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ORIGINAL ARTICLE

Perioperative infusion of dexmedetomidine at a high dose reduces postoperative analgesic requirements: a randomized control trial

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Abstract
Purpose We hypothesized that a high dose of dexmedetomidine (1 μg/kg/h) could reduce postoperative analgesic requirements of patients.
Methods This was a prospective, randomized, double-blind, placebo-controlled study carried out in Tohoku University Hospital. Thirty-two patients who underwent open gynecological abdominal surgery were randomly divided into a control (group C) and a dexmedetomidine group (group D). In both groups of patients, an epidural catheter was put in position prior to the induction of anesthesia, and continuous epidural infusion was started using a patient-controlled epidural analgesia (PCEA) pump. During the induction of anesthesia, group D patients received a loading dose of dexmedetomidine (1 μg/kg over 10 min), followed by a continuous infusion at a rate of 1 μg/kg/h. The patients in group C received a volume-matched infusion of normal saline as placebo. Consumption of PCEA bolus (local anesthetics) during the first postoperative 24 h, postoperative pain scores, and side effects related to the use of dexmedetomidine were recorded.
Results Dexmedetomidine (1 μg/kg/h) significantly reduced PCEA bolus consumption [15.9 ± 6.5 (group C) vs. 5.3 ± 5.0 ml (group D); $P = 0.0001$] and postoperative pain scores. The infusion of dexmedetomidine produced no serious side effects, such as hemodynamic changes.
Conclusions Among this small patient cohort, perioperative infusion of dexmedetomidine (1 μg/kg/h) resulted in antinociception without severe side effects. These results suggest that this method could be of interest with respect to improving postoperative pain status.

Keywords Dexmedetomidine · Postoperative pain · Patient-controlled analgesia

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Introduction

Analgesic and anesthetic sparing effects are beneficial properties of dexmedetomidine [1, 2]. Significant antinociceptive effects of the systemic and intrathecal administration of dexmedetomidine have been demonstrated in animal models [3, 4]. However, the systemic administration of dexmedetomidine at the doses recommended for sedation (maintenance infusion of 0.2–0.7 μg/kg/h or the estimated target serum concentration of 0.3–1.25 ng/ml) in the product information has been found to have inconsistent analgesic effects in human volunteer and postoperative patients. In one study, the systemic infusion of dexmedetomidine (0.09–1.23 ng/ml) was not effective against heat and electrical pain at doses inducing mild to severe sedation in human volunteers [5]. In another study, the intraoperative systemic infusion of dexmedetomidine at the recommended dose for sedation (0.4 μg/kg/h) did not result in postoperative analgesic effects in patients undergoing lower abdominal surgery [6]. On the other hand, there are

reports of postoperative opioid demand in postoperative patients being lower following the intraoperative infusion of dexmedetomidine (0.4 and 0.5 μg/kg/h) [7, 8] and of dexmedetomidine (0.3 μg/kg/h) providing a modest analgesic effect on pain control in patients after knee arthroscopy [9].

We hypothesized that a high dose of dexmedetomidine could reduce the analgesic requirements of postoperative patients. To test this hypothesis, we examined the effects of perioperative infusion of dexmedetomidine at 1 μg/kg/h on the postoperative pain status of patients who received local anesthetics via a patient-controlled epidural analgesia (PCEA) pump. The dose of 1 μg/kg/h was chosen because (1) the pain rating progressively decreases as the dexmedetomidine dose increases in healthy volunteers [1]; (2) dexmedetomidine administered at 1.23 ng/ml (approximately equivalent dose to 0.7 μg/kg/h) does not have analgesic effects [5]; (3) much higher doses could potentially induce adverse side effects, such as low blood pressure and prolonged emergence. Doses that are too low doses may provide insignificant pain relief, while those that are too high may induce an unacceptable number of adverse side effects. PCEA bolus (local anesthetics) consumption during the first postoperative 24 h, time to first request by patient for rescue analgesia by the PCEA pump, and postoperative pain scores using a visual analogue scale (VAS) were evaluated. Hemodynamic changes [heart rate (HR), mean arterial pressure (MAP), and cardiac index (CI)] and other side effects (respiratory depression, anesthesia awareness, prolonged emergence, nausea, vomiting, and pruritus assessed based only on complaint of patient) related to perioperative infusion of dexmedetomidine were also recorded during the first 24 h postsurgery.

Methods

This study was approved (no. 2006-385) by the Human Ethical Committee of Tohoku University Graduate School of Medicine (Chairperson Prof. T. Kobayashi) on 9 March 2007 and conforms to the Ethical Guidelines for Clinical Studies in Japan established by the Ministry of Health, Labor, and Welfare.

After obtaining individual written informed consent, 32 patients undergoing open abdominal surgery for malignant gynecological disease were randomly divided into two groups: a control group (group C) and a dexmedetomidine group (group D). Treatment allocation to the two study groups was by blocked randomization (sealed envelope assignment, block size of 8 patients). The attending anesthesiologist who was not involved in the study opened a sealed envelope that contained the information on group allocation (a piece of paper on which was written group C or D) and prepared the drug/placebo for dexmedetomidine administration before the patient was admitted to the operation room. Patients who underwent radical hysterectomy for cervical carcinoma or abdominal total hysterectomy plus bilateral salpingo-oophorectomy plus resection of pelvic and para-aortic lymph nodes for endometrial carcinoma or ovarian carcinoma were included in this study. The surgical procedure was a midline longitudinal incision from 10 cm above the navel to lower abdomen for all patients. Exclusion criteria were age >75 years, known hypersensitivity to ropivacaine, history of mental illness, use of psychotropic medicine, pain medications prior to surgery, and a history of impaired sensation. All patients were American Society of Anesthesiologists (ASA) physical status I or II and were instructed on the use of the pump for PCEA (Daiken Iki Corp, Osaka, Japan) and the VAS. The VAS comprised a 10-point continuum score ranging from 0 (no pain at all) to 10 (the worst possible pain). Patients completed this pain assessment preoperatively and postoperatively. This study was conducted in a prospective, randomized, double-blind, placebo-controlled fashion in Tohoku University Hospital, which is a regional hospital serving a population of approximately 1 million people.

An epidural catheter was placed through a 17-gauge Tuohy needle using the loss-of-resistance technique at the Th10–Th11 interspace. After a negative test dose with 3 ml of 0.375% ropivacaine, group C and group D patients were administered 9 ml of 0.375% ropivacaine epidurally prior to the induction of general anesthesia. The dermatomal analgesic level was evaluated by using an alcohol swab 10 min postepidural administration. Patients were excluded from the study if the epidural catheter could not be placed or dosed to a Th6 sensory level before the induction of general anesthesia.

General anesthesia was induced with propofol (2 mg/kg), and vecuronium (0.1 mg/kg) was used to facilitate tracheal intubation. To prevent the stress associated with tracheal intubation we administered 3% sevoflurane to patients during mask ventilation. After general anesthesia had been induced, a loading dose of dexmedetomidine, 1 μg/kg intravenous (i.v.) over 10 min, was started by the anesthesiologist who was blinded to the study; this was followed by a continuous infusion at 1 μg/kg/h in group D. The infusion rate was reduced to 0.2 μg/kg/h at 30 min before the anticipated end of surgery and continued for 2 h postsurgery. Dexmedetomidine (400 μg/4 ml) was diluted with 46 ml of normal saline, and 50 ml of normal saline without dexmedetomidine was used for placebo. The patients in group C received a volume-matched infusion of placebo. Anesthesia was maintained with sevoflurane in 1 l/min O_2, 2 l/min air to maintain the bispectral index (BIS) values within 45 ± 5 and intermittent doses of vecuronium (1–2 mg) as clinically

indicated. Continuous epidural infusion with 0.2% ropivacaine at 5 ml/h was started at 30 min after the start of surgery for 24 h. Upon early signs of intraoperative pain (increasing BP, HR, pupil dilation, etc.), additional epidural 0.375% ropivacaine (3–5 ml) was administered, as judged by the anesthesiologist who was blinded to the study protocol. Electrocardiogram, end-tidal CO_2, end-tidal concentration of sevoflurane, and hemoglobin oxygen saturation were continuously monitored throughout surgery. MAP and CI were monitored using the Vigileo System (Edward lifesciences, Irvine, CA). A decrease in MAP of >20% below the preanesthetic baseline value was treated by i.v. increments of ephedrine (4–8 mg), continuous administration of dopamine, and i.v. fluid administration.

Upon completion of surgery, the trachea was extubated and the patients transferred to the intensive care unit (ICU). The patients were once again instructed on the use of the PCEA pump and VAS shortly (10 min) after their admission to the ICU.

Postoperative pain was treated by the continuous basal administration of epidural 0.2% ropivacaine at 5 ml/h using the PCEA pump which could be set to deliver 3 ml of 0.2% ropivacaine bolus according to patient request with a lockout interval of 30 min.

The primary outcome of this study was the PCEA bolus (local anesthetics) consumption between groups. We also compared the time to the first request for rescue analgesia via the PCEA pump and the postoperative pain scores of patients assessed using the VAS at 2, 4, 6, 24, and 72 h postoperatively by the anesthesiologist who was not involved in the intraoperative anesthetic management and was blinded to the study. We also recorded perioperative hemodynamic changes and side effects related to the use of dexmedetomidine at 1 μg/kg/h during the first 24 h postsurgery. Prolonged emergence (more than 30 min needed for eye opening with calling of the patient's name at 1-min intervals) was reported by the anesthesiologist who was unaware of the study protocol, and anesthesia awareness was checked during the postoperative interview. Nausea, vomiting, and pruritus were assessed based solely on the complaint of patients. Nausea and vomiting were treated with 10 mg intravenous metoclopramide upon patient request.

This study was powered on the basis of preliminary results showing 15 ml of PCEA consumption in the control group with a standard deviation (SD) of 6 ml. A sample size of 16 patients in each group was calculated using StatMate (ver. 2.0; GraphPad Software, San Diego, CA) to have at least 80% power with α value of 0.05 (two-sided) in order to detect a 40% reduction in PCEA bolus consumption. Statistical analysis was performed using PRISM (ver. 5.02; GraphPad Software, San Diego, CA). The data on the consumption of the PCEA bolus during the first postoperative 24 h and the time to first request for rescue analgesia via the PCEA pump were analyzed using the unpaired t test. The Mann–Whitney U test was used for analysis of the VAS scores, and the hemodynamic changes were analyzed by two-way repeated measures analysis of variance with subsequent comparison made using the Bonferroni post test. A P value <0.05 was considered significant.

Results

The dataset comprises data collected on 32 patients between February 2008 and March 2009. These 32 patients were randomly allocated into two groups to receive placebo or dexmedetomidine. No patient was removed from the study once the trial had started. Demographic and medical information (duration of operation, analgesic level before operation, and end-tidal concentration of sevoflurane) are summarized in Table 1. There was no significant difference between the groups, with the exception of end-tidal concentration of sevoflurane. The requirement for sevoflurane to maintain a BIS value of 45 was significantly attenuated by dexmedetomidine. The sedation level of the patients in both groups upon their admission of ICU seemed to be Ramsay sedation scale score 2 or 3 because the dose of dexmedetomidine was reduced to 0.2 μg/kg/h at 30 min prior to the end of surgery in group D; consequently, all patients were well-oriented and understood the instructions on how to use of the PCEA pump and VAS scoring system.

As shown in Fig. 1, perioperative infusion of dexmedetomidine at 1 μg/kg/h significantly reduced the PCEA bolus consumption and prolonged the time to the first request for rescue analgesia via the PCEA pump Postoperative pain scores in group D were also decreased by the administration of dexmedetomidine at all corresponding times (Fig. 2).

Dexmedetomidine at 1 μg/kg/h produced no severe hemodynamic changes perioperatively (Fig. 3). The infusion of dexmedetomidine significantly suppressed the increases of HR and CI at extubation time. Systolic blood pressure increased to approximately 180 mmHg in two patients during the initial loading phase of dexmedetomidine, but the effect was transient and required no treatment. We did not observe severe hypotension (MAP <50 mmHg), decrease in cardiac output (CI <2.0 l/min/m^2), or bradycardia (HR <40 bpm) in any subjects for the first postoperative 24 h in the ICU.

Two patients in group C and three patients in group D complained of nausea and vomiting. All five patients were successfully treated with metoclopramide (10 mg). No other complication, such as respiratory depression, anesthesia

Table 1 Background of patients and summary of anesthesia

Demographic and medical background	Group C (control) ($n = 16$)	Group D (dexmedetomidine) ($n = 16$)
Age (years)	55.6 ± 7.2	56.1 ± 5.8
Weight (kg)	52.1 ± 8.7	54.6 ± 5.8
Height (cm)	153.7 ± 7.2	156.1 ± 5.8
Duration of surgery (min)	233 ± 69	250 ± 66
Analgesic level	Th4 (3–5)	Th4 (4–5)
End-tidal concentration of sevoflurane (%)	1.6 ± 0.3	1.1 ± 0.1*
BIS (bispectral index) value	43 (42–46)	44 (42–47)

Data are expressed as the mean ± standard deviation, or as the median with the interquartile values in parentheses ($n = 16$). There were no differences between groups except in the end-tidal concentration of sevoflurane values

BIS bispectral index, *Th* thoracic

* $P = 0.0001$ versus group C

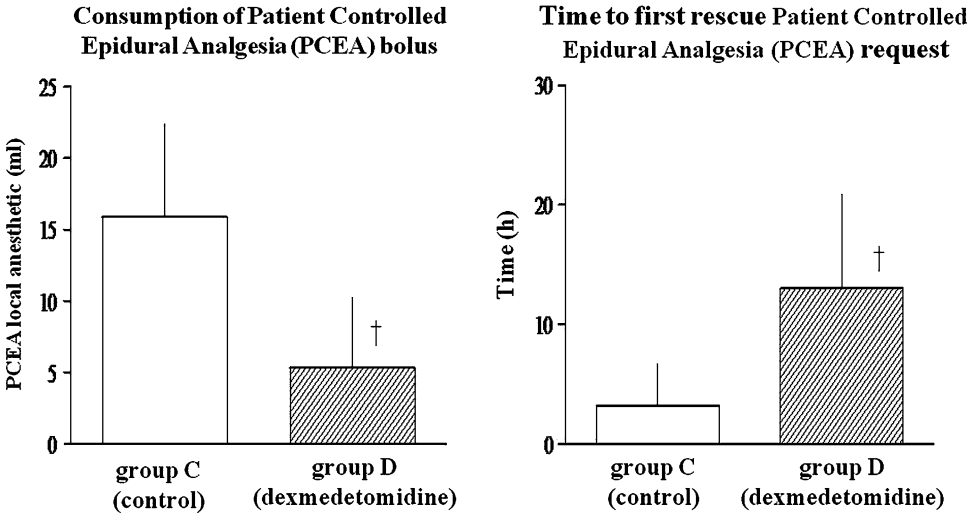

Fig. 1 The consumption of patient-controlled epidural analgesia (*PCEA*) bolus and the time to first request for rescue analgesia via the PCEA pump. Data are expressed as the mean ± standard deviation (SD; $n = 16$). $^{\dagger}P = 0.0001$ versus group C

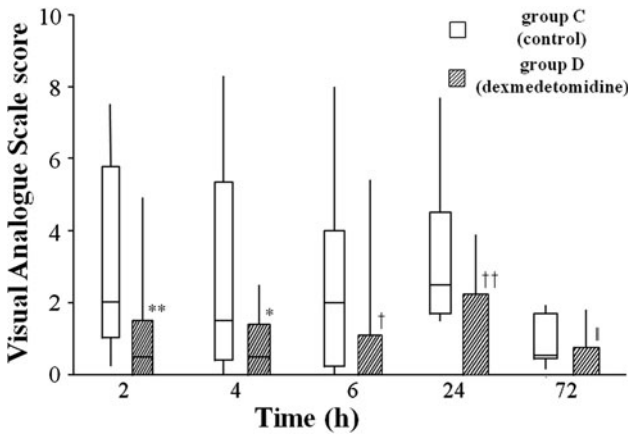

Fig. 2 Postoperative visual analogue scale (VAS) pain scores. Postoperative pain status of patients at rest was assessed using the VAS pains scores at 2, 4, 6, 24, and 72 h postsurgery. *Box* 25th–75th percentiles, *solid line* median. *Extended bars* 10th–90th percentiles ($n = 15$). *$P = 0.0153$, **$P = 0.0034$, $^{\dagger}P = 0.0152$, $^{\dagger\dagger}P = 0.0111$, $^{\|}P = 0.0076$ versus group C

awareness, and prolonged emergence was observed in the patients of this study.

Discussion

The key results of this study are: (1) the perioperative systemic infusion of dexmedetomidine at 1 μg/kg/h significantly reduced the PCEA bolus consumption and prolonged the time to first request for rescue analgesia via the PCEA pump; (2) the dexmedetomidine infusion also decreased the postoperative pain scores of patients; (3) the dexmedetomidine infusion produced no severe side effects, such as hemodynamic change, respiratory depression, and prolonged emergence. These results suggest that perioperative systemic infusion of dexmedetomidine at a high dose (1 μg/kg/h) is a potentially useful method to reduce postoperative pain because this technique produced no serious side effects.

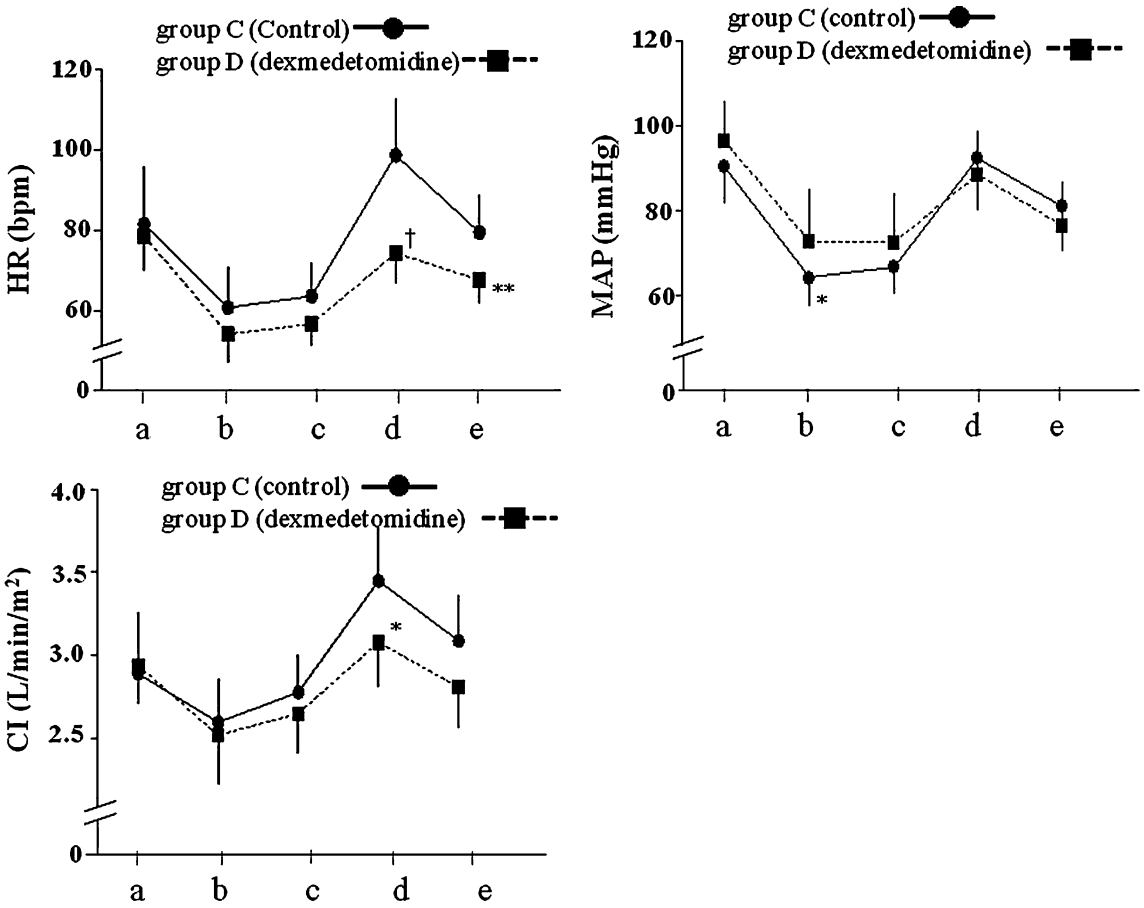

Fig. 3 Effects of the infusion of dexmedetomidine at a high dose on hemodynamic values. Mean arterial pressure (*MAP*), heart rate (*HR*), and cardiac index (*CI*) were recorded at different time points: *a* prior to induction of general anesthesia, *b* postinduction of general anesthesia, *c* 30 min after beginning surgery, *d* just before extubation, *e* admission of patient to intensive care unit. Data are expressed as the mean ± SD ($n = 16$). $^{\dagger}P < 0.001$, $^{*}P < 0.05$, $^{**}P < 0.01$ versus group C

As the elimination half-life of dexmedetomidine is about 2 h, the postoperative pain status could be largely improved by the intraoperative effect of dexmedetomidine. In other words, the stimulus from nerve injury and inflammatory responses produced by surgery might be effectively controlled with intraoperative infusion of dexmedetomidine. Surgery-induced pain responses are very complicated [10, 11], i.e., they are involved in both nociceptive/inflammatory and neuropathic/neurogenic components. Conventional analgesics, such as opioids and anti-inflammatory agents, often fail to treat the latter components [10, 12]. However, it has been demonstrated that α2-receptor agonists are able to successfully manage the neuropathic/neurogenic components [13, 14]. In our study, dexmedetomidine was administered not only during the intraoperative period but also during the postoperative period during which time the stimulus from nerve injury and inflammatory responses continue. The different recommended doses of dexmedetomidine for sedation and the administration of dexmedetomidine only intraoperatively may have contributed to the previously reported conflicting results on the role of the intraoperative infusion of dexmedetomidine in postoperative pain status. Indeed, higher doses [1] and both the intra- and postoperative administration [15] of dexmedetomidine have been shown to improve pain status, such as pain scores and postoperative analgesic consumption. Our results are consistent with those of these latter two studies.

Hemodynamic changes associated with the administration of the high dose (1 μg/kg/h) of dexmedetomidine were negligible among our patients. During the initial loading dose, transient hypertension appeared in two patients, but it required no treatment. Although the HR and CI were significantly decreased by the higher dose of dexmedetomidine, the magnitude of decrease was not clinically significant and the MAP was stable. No patients required intervention for the hemodynamic changes. The decrease in the HR and CI may contribute to the suppression of the stress responses by dexmedetomidine. In other words, the dexmedetomidine could attenuate the increase in HR and CI during extubation periods. Except for a few episodes of nausea and vomiting which were easily treatable, no severe adverse effects were

observed. These findings demonstrate the potential usefulness of administering dexmedetomidine perioperatively at 1 μg/kg/h under sevoflurane–epidural-based anesthesia, although much larger case studies are needed to identify the safety of this drug.

In our study, the requirement for sevoflurane to maintain a BIS value of 45 was significantly attenuated by the administration of dexmedetomidine at 1 μg/kg/h. It is not known whether BIS is a reliable method by which to estimate the level of dexmedetomidine-induced sedation; thus, it is not clear whether a BIS of 45 actually reflects the same level of anesthesia in patients receiving sevoflurane with or without dexmedetomidine. However, prolonged emergences were not observed among our patient cohort, and no patients complained of anesthesia awareness in the postoperative interview. In addition, it has been reported that the emergence times at BIS values of 45 in patients who were anesthetized by sevoflurane with dexmedetomidine are similar to those of patients not receiving dexmedetomidine [16]. All of these findings support the notion that the depth of anesthesia in both of our patient groups was similar.

There are a number of limitations to this study. First, we did not check the precise sedation scores of patients. It is therefore difficult to determine whether the reduced PCEA bolus consumption was due to the analgesic or sedative effects of dexmedetomidine. However, several lines of evidence indicate that dexmedetomidine had only a small effect on the sedative state of the patients in our study with respect to their use of the PCEA pump postoperatively. The dose of dexmedetomidine was reduced to 0.2 μg/kg/h at 30 min before the anticipated end of surgery, and the estimated concentration of dexmedetomidine in our patients after extubation was approximately 0.7 ng/ml, with gradual decrease thereafter. It has been demonstrated that a plasma concentration of dexmedetomidine 0.7 ng/ml results in an Observer's Assessment of Alertness/Sedation score of 18, with 20 indicating maximum alertness [1]. In addition, in our study, the VAS pain scores as well as PCEA consumption were decreased by the administration of dexmedetomidine, suggesting that the analgesic but not the sedative effects of dexmedetomidine contribute to the reduction of PCEA consumption. In our study, the patients had a good understanding of the instructions for use of the PCEA pump and VAS shortly after their admission to the ICU under the infusion of dexmedetomidine at 0.2 μg/kg/h. Patients actually required additional morphine via the PCEA pump to achieve analgesia during the 0.4 μg/kg/h dexmedetomidine infusion postoperatively [8]. Although the sedative effects of dexmedetomidine might partially affect the patient's attempt to use the PCEA pump, the analgesic effects of dexmedetomidine could be responsible for the reduction of PCEA bolus consumption. Secondly, we examined only a single dose of perioperative infusion of dexmedetomidine. The limitation of the study design leads the immediate question of whether a lower or, conversely, a much higher dose of dexmedetomidine than that used in our study would provide sufficient or much superior effects, respectively. The reason why we did not select much higher doses is due to the fear for side effects. Further investigation will be needed to answer this question along with the known side effects noted earlier. In addition, we did not examine the dose–response effects of dexmedetomidine, including those of the recommended dose for sedation. Intraoperative systemic infusion of dexmedetomidine at the recommended dose for sedation (0.4 μg/kg/h) did not result in postoperative analgesic effects in patients undergoing lower abdominal surgery in our previous study [6]. The patients in our previous study underwent surgery for benign gynecological disease, in contrast to the patients in the present study who underwent surgery for malignant disease. The speculation that the recommended dose of dexmedetomidine could not have any analgesic effects under very stressful surgical conditions precluded examination of the effects of dexmedetomidine at the recommended dose.

In conclusion, the perioperative systemic infusion of dexmedetomidine at 1 μg/kg/h reduced PCEA bolus consumption, prolonged the time for first request for rescue analgesia via the PCEA pump, and postoperative pain scores without severe side effects. Based on these results, we suggest that dexmedetomidine at the high dose (1 μg/kg/h) used here has the potential to improve postoperative pain status.

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References

1. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93:382–94.
2. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine—a novel α2-adrenoceptor agonist—in healthy volunteers. Pain. 1991;46:281–5.
3. Idänpään-Heikkilä JJ, Kalso EA, Seppälä T. Antinociceptive actions of dexmedetomidine and the kappa-opioid agonist U-50, 488H against noxious thermal, mechanical and inflammatory stimuli. J Pharmacol Exp Ther. 1994;271:1306–13.
4. Sabbe MB, Penning JP, Ozaki GT, Yaksh TL. Spinal and systemic action of the alpha 2 receptor agonist dexmedetomidine in dogs. Antinociception and carbon dioxide response. Anesthesiology. 1994;80:1057–72.
5. Angst MS, Ramaswamy B, Davies MF, Maze M. Comparative analgesic and mental effects of increasing plasma concentrations

of dexmedetomidine and alfentanil in humans. Anesthesiology. 2004;101:744–52.
6. Kida K, Ohtani N, Shoji K, Yasui Y, Masaki E. Postoperative pain status after intraoperative systemic dexmedetomidine and epidural neostigmine in patients undergoing lower abdominal surgery. Eur J Anaesthesiol. 2008;25:869–75.
7. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anesth. 2006;53:646–52.
8. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg. 2004;98:153–8.
9. Gómez-Vázquez ME, Hemández-Salazar E, Hemández-Jiménez A, Pérez-Sánchez A, Zepeda-López VA, Salazar-Páramo M. Clinical analgesic efficacy and side effects of dexmedetomidine in the early postoperative period after arthroscopic knee surgery. J Clin Anesth. 2007;19:576–82.
10. MacFarlane BV, Wright A, O'Callaghan J, Benson HA. Chronic neuropathic pain and its control by drugs. Pharmacol Ther. 1997;75:1–19.
11. Gracely RH, Lynch SA, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. Pain. 1992;51:175–94.
12. Arnér S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. Pain. 1988;33:11–23.
13. Yaksh TL, Pogrel JW, Lee YW, Chaplan SR. Reversal of nerve ligation-induced allodynia by spinal alpha-2 adrenoceptor agonists. J Pharmacol Exp Ther. 1995;272:207–14.
14. Pan HL, Chen SR, Eisenach JC. Intrathecal clonidine alleviates allodynia in neuropathic rats: interaction with spinal muscarinic and nicotinic receptors. Anesthesiology. 1999;90:509–14.
15. Wahlander S, Frumento RJ, Wagener G, Saldana-Ferretti B, Joshi RR, Playford HR, Sladen RN. A prospective, double-blind, randomized, placebo-controlled study of dexmedetomidine as an adjunct to epidural analgesia after thoracic surgery. J Cardiothorac Vasc Anesth. 2005;19:630–5.
16. Ohtani N, Kida K, Shoji K, Yasui Y, Masaki E. Recovery profiles from dexmedetomidine as a general anesthetic adjuvant in patients undergoing lower abdominal surgery. Anesth Analg. 2008;107:1871–4.