and sedative properties (3). Various clinical trials have identified that intra-operative administration of DEX may promote recovery, enhance the analgesic properties of morphine in patient-controlled analgesia and reduce morphine consumption along with its associated adverse effects (4,5). A recent study indicated that in patients undergoing cervical spine surgery, the intra-operative and post-operative use of DEX was able to reduce the post-operative requirement of analgesics and promote recovery (6). Multiple studies have indicated that DEX has an active influence on recovery (7-9), even at a single dose (10). However, few studies have assessed the effects of DEX on analgesia and general anesthesia recovery in patients with burns. Of note, DEX provides sedation and improves the conditions for induction of general anesthesia, and its use has been reported in patients with burns during dressing changes or mechanical ventilation during intensive care unit sedation (11,12). In addition, it has been revealed that intra-operative DEX infusion reduces the stress response and therefore improves the quality of recovery following major spinal surgery (9).

Based on the evidence above, the present randomized, double-blinded, placebo-controlled study, was performed to test the hypothesis that the use of DEX improves the analgesic effects of sufentanil-based patient-controlled intravenous analgesia (PCIA) and promotes the quality of recovery of patients treated for moderate-to-severe burns under general anesthesia.

Materials and methods

The present study was approved by the Ethics Committee of Yantai Yuhuangding Hospital of Qingdao University (Yantai, China). Written informed consent was obtained from all participants prior to randomization. A total of 60 consecutive patients (age, 18-65 years) were enrolled in the present study between January 2017 and November 2017. Patients exhibited American Society of Anesthesiologists (ASA) grade II or III burns (13), with burn surface areas that met the criteria for moderate-to-severe burn. Patients were conscious and actively cooperated and underwent general anesthesia for tangential excision skin grafting. The exclusion criteria were as follows: Known or suspected allergy to α-2 receptor agonists or non-steroidal anti-inflammatory drugs; sinus bradycardia; myocardial dysfunction; chronic respiratory insufficiency; impaired renal or hepatic function; regular use of sedatives or anti-depressants; additional respiratory tract burns and/or severe complex injuries. Patients were instructed regarding the use of the Visual Analogue Scale (VAS) (14), where 0 indicated no pain and 10 indicated the worst pain imaginable, and the PCIA pump.

Patients were randomly assigned to two groups using computer-generated random numbers and the sequentially numbered opaque sealed envelope technique. The DEX group (Group D) received an intravenous (i.v.) single-dose bolus injection of 0.5 μg/kg DEX (Precedex; Aibeinin, Inc., Henrui Pharmaceutical, Lianyungang, China) >10 min prior to induction of anesthesia. PCIA was provided to patients at the end of the surgery, which consisted of 100 μg sufentanil plus 200 μg DEX. The control group (Group C) received volume-matched normal saline prior to the induction of anesthesia and 100 μg sufentanil infusion in PCIA. To ensure that the study was blinded, the test drug infusion was prepared by a different anesthesiologist. In addition, the VAS score was evaluated by another anesthesiologist.

Routine monitoring, including measurement of the heart rate (HR), blood pressure (BP), pulse oxygen saturation, electrocardiograms and depth of sedation according to the bispectral index (BIS), was performed at 5-min intervals. General anesthesia was induced with midazolam (0.05 mg/kg), propofol (1.5-2.0 mg/kg), fentanyl (3.0 μg/kg) and cisatracurium (0.15 mg/kg) as described previously (8,15). After the administration of cisatracurium, orotracheal intubation was performed using a 6.5- and 7.5-mm tracheal tube for female and male patients, respectively. Mechanical ventilation was maintained with a 6-8 ml/kg tidal volume and a respiratory rate of 12-15 breaths per min (inspiratory-to-expiratory time ratio, 1:2), which maintained the end-tidal CO_2 at 35-45 mmHg. The i.v. infusion was switched to a maintenance syringe pump at a rate of 0.06-0.10 μg/kg/min for remifentanil and a 1.0-2.5 minimal alveolar concentration of sevoflurane in order to maintain a BIS of 45-60 during the surgery (16,17). Cisatracurium (0.05 mg/kg) was intermittently used for muscle relaxation. Bradycardia (HR, <50 beats/min) was treated with i.v. atropine (0.5 mg). Tachycardia (HR >100 beats/min) was treated with i.v. esmolol in 20-mg increments. Hypotension [systolic BP (SBP) <25% of baseline level] was treated with i.v. phenylephrine (20 μg). Hypertension (SBP >25% of baseline level) was treated with i.v. nitroglycerin (10 μg). Neuromuscular blockade was antagonized by i.v. administration of 1.0 mg neostigmine and 0.5 mg atropine. Following extubation, patients were transferred to the post-anesthesia care unit (PACU) and received nasal O_2 supplementation.

All patients were transferred to the ward once they met the recovery room criteria. A PCIA pump (Disposable Infusion Pump; WZ-6523C-4; Fornia Medical Device Co., Zhuhai, China) was connected to the i.v. line and configured to administer sufentanil and DEX or 1 μg/ml sufentanil diluted in 100 ml normal saline with a basal infusion of 2 ml/h with a lockout period of 15 min (the self-controlled doses were set at 0.5 ml each). If the VAS at rest was ≥4, the PCIA button was pressed. If the pain was not alleviated, the rescue anesthetic tramadol (0.1 g) was orally administered.

The primary outcomes were the patient's VAS at rest and during movement, and the 40-item quality of recovery questionnaire (QoR-40) score. The secondary outcomes were the number of PCIA pressings, the cumulative dose of sufentanil and any opioid-associated side-effects. The VAS at rest and during movement, the number of times the patient pressed the PCIA pump, the cumulative dose of sufentanil and any opioid-associated side-effects were recorded for the first 24 h and then every 4 h post-surgery. The QoR-40 was used to evaluate the quality of post-operative recovery at 24 h, as described previously (18,19). Five categories of recovery were included in the QoR-40: Emotional state (9 items), physical comfort (12 items), psychological support (7 items), physical independence (5 items) and pain (7 items). Each item was graded on a 5-point scale, and global scores ranged from 40 (poor quality of recovery) to 200 (excellent quality of recovery).

Statistical analysis. The sample size of the study was calculated according to previous studies, and was based on a pilot study (6,20). A total of 25 patients in each group were required to assess their pain using the VAS scoring system; the statistical power and type I error of the subsequent analysis was 0.85 and 0.05, respectively. A total of 67 patients scheduled for tangential excision skin grafting under general anesthesia were assessed for eligibility. To achieve a statistical power of at least 85% using repeated-measures analysis of variance (ANOVA) with a significance level of 0.05 and a dropout rate of 10%, at least 28 subjects were recruited in each group. A total of 60 patients were therefore enrolled and assigned to Group D (n=30) and Group C (n=30).

Statistical analyses were performed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA). All quantitative data were expressed as the mean ± standard deviation. Parameters including age, weight, body mass index (BMI), duration of surgery, duration under anesthesia, duration of extubation, duration in the PACU, number of times the patient pressed the PCIA pump, sufentanil consumption and recovery scores were

Table I. Patient characteristics and surgery or anesthesia-associated information.

Parameter	Group D (n=30)	Group C (n=30)	P-value
Age (years)	37.10±12.17	37.57±11.07	0.877
Sex (M/F)	21/9	20/10	0.781
Weight (kg)	68.68±6.68	70.73±8.33	0.298
BMI (kg/m^2)	22.43±2.30	23.07±2.35	0.283
Duration of surgery (min)	90.00±15.69	87.37±20.18	0.575
Duration of anesthesia (min)	132.73±15.94	131.97±18.30	0.767
Duration of extubation (min)	9.67±3.25	11.57±2.70	0.772
Duration of stay at the PACU (min)	33.73±5.62	33.43±5.38	0.833

Values are expressed as the mean ± standard error of mean. BMI, body mass index; PACU, post-anesthesia care unit; M, male; F, female; D, dexmedetomidine; C, control with normal saline.

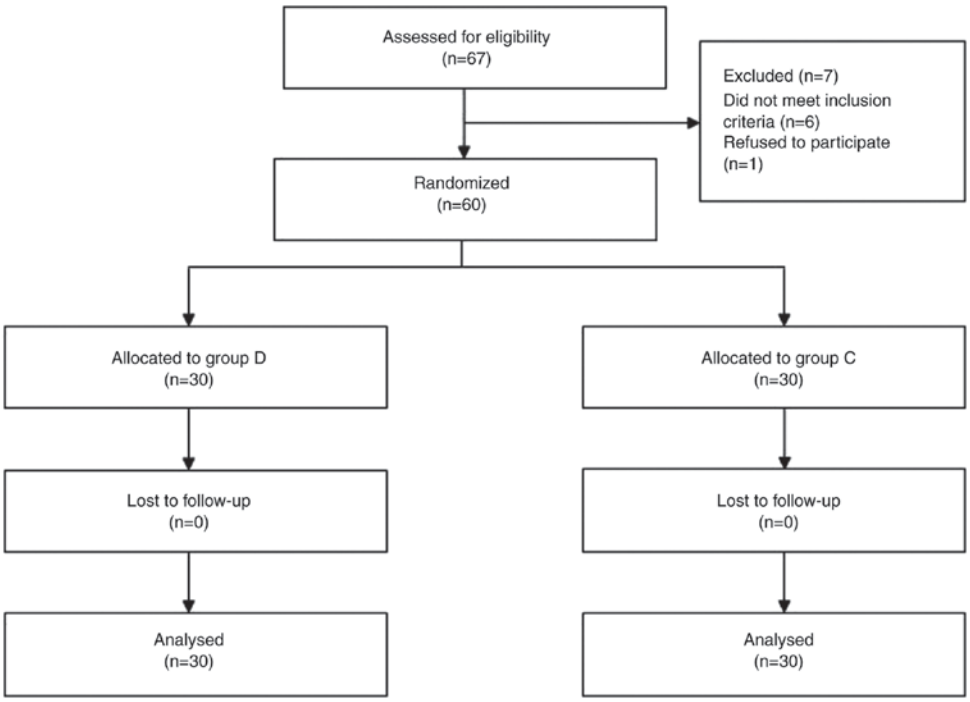

Figure 1. Flow chart displaying randomized patient assignment to the study groups and treatment protocols. Group D and C were treated with sufentanil. D, dexmedetomidine; C, control with normal saline.

compared between the two groups using an unpaired Student's t-test. HR, mean arterial pressure (MAP) and VAS score at different time-points (2, 4, 8, 12 and 24 h post-surgery) were compared between the two groups using two-way ANOVA followed by Bonferroni's post-hoc test. ASA grade, sex and post-operative adverse effects were evaluated using the χ^2 test or Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Demographic data and anesthesia-related information. A total of 67 patients scheduled for tangential excision skin grafting under general anesthesia were assessed for eligibility, of which 7 excluded due to ineligibility. Subsequently, a total of 60 patients were enrolled in the present clinical trial and randomized into two groups: Group D (n=30) and Group C (n=30). All patients completed the study (Fig. 1). There were no significant differences between the two groups in terms of patient characteristics, type of surgery undergone or anesthesia-associated variables, including age, sex, weight, BMI, duration of surgery, duration under anesthesia, duration of extubation and duration of stay at the PACU (Table I).

MAP and HR at different time-points. MAP and HR during surgery and at 24 h post-surgery were determined (Fig. 2). The two groups were comparable with regard to their baseline HR and MAP. In addition, the two groups exhibited reductions in HR and MAP upon induction of anesthesia. Furthermore, Group D and Group C exhibited increases in HR and MAP in response to intubation. However, Group D demonstrated

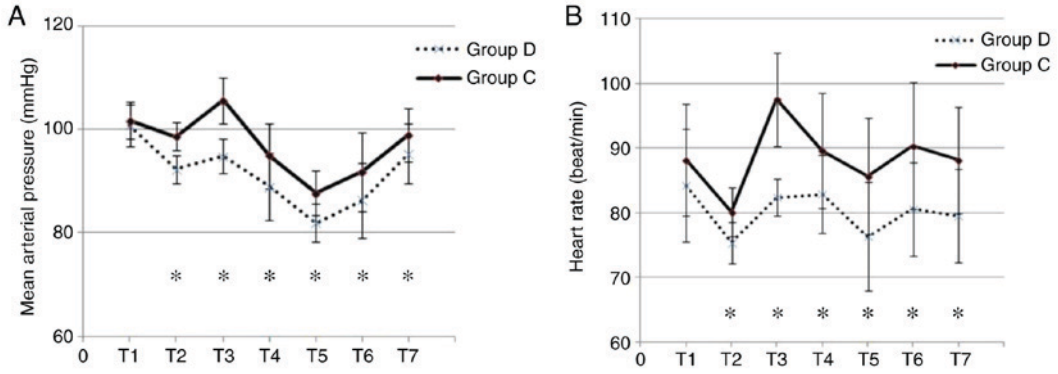

Figure 2. MAP and HR. (A) MAP and (B) HR at different time-points. *P<0.05, group D vs. C. T1, baseline; T2, induction; T3, intubation; T4-T7, 4, 8, 12 and 24 h post-surgery, respectively; MAP, mean arterial pressure; HR, heart rate; D, dexmedetomidine; C, control with normal saline.

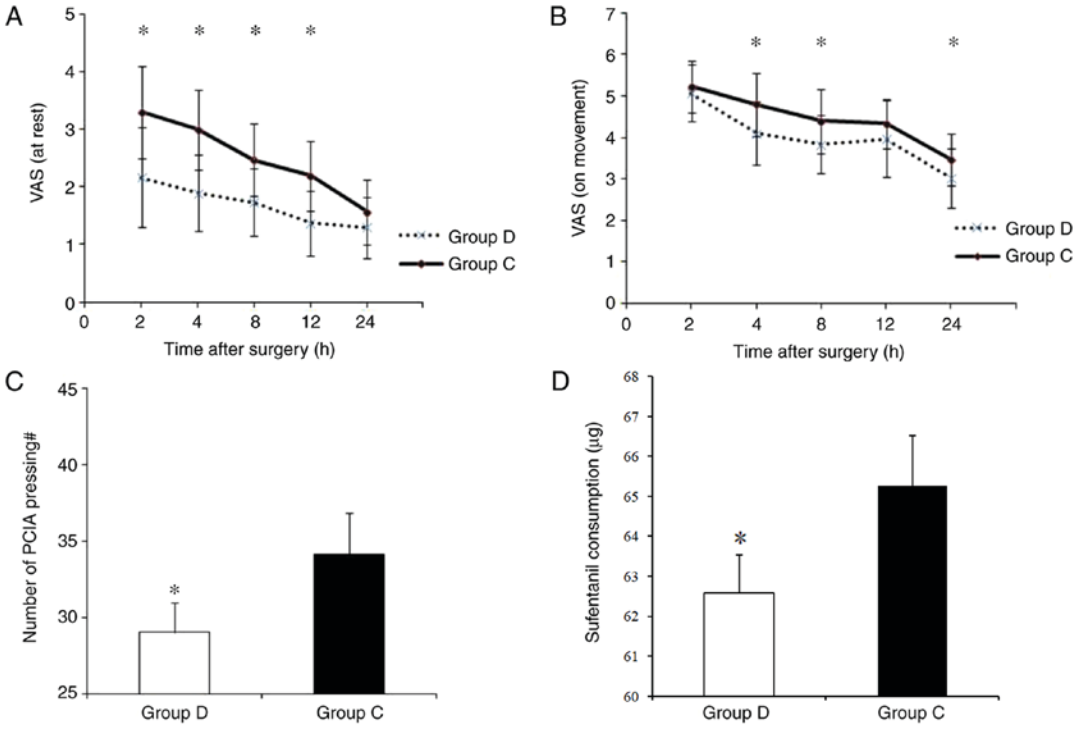

Figure 3. Efficacy of 24-h PCIA. (A and B) VAS pain score (A) at rest and (B) during movement at different time-points in the two groups. (C and D) Number of PCIA pump presses and sufentanil consumption during the first 24 h post-surgery. *P<0.05, group D vs. C. PCIA, patient-controlled intravenous analgesia; VAS, Visual Analogue Scale.

a greater hemodynamic stability during the induction and intubation compared with Group C. Subsequently, the MAP and HR gradually returned to baseline levels within 24 h of surgery (Fig. 2A and B).

Postoperative PCIA evaluation. Post-operative pain was assessed using the VAS, and the number of pain-induced pump presses and sufentanil consumption was also recorded. During the first 24 h post-surgery, patients in Group D exhibited a lower VAS score at rest (at 2, 4, 8 and 12 h post-surgery, P<0.05; Fig. 3A) and during movement (at 4, 8 and 24 h post-surgery, P<0.05; Fig. 3B). Compared with that in Group D, patients in Group C also exhibited a higher number of PCIA pump presses (29.17±1.91 vs. 34.13±2.73; P<0.05; Fig. 3C) and a higher sufentanil consumption (62.58±0.96 μg vs. 65.27±1.26 μg; P<0.05; Fig. 3D).

Quality of recovery. The QoR-40 scores at 24 h post-surgery were determined (Table II). The mean global QoR-40 score in Group D was 175.97±9.68, which was significantly higher than the QoR-40 score of 133.53±13.77 in Group C (P<0.01).

Postoperative adverse effects. At 24 h post-surgery, tramadol (0.1 g) was orally administered to 2 patients in Group D and 6 patients in Group C, whose VAS scores were ≥4 at rest (P=0.255). No significant difference was observed in the post-operative adverse effects between Group D and Group C during the first 24 h post-surgery (Table III).

Discussion

The results of the present prospective, double-blinded, randomized controlled study indicated that administration

Table II. Scores of the 40-item quality of recovery questionnaire in different sub-categories and global score at 24 h post-surgery.

Item	Group D (n=30)	Group C (n=30)	P-value
Emotional state	39.90±4.61	30.03±3.81	<0.001
Physical comfort	54.60±3.18	39.93±7.33	<0.001
Psychological support	30.30±2.95	24.33±4.56	<0.001
Physical independence	20.63±2.66	18.13±4.04	0.006
Pain	30.53±3.05	21.13±3.40	<0.001
Global score	175.97±9.68	133.53±13.77	<0.001

Values are expressed as the mean ± standard error of mean. D, dexmedetomidine; C, control with normal saline.

Table III. Post-operative side effects.

Adverse effect	Group D (n=30)	Group C (n=30)	P-value
Nausea	2 (6.67)	3 (10.00)	0.999
Vomiting	1 (3.33)	3 (10.00)	0.612
Itch	0 (0.00)	0 (0.00)	-
Respiratory depression	0 (0.00)	0 (0.00)	-
Dizziness	0 (0.00)	1 (3.33)	1
Bradycardia	2 (6.67)	0 (0.00)	0.492

Values are expressed as n (%). D, dexmedetomidine; C, control with normal saline.

of 0.5 μg/kg DEX pre-operatively followed by 200 μg DEX and 100 μg sufentanil by post-operative PCIA was effective in promoting the analgesic efficacy of sufentanil-based PCIA without any significant side effects. Furthermore, it enhanced the patient-reported global quality of recovery at 24 h following tangential excision skin grafting. Patients with moderate-to-severe burns eligible for tangential excision skin grafting were recruited. Moderate-to-severe burns are defined as second-degree burn injuries covering <29% of the body surface area or third-degree burn injuries covering <10% of the body surface area. Patients with burns undergo excruciating pain as a result of their injuries and during the procedures that are associated with surgery and wound care (21). Perception of the pain depends on the degree of the burn and the sensory input into the burn area, and also displays an inter-patient variability. The aim of the present study was to explore whether DEX infusion provides any beneficial effects as an effective multi-modal analgesic regimen with PCIA sufentanil and improve the recovery after surgery.

Opioids are the fundamental drugs used for post-operative analgesia. Sufentanil is specifically suitable for post-operative PCIA due to its fast response and excellent analgesic effects. However, with increasing doses, sufentanil produces dose-dependent adverse reactions, and studies have been performed to identify novel drugs, consolidate currently available drugs and reduce opioid use in order to avoid side effects, including nausea, vomiting and itching (22). DEX is an α-2 adrenergic agonist that was developed in the 1990s and was first used as a short-term sedative in intensive care units (23). Clinical trials have confirmed that combining DEX with sufentanil for PCIA allows for a significant reduction in the amount of sufentanil administered and improves analgesia (24,25). Furthermore, similar results were obtained in a previous study for thoracic surgery where an infusion dose of 0.04 μg/kg/h DEX in combination with 0.02 μg/kg/h sufentanil reduced post-operative pain during the initial 72 h post-surgery (26). In the present study, DEX was administered at an infusion dose of ~0.03 μg/kg/h DEX, which is an approach that has been used for patient-controlled analgesia in Asian patients (7). The present results indicated that the combined use of DEX with sufentanil had an improved capacity to relieve post-operative acute pain at rest and during movement compared with sufentanil alone. Specifically, pre-operative administration of 0.5 μg/kg DEX followed by post-operative DEX and sufentanil by PCIA improved the QoR-40 pain scores in patients that underwent tangential excision skin grafting at 24 h post-surgery. In addition, the number of PCIA pump presses and the sufentanil consumption were reduced. However, there was no significant difference between Groups C and D with regard to the supplemental requirement for tramadol. Of note, the analgesic and opioid dose-reducing/sparing effects of DEX have been well documented in previous studies in adult and pediatric patients (7,8,27). Together with these results, the present study demonstrated that pre-operative administration of 0.5 μg/kg DEX and the administration of DEX in combination with sufentanil PCIA provided effective analgesia following tangential excision skin grafting.

DEX has been reported to cause common treatment-associated adverse effects, including hemodynamic changes, including hypotension (30%), hypertension (12%) and bradycardia (9%) where mean infusion dose was 7.1 μg/kg (the percentages represent the frequencies at which they occurred in subjects) (23). For general anesthesia, DEX may be applied in three primary ways, namely continuous infusion, a single injection and a loading dose injection followed by continuous infusion (15). A loading dose followed by a continuous injection is most likely to cause adverse events. A recent study indicated that a single pre-operative dose of DEX for central venous catheter insertion reduced procedural pain and provided clinically acceptable sedation (28). In the present study, a single-dose bolus injection of DEX was administered to patients prior to induction of anesthesia. In contrast to previous studies, where DEX in a dose range of 1-2 μg/kg was used (29,30), it was decided that 0.5 μg/kg DEX would be used in the present study; DEX has a moderate analgesic effect and achieves a significant capping effect at 0.5 μg/kg. However, in a preliminary experiment that used a dose of 1 μg/kg, significant bradycardia and hypotension was observed in the majority of patients, who therefore required pharmacological intervention. In the present study, in order to avoid hypertension, hypotension and bradycardia, a single dose of 0.5 μg/kg DEX was safely applied >10 min prior to induction of anesthesia, as described previously (31). In certain clinical studies, intravenous administration of lower doses of DEX (0.5-0.6 μg/kg) was reported to attenuate

pressor responses (32,33). In Group D of the present study, where a single-dose bolus injection of DEX was applied, a significant difference in HR and MAP from that in Group C was observed, and the profiles suggested that administration of DEX provided more stable hemodynamics. Of note, DEX attenuated the increase in HR and MAP following intubation. A significant reduction in HR and MAP following induction of anesthesia was also observed; however, values remained within the normal clinical range during the surgery. These results demonstrate the safety of using a low-dose (0.5 μg/kg) DEX infusion.

The QoR-40 is a useful objective measure of the quality of recovery following anesthesia and surgery. It is a valid, reliable and clinically acceptable method to assess the recovery score, which may be comparable to the VAS score and a nine-item questionnaire (19,34). In the present study, the global QoR-40 scores were significantly higher in Group D compared with those in Group C, which is consistent with the results of a recent study by Lee *et al* (35). In the present study, it was observed that the QoR-40 scores referring to all categories were improved among patients in Group D compared with those in Group C. Population-based studies have suggested an association between the efficacy of intra-operative DEX infusion and patient-perceived quality of recovery as a initial evaluation method (4,5,7,36). In previous studies, the QoR-40 scores were different between the DEX and control groups following abdominal colectomy and radical mastectomy (5,37). Together with these previous results, the present study indicated that pre- and post-operative administration of DEX promotes recovery, alleviates pain and reduces opioid-induced adverse effects, including nausea and vomiting, in the early post-operative period.

Of note, the present study had certain limitations. First, evaluation using the QoR-40 questionnaire was not performed pre-operatively or on days 2 and 3 following surgery. Furthermore, even though an anesthesiologist who was not involved in the present study prepared the test drug infusion, administration of DEX may cause significant hemodynamic changes compared with the placebo, which may have been identified during surgery; this may have caused a certain bias to observers. Overall, based on the relatively restricted sample sizes, the present study provided reliable and valid results.

In conclusion, pre-operative administration of 0.5 μg/kg DEX followed by post-operative PCIA of 200 μg DEX and 100 μg sufentanil improved the quality of analgesia and recovery compared with that of 100 μg sufentanil by PCIA only at 24 h following tangential excision skin grafting in patients with moderate-to-severe burns.

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Availability of data and materials

The analyzed datasets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

MJ and QS performed the study and were also major contributors in writing the manuscript. QS and GL analyzed data. JM and HQ designed the study and revised manuscript. JM revised manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Human Investigations Committee of Yantai Yuhuangding Hospital of Qingdao University and IRB. All patients provided their written informed consent.

Patient consent for publication

All patients provided written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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