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Sex Differences in the Morphine-Sparing Effects of Intraoperative Dexmedetomidine in Patient-Controlled Analgesia Following General Anesthesia

A Consort-Prospective, Randomized, Controlled Clinical Trial

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Abstract: Previous studies have reported that intraoperative dexmedetomidine has morphine-sparing effects in patient-controlled analgesia (PCA). The present study was designed to investigate the possible sex differences in the morphine-sparing effects of intraoperative dexmedetomidine following general anesthesia. A total of 223 patients scheduled for surgeries under general anesthesia were divided into female and male groups. Each group was then subdivided into 2 subgroups that were maintained using propofol/remifentanil/dexmedetomidine (PRD) or propofol/remifentanil/saline (PRS). During the first 24 hours postsurgery, both female and male PRD patients had lower scores on a visual analog scale (VAS) (fPRS vs fPRD, $P < 0.05$ or $P < 0.01$; mPRS mPRD, $P < 0.05$, $P < 0.01$, or $P < 0.001$) and consumed less morphine than their controls from the PRS group (fPRS vs fPRD, $P = 0.0392$; mPRS vs mPRD, $P = 0.0041$). Interestingly, the female PRD patients had similar VAS scores (fPRD vs mPRD, $P > 0.05$) and consumed comparable morphine compared to the male PRD patients (fPRD vs mPRD, $P = 0.4238$). However, when normalized to body weight, they consumed much more morphine than male PRD patients (fPRD vs mPRD, $P < 0.001$), and this effect was not seen in the PRS patients. Intraoperative administration of dexmedetomidine appeared to have a stronger morphine-sparing effect in controlling postoperative acute pain in male patients than in female patients.

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Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, BMI = body mass index, DEX = dexmedetomidine, HR = heart rate, MBP = mean blood pressure, PACU = postanesthesia care unit, PCA = patient-controlled analgesia, VAS = visual analog scale.

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INTRODUCTION

Postoperative pain is one of the key causes of prolonged convalescence following surgery with general anesthesia.[1,2] Opioid-based PCA (patient-controlled analgesia) is well established and has been widely used for postoperative analgesia.[3] Currently, the main challenge with PCA is to reduce opioid consumption to avoid any related side effects.

Anesthesia management, such as the use of new drugs, can modulate surgery-induced postoperative acute pain.[4] Clinical and basic animal studies have reported that the highly selective alpha-2 adrenergic receptor (α2-AR) agonist dexmedetomidine has analgesic effects, and it prolongs the analgesic time of local anesthetics for up to 24 hours after dental and osteopathic surgeries.[5,6] The analgesic and opioid-sparing effects of dexmedetomidine have also been well described in previous studies both in adults and children.[7–9] Our recent study also reported that intraoperative DEX had significant morphine-sparing effects in postoperative acute pain control patients following abdominal colectomy.[10] Animal studies revealed that clonidine, another α2-AR agonist, produced significant antinociceptive effects in male and ovariectomized female rats but not in estradiol-treated ovariectomized female rats, which indicated that the effects of α2-AR activation might be influenced by sex.[11,12] Based on this evidence, we hypothesized that there might be sex differences in the intraoperative DEX-induced morphine-sparing effects in controlling postoperative acute pain.

METHODS

Subjects

This study was approved by the Institutional Medical Ethics Committee of Nanjing Medical University and Shanghai JiaoTong University and was conducted in accordance with the approved guidelines. Informed consent was obtained from all of the subjects. This study was registered at chictr.org (ChiCTR-TRC-14004313) on February 26, 2014, and was performed at Huai'an First People's Hospital. The sample size of the study was calculated according to previous studies[13,14] using free software (http://www.statpages.org/#Power) and was based on a pilot study. Twenty-one patients in each group were required to detect a difference of "1 over 10" in the VAS score (primary outcome) with a power of 0.8 and type I error of 0.05.[13] To compensate for dropouts and deviation from normality, 241 patients were enrolled and assigned to 4 groups using a computer-generated randomized table. The 4 groups were: the female PRS group, the female PRD group, the male PRS group, and the male PRD group. Three of 54 female patients and 4 of 57 male patients from the

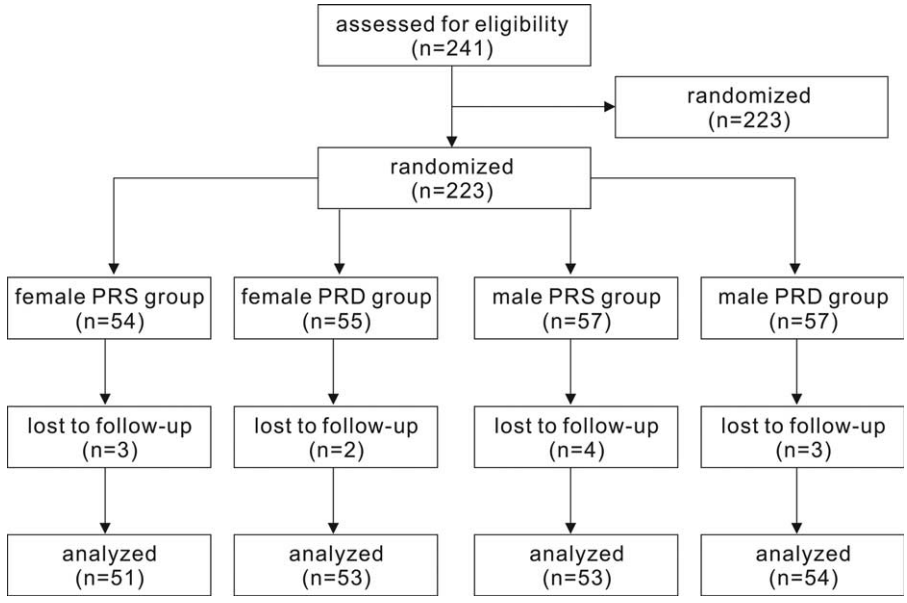

FIGURE 1. Flow diagram of this study.

PRS group were lost because of noncooperation; 2 of 55 female patients and 3 of 57 male patients from the PRD group were lost (Figure 1). The PRS and PRD patients received either propofol, remifentanil, and saline or dexmedetomidine for general anesthesia maintenance. We targeted an 80% probability (β=0.2) with a significance level of 0.05 and an ~10% dropout rate. The maintenance syringe pumps were prepared by a different anesthesiologist to maintain this study as a randomized, double-blinded investigation. Postoperative evaluations were performed by another anesthesiologist. Patients matching the following criteria were included in this study: between 35 and 65 years old; an American Society of Anesthesiologists (ASA) grade I or II; and a weight of 45–85 kg. Patients were excluded if they had ischemic heart disease, opioid addiction, long-term alcohol abuse, long-term smoking history, sedative–hypnotic drug (s) use, obesity (BMI>30), a history of postoperative nausea and vomiting, and neuropsychiatric diseases or a related treatment history. Patients were instructed in the use of the visual analog scale (VAS; 0, no pain, to 10, worst possible pain) and the *i.v.* PCA pump (50 mg morphine and 8 mg ondansetron in 100 mL saline, every pump press resulting in a 2 mL infusion). No important changes to the methods were made after commencement of the trial. Full details of the trial protocol can be found in the supplementary appendix, http://links.lww.com/MD/A950.

ANESTHESIA

On arrival, electrocardiography, blood pressure, oxygen saturation, and the bispectral index (BIS) were monitored every 5 minutes. A BIS value <60 was used to adjust the titration of anesthetics on the basis of amnesia. For induction, patients from both groups received midazolam (0.05 mg/kg), remifentanil (1–2 μg/kg), propofol (1.5–2 mg/kg), and cisatracurium (0.2 mg/kg). Immediately after intubation, the patients were ventilated with an oxygen and air mixture ($FiO_2 = 0.4$) with a PetCO2 of 30 to 35 mm Hg. Intravenous infusion was switched to a maintenance syringe pump at a rate of 50 to 80 μg/kg/min for propofol, 0.15 to 0.2 μg/kg/min for remifentanil, and 0.4 μg/kg/h for dexmedetomidine. Cisatracurium (0.05 mg/kg) was intermittently used for muscle relaxation.

Data Collection

Patient demographic information was collected on admission. Hemodynamic indices and BIS were recorded during surgery every 5 minutes, and data from selected time points were used for analysis. Postoperative pain at rest and after cough was evaluated with a VAS at different time points postsurgery. PCA pump pressing numbers were noted.

Statistical Analysis

All of the data in the present study were analyzed using GraphPad Prism software, version 5.0. Parameters such as age, weight, operation time, anesthesia time, PACU stay time, and morphine consumption were compared between 2 groups using an unpaired *t* test. VAS at different time points were compared between groups by *2-way ANOVA,* followed by *Bonferroni's post-test*. ASA grade and percentage of surgery types were analyzed with *Fisher's test*. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic Data and Surgery/Anesthesia-Related Information

Patients from 2 groups (PRS and PRD) of the same sex had comparable demographic and surgery/anesthesia-related variables, including age, weight, BMI, ASA class, operation time, anesthesia time, and PACU stay time. Male patients had a larger body weight than female patients (Table 1). The PRS and PRD patients received either propofol, remifentanil, saline, or dexmedetomidine for general anesthesia maintenance, and they received the same treatments for induction and PCA (Figure 2).

TABLE 1. Basic Demographic Data and Surgery/Anesthesia-Related Information

Age, y	54.54 ± 15.14	56.43 ± 18.92	56.05 ± 17.03	56.11 ± 17.03
Weight, kg	60.72 ± 8.36	62.16 ± 12.24***	77.08 ± 17.22	74.18 ± 13.15***,###
BMI, kg/m^2	23.19 ± 2.52	24.57 ± 2.14	23.76 ± 2.43	24.26 ± 2.11
ASA I/II	34/17	32/21	30/23	29/25
Surgery type: lumbar diskectomy abdominal colectomy	18 33	17 36	16 37	18 36
Anesthesia time, min	188.55 ± 35.22	185.23 ± 54.96	197.36 ± 52.33	186.11 ± 50.17
PACU time, min	38.17 ± 13.99	33.57 ± 20.59	32.54 ± 16.33	34.16 ± 16.01

Data are shown as mean (SD). fPRS vs fPRD.
ASA = American Society of Anesthesiologists, BMI = body mass index, PACU = postanesthesia care unit, SD = standard deviation.
***$P < 0.001$; mPRS vs mPRD.
***$P < 0.001$; fPRD vs mPRD.
###$P < 0.001$.

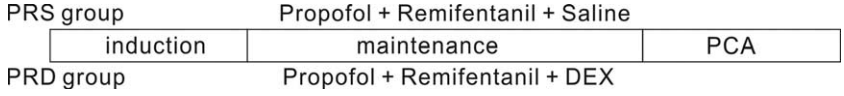

FIGURE 2. Schematic of general anesthesia and PCA. PCA = patient-controlled analgesia.

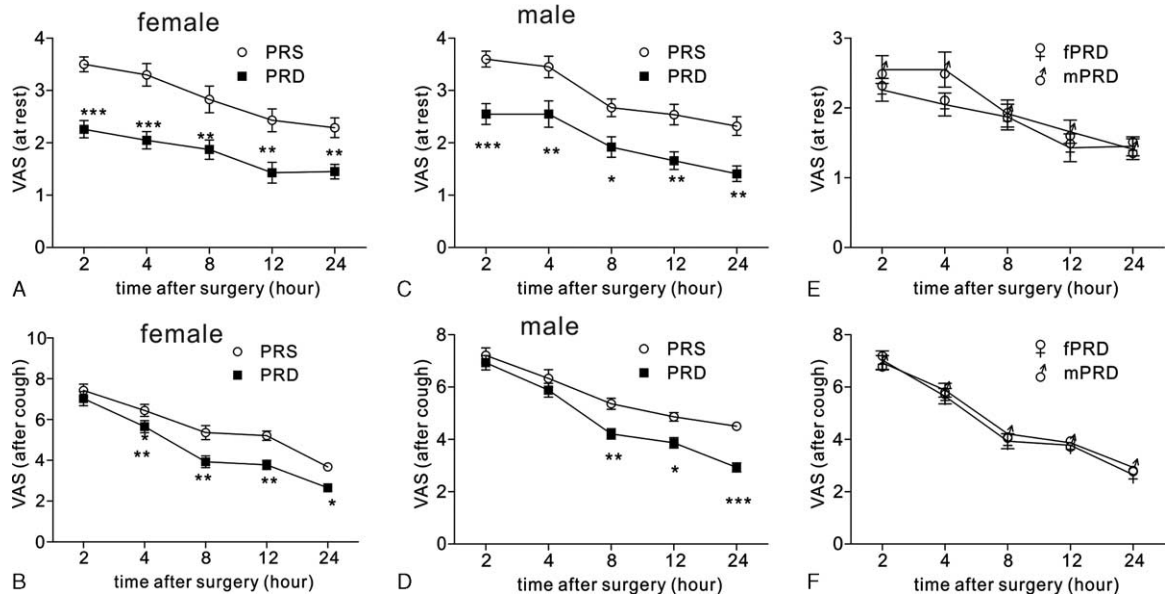

FIGURE 3. Twenty-four hour PCA evaluation and morphine consumption. (A) VAS scores at rest at different time points in the female PRS and PRD patients (*$P < 0.05$, **$P < 0.01$). (B) VAS scores after coughing at different time points in the female PRS and PRD patients (**$P < 0.01$, ***$P < 0.001$). (C) VAS scores at rest at different time points in the male PRS and PRD patients (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). (D) VAS scores after coughing at different time points in the male PRS and PRD patients (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). (E) VAS scores at rest at different time points in the female and male PRD patients. (D) VAS scores after coughing at different time points in the female and male PRD patients. PCA = patient-controlled analgesia, PRD = propofol/remifentanil/dexmedetomidine, PRS = propofol/remifentanil/saline, VAS = visual analog scale.

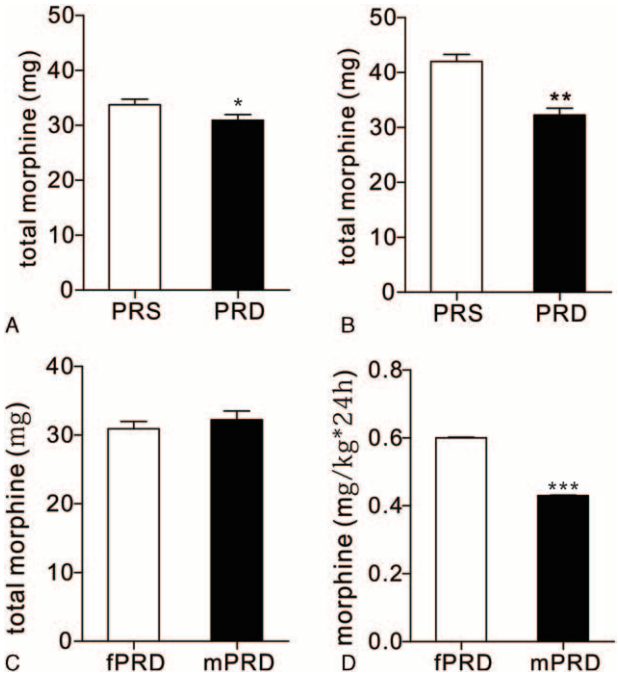

FIGURE 4. Gender difference in morphine consumption. (A) Twenty-four hour PCA morphine consumption in the female PRS and PRD patients ($^{*}P = 0.0392$). (B) Twenty-four hour PCA morphine consumption in the male PRS and PRD patients ($^{**}P = 0.0041$). (C) Twenty-four hour PCA morphine consumption in the female and male PRD patients. (D) Normalized 24 hour PCA morphine consumption in the female and male PRD patients (morphine consumption was normalized to body weight, $^{***}P < 0.001$). PCA = patient-controlled analgesia, PRD = propofol/remifentanil/dexmedetomidine, PRS = propofol/remifentanil/saline.

Postoperative PCA Evaluation

After surgery, the patients received a morphine-based PCA pump. Postoperative pain was assessed with a VAS, and the pain-induced pump press number was used to calculate morphine consumption. During the first 24 hours, both female and male patients from the PRD group had a lower VAS score in both the resting state and the movement state (Figure 3 A and B for females and Figure 3C and D for males, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$) compared to the PRS group. No differences were observed between the female and male PRD patients over time at either the resting state or the movement state ($P > 0.05$).

Postoperative Morphine Consumption

Both female and male PRD patients consumed less morphine than their PRS controls (Figure 4A and B, $^{*}P = 0.0392$, $^{**}P = 0.0041$). Interestingly, the female PRD patients consumed comparable morphine amounts as the male PRD patients (Figure 4C). Because male patients had heavier body weights than female patients, we normalized the morphine consumption to their body weight and found that female PRD patients consumed significantly more morphine than male PRD patients during the first 24 hours after surgery (Figure 4D).

DISCUSSION

In the present study, we found that intraoperative administration of dexmedetomidine had a stronger morphine-sparing effect in controlling postoperative acute pain in male patients than in female patients.

It is widely known that patients undergoing surgeries experience severe acute postoperative pain, which can lead to chronic pain.[15,16] Opioids, especially morphine-based patient-controlled analgesia, are widely used for pain control.[17,18] To combat the side effects, such as nausea, vomiting, and itching, studies have sought to identify novel drugs or to generate more information regarding combining the currently available drugs to reduce morphine consumption. Alpha 2 receptor agonists, such as clonidine (α2R:α1R at a ratio of 200:1), have been used as pain treatments for decades.[19,20] A recent study reported that α1 receptor activation encountered α2R-related analgesia and suggested that an agonist with higher α2R selectivity would show a more potent analgesic effect and would be more suitable for pain treatment.[21] DEX is an α2R agonist that was developed in the 1990s, and it was first used as a short-term sedative in intensive care units.[4] Clinical studies have confirmed its potential as an adjuvant for pain treatment, mostly in acute perioperative settings. This use suggests that DEX could be used for surgery-induced acute pain control.

Dexmedetomidine induces hemodynamic changes, such as hypertension, hypotension, and bradycardia, especially after a loading dose. Thus, in the present study, we administered a continuous infusion without a loading dose. In the present study, we combined dexmedetomidine with propofol and remifentanil to maintain the general anesthesia in patients undergoing spinal and abdominal colectomy, and we found that, in both female and male patients, intraoperative dexmedetomidine was helpful in relieving both resting and moving postoperative acute pain. Moreover, both female and male patients from the PRD group who received intraoperative dexmedetomidine consumed less morphine than those in the PRS group. The analgesic and opioid-sparing effects of dexmedetomidine have been well described in previous studies both in adults and children.[7–9] Similar to the present data, these studies reported significantly lower VAS scores and morphine consumption and fewer morphine demands. Together with these findings, the present study indicates that intraoperative administration of dexmedetomidine could potentially be used to promote morphine-based PCA following general anesthesia surgery.

We observed comparable analgesic effects (comparable VAS scores) in the female and male PRD patients. Additionally, the female and male PRD patients consumed comparable amounts of morphine during the first 24 hours postoperatively. As the female PRD patients had smaller body weights, this indicated that female patients need more morphine to reach the analgesic state. Because male patients had heavier body weights than female patients, we normalized the morphine consumption to body weight, and the most interesting finding was that the female PRD patients consumed much more morphine than the male PRD patients. However, we did not see the same effect in PRS patients; male PRS patients still consumed more morphine than female PRS patients. Additionally, we did not observe any differences in normalized morphine consumption (see supplementary file, http://links.lww.com/MD/A950). The mechanisms underlying this effect are still unknown. Animal studies reported that the action of estrogen attenuated α2-AR-mediated analgesia,[12]

and female patients had a higher prevalence of pain syndromes. Therefore, estrogen might be a factor that is responsible for this difference. Estrogen receptors are known to be expressed in the dorsal horn of the spinal cord and the trigeminal region, which are 2 important pain-modulating hubs.[22,23] Estrogen has been reported to decrease α2-AR mRNA expression levels and α2-AR binding density; therefore, it might directly decrease coupling of α2-AR to G proteins (Gi/Go).[11] Future clinical and basic animal studies should be performed to investigate the underlying mechanisms.

A recent meta-analysis of human experimental and clinical studies suggested that female patients have a greater morphine efficiency, which indicated that male patients would consume more morphine at the same level of postoperative analgesia, and this was consistent with our findings in patients from the PRS groups. Unexpectedly, the present study reported a more significant morphine-sparing effect of dexmedetomidine following general anesthesia although dexmedetomidine resulted in significantly reduced morphine consumptions in both female and male patients. Clearly, the focus of these 2 studies is different: their study is focused on the morphine consumption and our study is focused on the morphine-sparing effect.

Our study may have some limitations. We used a VAS for postoperative pain evaluation. The numerical rating scale (NRS) is another well-established and widely used method for pain evaluation, and it was reported to be more reliable than the VAS in some cases.[24] Our hospital is located on the demarcation line between North China and South China, and we received patients from different provinces. The heavy accents with which some patients spoke might have been a limitation to the use of the NRS. For example, some patients from South China often pronounce the number ''10'' (''Shi'' in Chinese mandarin) as ''Si'' (which is the pronunciation of the number ''4''). Furthermore, the anesthesiologists who performed this study also came from different provinces of the country. Thus, to avoid misunderstandings, we used the VAS to evaluate postoperative pain. Nevertheless, we suggest that the NRS be used in future studies if the conditions are applicable because it is easier to perform, saves more time, and is more reliable than the VAS.

Taken together, maintenance with dexmedetomidine (0.4 μg/kg/h) promoted morphine-based PCA and reduced morphine consumption in both female and male patients. Additionally, intraoperative administration of dexmedetomidine appeared to have a stronger morphine-sparing effect in controlling postoperative acute pain in male patients than in female patients. This study provided useful information regarding the future use of intraoperative dexmedetomidine for promoting the analgesic effects of morphine in patient-controlled analgesia.

REFERENCES

1. Brennan TJ. Pathophysiology of postoperative pain. *Pain*. 2011;12:152.
2. Eipe N, Penning J, Yazdi F, et al. Perioperative use of pregabalin for acute pain-a systematic review and meta-analysis. *Pain.* 2015;156:1284–1300.
3. Walder B, Schafer M, Henzi I, et al. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. *Acta Anaesthesiol Scand.* 2001;45:795–804.
4. Grosu, I. & Lavand'homme, P. Use of dexmedetomidine for pain control. F1000 Med Rep 2, M2–90 (1000).
5. An LX, Chen X, Ren XJ, et al. Electro-acupuncture decreases postoperative pain and improves recovery in patients undergoing a supratentorial craniotomy. *Am J Chin Med.* 2014;42:1099–1109.
6. Zhang H, Zhou F, Li C, et al. Molecular mechanisms underlying the analgesic property of intrathecal dexmedetomidine and its neurotoxicity evaluation: an in vivo and in vitro experimental study. *PLoS One*. 2013;8:7.
7. Gupta N, Rath GP, Prabhakar H, et al. Effect of intraoperative dexmedetomidine on postoperative recovery profile of children undergoing surgery for spinal dysraphism. *J Neurosurg Anesthesiol.* 2013;25:271–278.
8. Jones JS, Cotugno RE, Singhal NR, et al. Evaluation of dexmedetomidine and postoperative pain management in patients with adolescent idiopathic scoliosis: conclusions based on a retrospective study at a tertiary pediatric hospital. *Pediatr Crit Care Med.* 2014;15:e247–e252.
9. McQueen-Shadfar LA, Megalla SA, White WD, et al. Impact of intraoperative dexmedetomidine on postoperative analgesia following gynecologic surgery. *Curr Med Res Opin.* 2011;27: 2091–2097.
10. Ge DJ, Qi B, Tang G, et al. Intraoperative dexmedetomidine promotes postoperative analgesia in patients after abdominal colectomy: a consort-prospective, randomized, controlled clinical trial. *Medicine*. 2015;94:1514.
11. Nag S, Mokha SS. Activation of alpha2-adrenoceptors in the trigeminal region produces sex-specific modulation of nociception in the rat. *Neuroscience.* 2006;142:1255–1262.
12. Thompson AD, Angelotti T, Nag S, et al. Sex-specific modulation of spinal nociception by alpha2-adrenoceptors: differential regulation by estrogen and testosterone. *Neuroscience.* 2008;153:1268–1277.
13. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? *Indian J Psychol Med.* 2013;35: 121–126.
14. Hwang W, Lee J, Park J, et al. Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study. *BMC Anesthesiol.* 2015;15:015–24.
15. Grosu I, de Kock M. New concepts in acute pain management: strategies to prevent chronic postsurgical pain, opioid-induced hyperalgesia, and outcome measures. *Anesthesiol Clin.* 2011;29: 311–327.
16. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology.* 2000;93:1123–1133.
17. Movafegh A, Shoeibi G, Ansari M, et al. Naloxone infusion and post-hysterectomy morphine consumption: a double-blind, placebo-controlled study. *Acta Anaesthesiol Scand.* 2012;56: 1241–1249.
18. George RB, McKeen DM, Andreou P, et al. A randomized placebo-controlled trial of two doses of pregabalin for postoperative analgesia in patients undergoing abdominal hysterectomy. *Can J Anaesth.* 2014;61:551–557.
19. Engelman E, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *Br J Anaesth.* 2013;110:21–27.
20. Lambert P, Cyna AM, Knight N, et al. Clonidine premedication for postoperative analgesia in children. *Cochrane Database Syst Rev.* 2014;28:.
21. Gil DW, Cheevers CV, Kedzie KM, et al. Alpha-1-adrenergic receptor agonist activity of clinical alpha-adrenergic receptor agonists interferes with alpha-2-mediated analgesia. *Anesthesiology.* 2009;110:401–407.

22. Flores CA, Shughrue P, Petersen SL, et al. Sex-related differences in the distribution of opioid receptor-like 1 receptor mRNA and colocalization with estrogen receptor mRNA in neurons of the spinal trigeminal nucleus caudalis in the rat. *Neuroscience.* 2003;118:769–778.

23. Bereiter DA, Cioffi JL, Bereiter DF. Oestrogen receptor-immunoreactive neurons in the trigeminal sensory system of male and cycling female rats. *Arch Oral Biol.* 2005;50:971–979.

24. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. *Pain.* 2011;152:2399–2404.