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The optimal dose of dexmedetomidine added to an sufentanil-based analgesic regimen for postoperative pain control in spine surgery

A probit analysis study

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Abstract

Postoperative spinal patients remain a challenge for provision of postoperative analgesia. Patient-controlled intravenous analgesia (PCIA) is a major method in reducing the severe pain after the surgery in our institution, but some adverse effects prevent the use of adequate dosage opioids.

This study was determined using the probit analysis to investigate the optimal dose of dexmedetomidine (DEX) infusion for postoperative analgesia combined with sufentanil (SUF) in spine surgery.

The dose of DEX needed to produce satisfactory analgesia conditions following combination of 3.0 μg/kg SUF in PCIA pump, which was diluted to 250 mL with a 4 mL/h as background infusion. Patients were recruited with age 35 to 65 years. The satisfactory criteria of postoperative analgesia were determined with a average satisfaction level of pain control, sedation, self-satisfaction, and adverse effects, among others. The dose of DEX was determined using the modified Dixon's up-and-down method (0.5 μg/kg as a step size). The first patient was test at 3.0 μg/kg DEX. The patient was assessed at 6, 12, 36 hours, and termination of PCIA following the continuous infusion of DEX-SUF mixture in PCIA after surgery.

Twenty-five patients were enrolled by predetermined criteria. The optimal dose of DEX required for satisfactory analgesic was 4.33 (SD, 0.38) μg/kg combined with 3.0 μg/kg SUF via a PCIA volume of 250 mL by background infusion of 4 mL/h. Using probit analysis, the ED_{50} of DEX was 4.12 μg/kg (95% confidence limits 3.74–4.52 μg/kg) for satisfactory postoperative analgesic in spine surgery, the ED_{95} of DEX was 4.85 μg/kg (95% confidence limits 4.48–7.13 μg/kg). There was no report of somnolence or respiratory depression, relevant bradycardia or hypotension, or over sedation in this study.

The optimal dose of DEX was 4.33 (0.38) $\mu g/kg^{-1}$ combined with 3.0 $\mu g/kg^{-1}$ SUF diluted to 250 mL with a background infusion of 4 mL/h for satisfactory analgesic after spine surgery. From probit analysis, ED_{50} and ED_{95} of DEX were 4.12 μg/kg (95% confidence limits 3.74–4.52 μg/kg) and 4.85 $\mu g.kg^{-1}$ (95% confidence limits 4.48–7.13 μg/kg), respectively.

Abbreviations: ASA = American society of anesthesiologists, DEX = dexmedetomidine, ED_{50} = 50% effective dose, ED_{95} = 95% effective dose, N&VS = nausea and vomiting scored, PACU = postanesthetic care unit, PCIA = patient-controlled intravenous analgesia, RSS = Ramsay sedation score, SpO_2 = pulse oxygen saturation, SSS = self-satisfaction scored, SUF = sufentanil, VAS = visual analogue score.

Keywords: dexmedetomidine, postoperative analgesia, probit analysis, spine surgery, sufentanil

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C-SD and YL contributed equally to the study and should be regarded as co-first authors.

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1. Introduction

Intractable pain remains a major challenge for patients during the postoperative period undergoing complex spine surgery owing to extensive damage of soft tissues and muscles surrounding the vertebral column. Inadequate pain relief has been shown to contribute to adverse outcomes like delayed recovery, poor rehabilitation, and progression to chronic pain.[1] Intravenous opioid offers a unique type of technique in patients who do not accept other interventional procedures undergoing spine surgery, and patient-controlled intravenous analgesia (PCIA) is one of the most common techniques for postoperative pain control since individual pharmacokinetic and pharmacokinetic variability allows individual titration.[2] Many of the patients control preoperative pain with opioid analgesics, which can result in tolerance and hyperalgesia even before the start of surgery.[3]

Dexmedetomidine (DEX) is a highly selective α_2 adrenergic receptor agonist that has sedative, analgesic, and antianxiety actions, but does not cause respiratory depression.[4] Of the multimodal protocols, combining DEX with an sufentanil (SUF) in PCIA after the surgery has been reported to allow reduce SUF consumption and improve patients' satisfaction compared with SUF in PCIA alone.[5] However, there has been no study investigating the optimal dose of DEX for postoperative analgesia combining SUF in PCIA in patients after the spine surgery.

The aim of this study was to determine the optimal dose of DEX required to provide satisfying pain control with PCIA pump using small-dose SUF without side effects related to PCIA drugs administration.

2. Methods

2.1. Study design

The study is a probit analysis-tested, double-blinded, randomized drug-controlled trial screening the optimal dose of DEX with combined with sufentanil (SUF) in a postoperative setting. After surgery, patients receive a postoperative pain control by the continuous background infusion of DEX combined with SUF using the PCIA pump for approximately 48 hours. Additionally, all patients were firstly allowed to push the PCIA button (self-administer their own PCA medications) to achieve a rescue analgesic, if still cannot satisfied, patients receive meperidine administered for insufficient analgesia. All of the patients were administered by an anesthetist who was blinded to study and did not participate in data collection. Furthermore, the anesthetist resident who collected postoperative data was blinded to study and this process continued to end of the study. Trial registration is ChiCTR-ONC-16008376.

2.2. Patients and anesthetic technique

This study was approved by the institutional review board at the third affiliated hospital of Anhui Medical University and written informed consent for the study was obtained from all patients. Young or middle-aged adult patients, ASA physical status I to II, undergoing general anesthesia for elective spine surgery were enrolled into the study. The exclusion criteria from enrollment included patients with a left ventricular ejection fraction <45%, heart rate <60 bpm, second- or third-degree atrioventricular block and rate-controlled atrial fibrillation, or a history of hypertension, ischemic heart disease, acute or chronic hepatitis, requirement for renal supplementation, or a known uncontrolled seizure disorder, a known or suspected physical or psychological dependence on an abused drug other than alcohol, or a serious central nervous system pathology, a psychiatric illness that would confound a normal response to sedative treatment or they were pregnant or lactating, or they were treated for chronic pain preoperatively.

The medical history was reviewed at 1 to 2 days before the operation, and the optimal surgical conditions were assessed for each patient in our institution. All patients received a standard anesthetic with SUF intravenous infusion for intraoperative analgesia in spine surgery, and patients were premedicated with 2 mg intravenous midazolam at 30 minutes before the operation. Anesthesia was induced with intravenous infusion using propofol 1.5 mg/kg, SUF (Sufentanil Citrate; Inc, RenFu Pharmaceutical, China) 0.4 μg/kg, and relaxation provided with 0.25 mg/kg cisatracurium. After intubation was performed, anesthesia was maintained using intravenous infusion of 100 to 200 μg/kg/min of propofol and 0.003 to 0.005 μg/kg/min of SUF, and ventilation was mechanically controlled to maintain 1% to 2% sevoflurane in 100% oxygen. The end-tidal carbon dioxide was maintained at between 35 and 45 mmHg. Narcotrend monitor (Narcotrend index: NI) was applied while anesthesia was given to obtain the appropriate anesthesia depth. Cisatracurium boluses were administered at 0.08 mg/kg/h, and fluid administration was adjusted as needed throughout the duration of anesthesia maintenance to maintain hemodynamic stability in all patients. Cisatracurium was discontinued 30 minutes before the completion of the procedure as were other procedure-related drugs as appropriate. Neostigmine and atropine were given to reverse residual neuromuscular block at the end of surgery. Extubation was performed after sufficient spontaneous breathing in an awake patient (NI > 95). Patients total recovery from anesthesia with stayed 1 hour in the post-anesthetic care unit (PACU) (as judged by the ability to obey verbal commands on request and stable hemodynamic variables). All patients were attached to an electronic infusion pump (JA5806 PCA; Inc., ShangHai ANGEL, ED, China) for PCIA and being fully awake allowed to back the general ward. The study commenced in the postoperative period.

2.3. Study protocol and pain measurement

A standard SUF in PCIA protocol was adopted throughout the studied period. This background infusion basically, the dose of SUF and DEX (Precedex; Aibeinin, Inc, Henrui Pharmaceutical, China) was mainly referred to the previous study in a similar infusion rate.[5,6] The PCIA protocol consisted of 3.0 μg/kg SUF and 3.0 μg/kg DEX diluted to 250 mL and administered at a continuous dose (with a background infusion) of 4 mL/h (both the SUF and DEX at a mean rate of 0.048 μg/kg/h) and a bolus dose of 2 mL, with a lock-out of 10 minutes. Patients were allowed to push the PCIA button (self-administer their own PCA medications) to achieve a rescue analgesic when they could not tolerate pain throughout the study period after surgery. The dose of DEX used for each patient was determined by the grade satisfaction (following description in several indicators) of the previously investigated patient using the modified Dixon up-and-down method (using 0.5 μg/kg as a step size).[7] If analgesia was unsatisfactory, which postoperative patients receive a background infusion and either self-administer medications after surgery, the DEX dose was increased by 0.5 μg/kg. And if it was satisfactory, it was decreased by 0.5 $\mu g/kg^{-1}$. During the study period, if patients required >3 self-administered PCIA of rescue medications within 1 hour, an adjunctive analgesic with intrave-

nous meperidine 50 mg (bolus) was administered as supplement rescue analgesic drug.

Postoperative analgesia satisfaction survey was evaluated according to scoring system described by following indicators: the visual analogue score (VAS) from 0 (pain free) to 10 (maximum level of pain). The restlessness score was estimated based on Ramsay sedation score (RSS) from 1 to 6 (1 = anxious and agitated, 2 = cooperative, tranquil, oriented, 3 = responds only to verbal commands, 4 = asleep with brisk response to light stimulation, 5 = asleep without response to light stimulation, 6 = non responsive).[8] Nausea and vomiting scored (N&VS) from 1 to 4 (1 = without nausea and vomiting, 2 = nausea without vomiting, 3 = <2 times vomiting, 4 = severe vomiting >2 times). Self-satisfaction scored (SSS) from 1 to 4 (1 = not satisfied, 2 = moderately satisfied, 3 = satisfied, 4 = very satisfied).[5,9]

The study background continuous infusion was started when patients were shifted to PACU. Before enrollment, patients were screened for study eligibility. A resident of anesthetist visited the patients before the operation and described the VAS for them. All patients were instructed on the operational use of PCIA system and received background infusion with SUF and DEX till termination of PCIA pump in the postoperative period. Electrocardiogram, blood pressure and oxygen saturation (SpO_2) were monitored continuously for at least 48 hours. Each patients was assessed and recorded at 2, 6, 12, 36, and the time of termination of PCIA after surgery. However, suitability for termination of PCIA pump was also reviewed during the visit. When any of severe adverse events (including SpO_2 <90%, HR <50 pdm, mean arterial blood pressure decreased >20 mmHg as preoperative value) occurred, PCIA was immediately suspended, and the patient was managed accordingly.

2.4. Outcome measures

2.4.1. Main outcome measure. The optimal infusion dose (microgram per kilogram) of DEX within the approximately 48 hours combined with SUF for the postoperative pain control using the PCIA.

Secondary outcome measures are:

(i) Baseline personal situation on the SSS (self-satisfaction scored) validated pain questionnaire.
(ii) The cumulative meperidine consumption (milligrams) within the approximately 48 hours after surgery (PCIA).
(iii) Systematic quantitative N&VS and any of adverse events (including SpO_2, HR, arterial blood pressure).

2.4.2. Satisfactory indicators. The primary outcome of this study was the postoperative pain control by the continuous background infusion of DEX combined with SUF at 4 mL/h using the PCIA pump, which could be set to deliver optimal dose of DEX according to the fixed rates with continuous infusion and also patient request with a self-administer medication. For each patient data, a mean number of VAS, RSS, N&VS, and SSS were calculated using 1-sample *t* test at the end of study period. All quantitative variables are presented as mean number and standard deviation (SD), and the cumulative amount of self-administered bolus medications and supplemental rescue meperidine analgesia were recorded throughout the duration after surgery. After obtaining these data, the patient was evaluated by following PCIA satisfaction criteria, that is the patient was considered satisfactory if the PCIA protocol by DEX dose has been established, which can be summarized as: mean VAS $\leq$3; mean RSS between 2 and 4; number of self-administer PCA medications was $\leq$3; there was no adjuvant other opioids analgesia throughout the postoperative period; and a mean SSS >2. Otherwise, the patient was considered as unsatisfactory.

2.5. Statistical analysis

Statistical analyses were performed using the statistical package SPSS 13.0 for windows (IBM, Chicago, IL). Data are expressed as mean (SD). The 50% effective dose (ED_{50}) of DEX enabling satisfied postoperative analgesia was determined by calculating the midpoint concentration of all independent pairs of patients after at least 7 crossover points (i.e., unsatisfactory to satisfactory of postoperative analgesia) were obtained. The ED_{50} was defined as average of the crossover midpoints in each pair. The up-and-down data were also analyzed by a probit analysis, which enabled us to derive the mean of the DEX dose with 95% confidence limits. The maximal likelihood estimators of the model variable were performed using a probit analysis that furnished the best-fitting sigmoid curve. $P < 0.05$ was considered significant.

3. Results

A total of 59 patients were assessed for eligibility. Then, 24 patients did not meet inclusion criteria, 7 patients refused to participate in this study, 1 patient did not receive allocated intervention and 2 patients were lost to follow-up. Therefore, 25 patients completed this study (Fig. 1). Twenty-five patients were enrolled into this study. All patients had spinal surgeries including spinal fusions, corpectomy, diskectomy, and laminectomy. In terms of spinal location including lumbar 16 cases, cervical 5 cases and thoracic 4 cases. The patients' characteristics and analgesic profiles at 2 hours to the time of termination of PCIA after the surgery were shown in Table 1.

Dose–response data for each patient obtained by the up-and-down method are shown in Figure 2. The continuous infusion dose of DEX required for satisfactory pain control during postoperative period using SUF-based PCIA drug mixure was 4.33 (0.38) μg/kg. The dose of DEX for satisfactory pain control in majority of patients was 4.5 μg/kg whereas its relative effective dose ranges were 3 to 5 μg/kg. From probit analysis, ED_{50} and ED_{95} of DEX were 4.12 μg/kg (95% confidence limits 3.74–4.52 μg/kg) and 4.85 μg/kg (95% confidence limits 4.48–7.13 μg/kg), respectively (Fig. 3). The trend of DEX dose–response in RSS and SSS (mean values) is shown in Figure 4. The trend of DEX dose–response in N&VS (mean values) is shown in Figure 5. There was no report of somnolence or respiratory depression, and without relevant bradycardia or hypotension, or over sedation in this study. None of the adverse events warranted terminating PCA use.

4. Discussion

SUF is widely used anesthesia because of its rapid peak, powerful analgesic activity and short half-life. Despite the recommendation of the French Society of Anesthesia and Intensive Care to use an opioid bolus for analgesia during painful procedures,[10] it may lead to many untoward side effects delaying discharge of patients.[5–7] DEX represents an important agent for the treatment of severe postoperative spinal pain as a supplemental agent with patients that do not achieve adequate analgesia from narcotics.[11] In this study, the continuous infusion dose of DEX required for satisfactory pain control during postoperative period using SUF-based PCIA drug mixure was 4.33 (0.38) μg/kg. Study

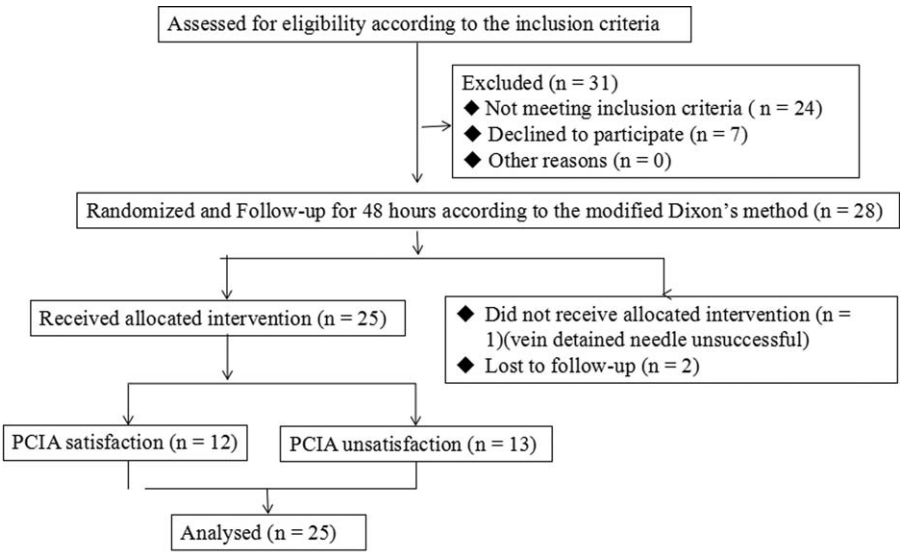

Figure 1. Patients enrollment flow diagram. PCIA = patient-controlled intravenous analgesia.

drugs were started in the postoperative period and continued for >48 hours; the ED_{50} and ED_{95} of DEX were 4.12 μg/kg (95% confidence limits 3.74–4.52 μg/kg) and 4.85 $\mu g/kg^{-1}$ (95% confidence limits 4.48–7.13 μg/kg), respectively.

DEX is currently indicated in the United States for sedation of adult mechanically ventilated patients in an intensive care setting with a maximum intravenous infusion rate of 0.7 μg/kg/h for 24 hours.[12] A recent study has shown that a 0.3-μg/kg/h infusion of DEX decreased morphine requirement by 54% for postoperative analgesia in spine surgery.[13] The recommended infusion dose of DEX is 0.2 to 0.7 μg/kg/h with 1.0 μg/kg loading dosage for sedation in elderly patients.[14] However, as the distribution half-life of DEX is known to be 5 to 10 minutes, and the elimination half-life of it is about 2 hours. The different recommended doses of DEX for sedation and the administration of DEX only intraoperatively may have contributed to the previously reported conflicting results on the role of the intraoperative infusion of DEX in postoperative pain status. Indeed, lower doses and both the intra- and postoperative administration of DEX have been shown to improve pain status, such as good postoperative analgesia with minimal side effects.[11,13] In line with study have demonstrated that the addition of DEX and SUF showed better analgesic effect and greater patient satisfaction without other clinically related side effects.[15,16] Improved analgesia by DEX might come from the synergistic analgesic interactions with opioids owing to its selective blockade of α_2 A receptors, inhibiting the release of pronociceptive transmitters and hyperpolarization of spinal interneuron's, reducing the excito-

Table 1

Patients' characteristics and analgesic profiles after the surgery.

Patients and procedures characteristics	
Age, y	53 (9)
Weight, kg	61 (9)
Sex (M/F)	16/9
Duration of anesthesia, min	183 (34)
Duration of surgery, min	162 (35)
Induction SUF consumption, μg	24 (4)
Intra-operative SUF consumption, μg	42 (11)
Excubated in operating room (number of patients)	17
Analgesic profiles after the surgery	
Duration of PCIA, h	55 (6)
Number of self-medications by PCIA pump	16 (12)
Postoperative SUF consumption, μg	186 (38)
Postoperative DEX consumption, μg	247 (47)
Dose of meperidine administration, mg	107 (62)

Data are mean (SD) or numbers. DEX = dexmedetomidine, M/F = male/female, PCIA = patient-controlled intravenous analgesia, SUF = sufentanil.

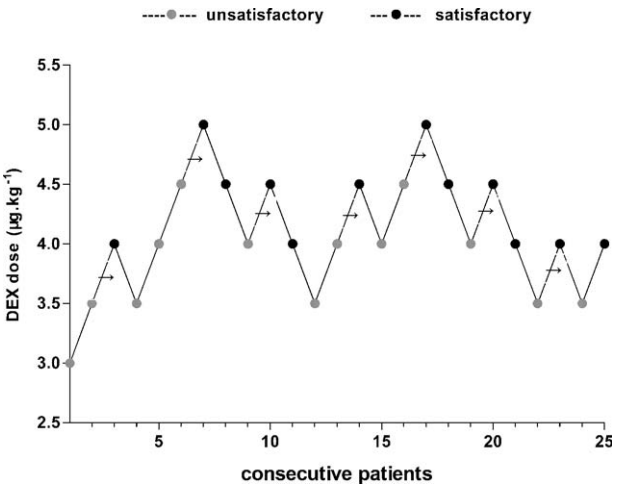

Figure 2. The responses of 25 consecutive patients in whom satisfactory analgesia were investigated and the dose of DEX. Arrows indicate the midpoint doses of all independent pairs of patients involving a cross-over (i.e., unsatisfactory to satisfactory). The optimal dose of DEX for postoperative analgesia at which a satisfactory pain control in 50% of patients was 4.33 (0.38) μg/kg. DEX = dexmedetomidine.

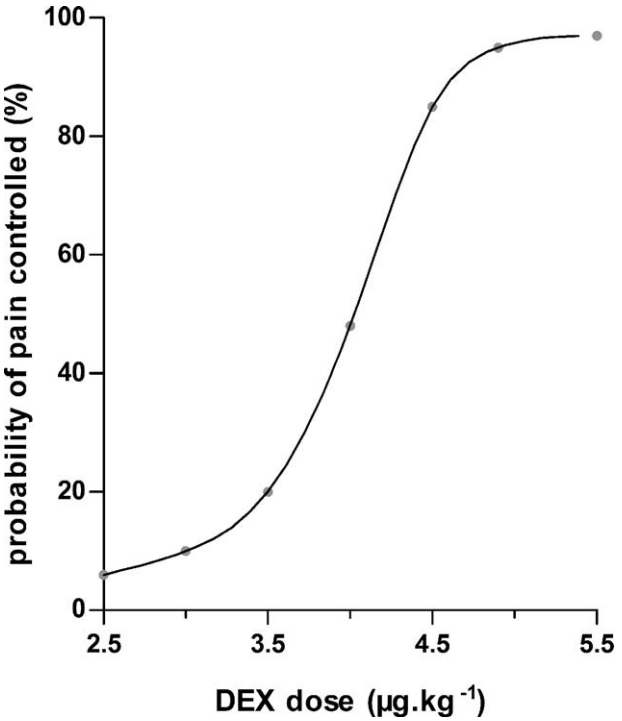

Figure 3. Dose–response curve from the probit analysis of individual DEX dose and the reaction to postoperative analgesia in the patients. The doses of DEX at which there was a 50% and 95% probability of satisfactory analgesia were 4.12 μg/kg[1] and 4.85 μg/kg, respectively. DEX = dexmedetomidine.

toxicity and improving the blood supply to the ischemic cerebral tissues.[17–19]

Although our results are consistent with those of these above studies, all cases were of moderate sedation, with a mean RSS of 1.2 to 2.7 when they achieved their steady dose of DEX without a bolus dose. The minimal optimum dose of DEX to avoid excessive sedation should be determined in postoperative analgesia, which is also usual practice to avoid the adverse reaction of it at our institution. The PCIA protocol consisted of

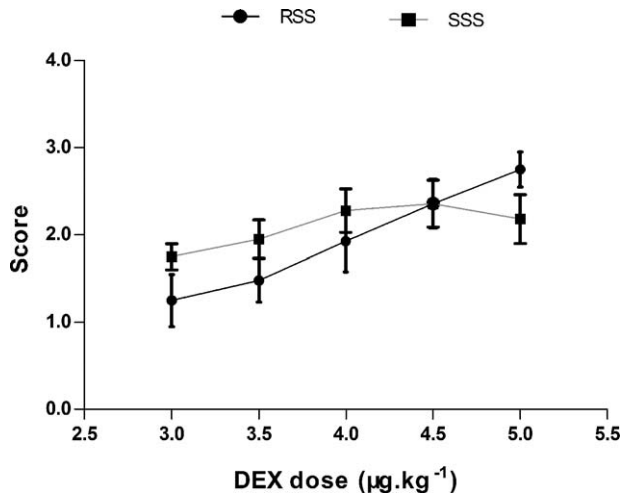

Figure 4. The trend of DEX dose–response in RSS and SSS (mean number). DEX = dexmedetomidine, RSS = Ramsay sedation score, SSS = self-satisfaction score.

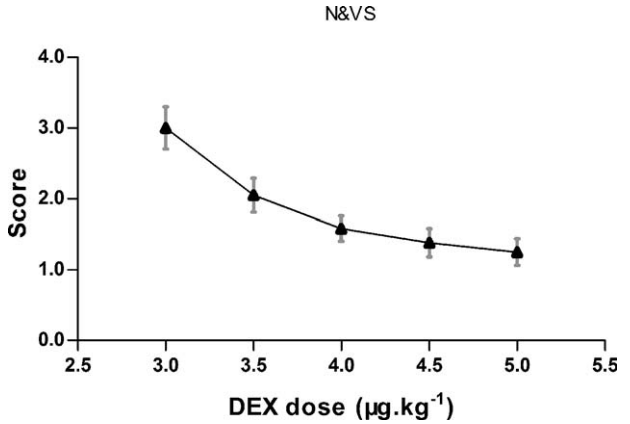

Figure 5. The trend of DEX dose–response in N&VS (mean number). DEX = dexmedetomidine, N&VS = nausea and vomiting score.

drugs diluted to 250 mL and all of these cases were initiated with DEX at 0.048 μg.kg/h. Despite all cases also received SUF at same a rate by continuous infusion for >50 hours of the postoperative period, in 48% of cases were satisfactory by a continuously infusion of DEX, doses from 4.0 to 5.0 μg/kg, and in the remainder of cases were unsatisfactory from 3.0 to 3.5 μg/kg. Based on the dosages, the duration of DEX received was a mean of 55 hours (SD 6, range 42–61 hours), and the pain score significantly decreased following the initiation of DEX. Our study also revealed that DEX added to a SUF-based PCIA drug mixture provided beneficial effect in that it reduced the frequency and dose of opioids used to treat postoperative pain after spine surgery, and the addition of a minimum dose DEX reduced the opioid or DEX-related adverse effects like nausea, bradycardia, hypotension, and respiratory depression.

One of the more worth noting in our study is that the preoperative infusion of SUF at 0.005 μg/kg/min might produce an influence on patients' pain intensity in the early postoperative period after spine surgery. A recent study by Peter et al[20] suggested that the postoperative pain intensity is influenced by the type of surgical incision but not the type of surgery nor the duration of surgery. Prolonged intraoperative administration of continuous intravenous opioid infusion may reduce opioid requirements in the immediate postoperative period. Based on the amount of drug used in our study, despite the dose of maintenance of anesthesia with SUF significantly higher than those of postoperative analgesic, the postoperative pain status could be largely improved by the postoperative effect of DEX. In other words, DEX-SUF mixture significantly enhances the analgesic effect of SUF and reduces the coexisting opioid-inducted adverse effects. However, in the presence of these effects, it is difficult to distinguish whether analgesic or sedative effects are responsible for reduced pain intensity.[21] In line with studies demonstrating opioid-sparing effects by DEX,[22] our study found that the sedative state of the patients is a highly satisfactory factor to reduce the postoperative pain.[23] In this manner, our results showed that patients are generally satisfied with PCIA system that had been a qualified sedation level with adjuvant combination of DEX to SUF in PCIA. Although a mild sedative and hypnotic effects was caused by SUF completed analgesic efficacy.[24] In clinical practice, the sedative effect after DEX administration is obvious. DEX intravenous with an appropriate dose, it produces sleepy but are easily aroused, at a higher dose, it produced faster onset of sedation without significant respiratory depression, and the drug possesses anxiolytic and

moderate analgesic effects.[25] When such a drug with anxiolysis and sedation effects is used as part of postoperative analgesic regimen, concerns regarding potentially reducing the number and severity of opioid-related side effects might appear.

Our study has some limitations. First, we did not measure the serum concentration of DEX in this study at any time point. Second, we only investigated young or middle-aged adults patients after spine surgery, so it remains to be proven whether our finding is also applicable to pediatric and elderly patients after spine surgery or patients undergoing other types of surgery. Finally, this study was performed at a single center.

In conclusion, the dose-finding study was determined to investigate for optimal balance between postoperative analgesia and adverse effects of this DEX-SUF combination. The optimal dose of DEX was found to be 4.33 (0.38) μg/kg combined with 3.0 μg/kg SUF diluted to 250 mL with a background infusion of 4 mL/h. From probit analysis, ED_{50} and ED_{95} of DEX were 4.12 μg/kg (95% confidence limits 3.74–4.52 μg/kg) and 4.85 μg/kg (95% confidence limits 4.48–7.13 μg/kg), respectively.

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