Medicine®

CLINICAL TRIAL/EXPERIMENTAL STUDY

OPEN

Dexmedetomidine in Postoperative Analgesia in Patients Undergoing Hysterectomy

A CONSORT-Prospective, Randomized, Controlled Trial

Chunguang Ren, MD, Meiying Chi, MM, Yanwei Zhang, MD, Zongwang Zhang, MD, PhD, Feng Qi, MD, PhD, and Zhong Liu, MD

Abstract: Both dexmedetomidine and sufentanil modulate spinal analgesia by different mechanisms, and yet no human studies are available on their combination for analgesia during the first 72 hours after abdominal hysterectomy.

This CONSORT-prospective, randomized, double-blinded, controlled trial sought to evaluate the safety and efficacy of the combination of dexmedetomidine and sufentanil in intravenous patient-controlled analgesia (PCA) for 72 hours after abdominal hysterectomy.

Ninety women undergoing total abdominal hysterectomy were divided into 3 equal groups that received sufentanil (Group C; 0.02 μg/kg/h), sufentanil plus dexmedetomidine (Group D1; 0.02 μg/kg/h, each), or sufentanil (0.02 μg/kg/h) plus dexmedetomidine (0.05 μg/kg/h) (Group D2) for 72 hours after surgery in this double-blinded, randomized study. The primary outcome measure was the postoperative sufentanil consumption, whereas the secondary outcome measures were pain intensity (visual analogue scale), requirement of narcotic drugs during the operation, level of sedation, Bruggrmann comfort scale, and concerning adverse effects.

The postoperative sufentanil consumption was significantly lower in Groups D1 and D2 than in Group C during the observation period ($P < 0.05$), but lower in Group D2 than in Group D1 at 24, 48, and 72 hours after surgery ($P < 0.05$). The heart rate after intubation and incision was lower in Groups D1 and D2 than in Group C ($P < 0.05$). On arrival at the recovery room, Groups D1 and D2 had lower mean blood pressure than Group C ($P < 0.05$). The intraoperative requirement of sevoflurane was 30% lesser in Groups D1 and D2 than in Group C. The sedation levels were greater in Groups D1 and D2 during the first hour ($P < 0.05$). Compared with Groups C and D1, Group D2 showed lower levels of the overall incidence of nausea and vomiting ($P < 0.05$).

Among the tested PCA options, the addition of dexmedetomidine (0.05 μg/kg/h) and sufentanil (0.02 μg/kg/h) showed better analgesic effect and greater patient satisfaction without other clinically relevant side effects for patients undergoing hysterectomy during the first 72 hours after abdominal hysterectomy.

(*Medicine* 94(32):e1348)

Abbreviations: BCS = Bruggrmann comfort scale, BIS = bispectral index, HR = heart rate, i.v. = intravenous, LOS = level of sedation, MBP = mean blood pressure, PACU = postanesthesia care unit, PCA = patient-controlled analgesia, VAS = visual analogue scale.

INTRODUCTION

Severe acute postoperative pain, which can be hastened by maximizing pain relief and minimizing the adverse effects of the analgesics, is a predictor of chronic pain and an important risk factor for postoperative recovery, as patients may experience higher incidence of associated comorbidities if the pain is poorly controlled.[1] Multimodal analgesia is now recommended for this purpose.[2]

Several trials have confirmed the efficacy of various multimodal analgesic protocols in the management of pain after minor surgery.[3–7] Among the various available protocols for postoperative pain management, combinations of one or more adjunct drugs with an opioid are being widely recognized as convenient regimens for intravenous (i.v.) patient-controlled analgesia (PCA).[8]

Studies have shown that α2-agonists, which were initially developed to treat hypertension and used to treat the opioid withdrawal syndrome, are efficient antihyperalgesic drugs and can also relieve opioid-induced hyperalgesia.[9] Dexmedetomidine, an α2-adrenergic receptor agonist, has been used and investigated as an analgesic adjuvant for anesthesia and pain therapy. Dexmedetomidine has a more favorable pharmacokinetic profile than clonidine: α2:α1 specificity ratio, 1600:1 versus 200:1; plasmatic half-life T1/2, 2 to 2.5 hours versus 9 to 12 hours; protein binding, 94% versus 50%; and lipophilic action, 3.5-fold that of clonidine.[10,11] Although clonidine and dexmedetomidine probably have similar properties, their fundamental pharmacodynamic properties are different. The former is no longer used in the management of hypertension, but is considered a good premeditating agent.[12] Although dexmedetomidine is a recognized sedative agent used in the management of patients in intensive care units, it is more often used to validate the usefulness of α2-agonists in anesthesiology. Dexmedetomidine also exhibits hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties.[13] It appears that dexmedetomidine has a slightly better benefice–risk balance than clonidine, but the reason for this difference still remains unclear.[14,15] Studies hitherto have failed to evaluate whether dexmedetomidine can reduce PCA sufentanil

Editor: Lili Xu.
Received: May 28, 2015; revised: July 9, 2015; accepted: July 13, 2015.
From the Department of Anesthesiology (FQ), Qilu Hospital of Shandong University, Jinan; and Department of Anesthesiology (CR, MC, YZ, ZZ, ZL), Liaocheng People's Hospital, Liaocheng, PR China.
Correspondence: Zhong Liu, Department of Anesthesiology, Liaocheng People's Hospital, NO.67 Dongchang West Road, Liaocheng City, Shandong Province, PR. China. 252000 (e-mail: 784253489@qq.com).
CR, ZZ, FQ, and ZL conceived and designed the trail; CR, MC, and YZ performed the experiment; ZL analyzed the data; CR, MC, FQ, and ZL wrote the paper.
This study was carried out at Liaocheng People's Hospital, Liaocheng, Shandong province, People's Republic of China.
Trial Registration: chictr.org (ChiCTR-TRC-14004313).
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001348

use over a period of >48 hours after surgery. This is the first study that seeks to investigate whether the addition of dexmedetomidine to PCA sufentanil can prolong the analgesic effect while also reducing the adverse effects of PCA sufentanil administration for 72 hours after surgery. The adverse events associated with the administration of the dexmedetomidine–sufentanil mixture were also investigated.

METHODS

Study Protocol

This double-blinded, randomized, controlled trail was conducted at Liaocheng People's Hospital, Shandong Province, PR China, and the protocol was approved by the institutional medical ethics committee. Informed consent for participation in this study and receiving the unknown anesthetic agent was obtained from all the patients before the start of the study. The study was registered at chictr.org (ChiCTR-TRC-14004313).

Patients

This study included women who underwent total abdominal hysterectomy at our institute between March 2014 and July 2014. Patients were enrolled in this study if they met the following inclusion criteria: age between 35 and 65 years and American Society of Anesthesiologists grade I or II. Patients were excluded if they had any of the following: ischemic heart disease; long-term abuse of or addiction to alcohol, opioid(s), or sedative–hypnotic drug(s); use of antidepressants or β-adrenoreceptor blockers; obesity (body mass index >30 kg/m^2); drug allergy; nausea and vomiting after previous surgery; and neuropsychiatric diseases. Before the surgery, the patients were instructed in the use of the visual analogue scale (VAS; 0, no pain, and 10, worst pain possible) and the i.v. PCA pump.

Randomization and Blinding

A computer-generated randomization table was used to allocate the patients into 3 equal groups (n = 30 per group) by an independent anesthetist before the surgery. After obtaining the patient's and their families' consent, the staff members involved in the Acute Pain Services, who were blinded to the purpose of this study, prepared the experimental drug (dexmedetomidine 200 μg diluted to 50 mL, 4 μg/mL in Groups D1 and D2 or 0.9% sodium chloride 50 mL in Group C) before the initiation of anesthesia and the postoperative PCA was programmed to deliver at the rate of 1 mL/h and 1 mL per demand with an 8-minute lockout interval; sufentanil (Group C: 0.02 μg/kg/h), sufentanil plus dexmedetomidine (Group D1: 0.02 μg/kg/h, each), or sufentanil (0.02 μg/kg/h) plus dexmedetomidine (Group D2: 0.05 μg/kg/h) on the day of surgery. They also evaluated the patients after surgery.

Anesthesia

None of the patients had received any medication before the induction of anesthesia. At the start of the anesthesia, a peripheral venous access was established in the right upper extremity, and five-lead electrocardiogram, blood pressure, and oxygen saturation were continuously monitored by using an automated system (Philips IntelliVue MP30 Philips Company, Beijing, China). After the experimental drug (dexmedetomidine in Groups D1 and D2 and 0.9% sodium chloride in Group C) was infused for 10 minutes at the same rate in the 3 groups, sufentanil (0.2 μg/kg), propofol (2 mg/kg), and cisatracurium (0.2 mg/kg) were administered intravenously; then, tracheal intubation was performed 3 minutes later. Immediately after intubation, i.v. infusion of sufentanil 0.3 μg/kg/h was initiated in all the 3 groups, whereas the dosage of the experimental drug was also adjusted to 0.3 μg/kg/h. During the period of anesthesia, cisatracurium (0.05 mg/kg) was intermittently added to maintain muscle relaxation. The concentration of sevoflurane was adjusted by 0.2% stepwise titration according to both acceptable hemodynamic limits (both mean blood pressure [MBP] and heart rate [HR] maintained between 20% less and 20% more than preoperative levels) and the bispectral index (BIS®, maintained between 40 and 60; BIS monitor, Aspect Medical System, Newton, MA). Under the premise of satisfactory depth of anesthesia, intraoperative vasoactive drugs were used to maintain hemodynamic stability. Administration of sufentanil with the experimental drugs and sevoflurane was discontinued about 30 minutes and 5 minutes before the completion of the surgery, respectively.

Postoperative Care

All patients were transferred to the postanesthesia care unit (PACU), where they were reminded about the method of operating the PCA system (programmed to deliver at the rate of 1 mL/h and 1 mL per demand with an 8-minute lockout interval). Sufentanil was delivered only via the PCA system. Patients in each group received sufentanil at a continuous dose of 0.02 μg/kg/h and a bolus dose of 0.02 μg/kg. In addition, patients in Groups D1 and D2 also received dexmedetomidine at a continuous dose of 0.02 μg/kg/h and 0.05 μg/kg/h and a bolus dose of 0.02 μg/kg and 0.05 μg/kg, respectively. Patients were encouraged to push the analgesic-demand button when they experienced pain during movement at a severity of VAS score of >4 (VAS_m). For patients with a poor response to sufentanil, VRS scores of >7 (VAS_m), or the occurrence of an obvious sufentanil-associated adverse effect, supplemental rescue boluses of 1 g i.v. paracetamol were administered. If the rescue analgesia was ineffective 2 hours after administration, i.v. injection of tramadol (100 mg) was given. The patients were monitored for adverse effects. Hypotension or bradycardia was treated with ephedrine or atropine, respectively, whereas respiratory depression was treated with naloxone and oxygen.

Outcome Measures

The trial was designed only to reach the endpoint of consumption of i.v. PCA sufentanil during the first 72 hours after surgery. The secondary outcome measures were the postoperative pain intensity scores both at rest (VAS_r) and movement (VAS_m); requirement of narcotic drugs; level of sedation (LOS; recorded on a 5-point scale: 0, fully awake; 1, drowsy/closed eyes; 2, asleep/easily aroused with light tactile stimulation or a simple verbal command; 3, asleep/arousable only by strong physical stimulation; 4, unarousable) and Bruggemann comfort scale (BCS: 0, persistent pain; 1, severe pain while deep breathing or coughing; 2, mild pain while deep breathing or coughing; 3, no pain while deep breathing; 4, no pain while coughing).

HR and MBP were recorded at the following time points: arrival at the operating room (T[arr]); before intubation (T[pre-int]); after intubation (T[post-int])); before incision (T[pre-inc]); 30 minutes after incision (T[inc+30']); 60 minutes after incision (T[inc+60']); on extubation (T[ext]); on arrival at the recovery room (T0); and 10 minutes (T0+10'), 20 minutes (T0+20'), 30 minutes (T0+30'), and 40 minutes (T0+40') after

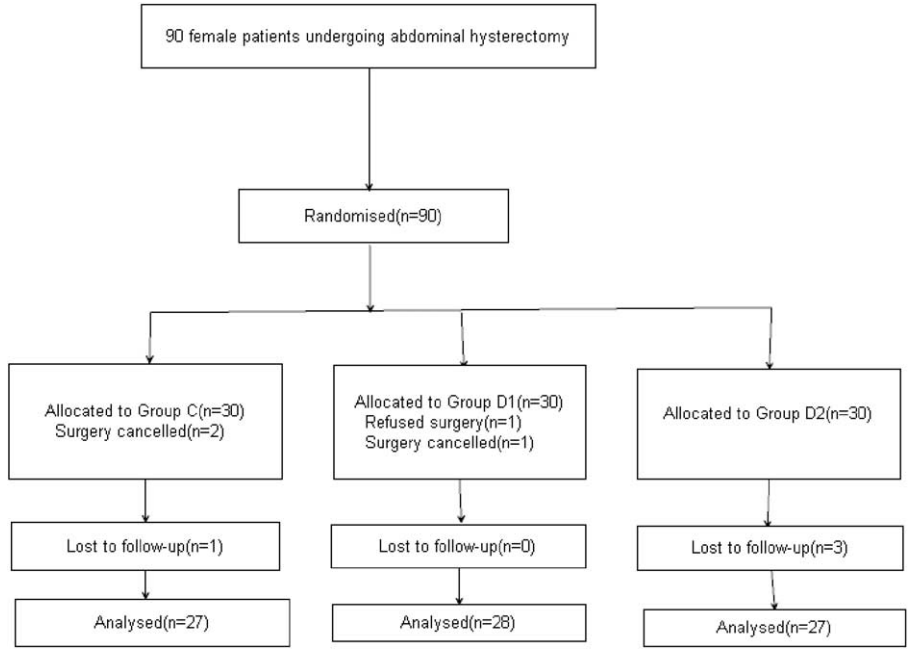

FIGURE 1. Patient enrollment flow diagram. This illustrates the flow of all patients screened, excluded, and randomized.

arrival at the recovery room. The consumption of i.v. sufentanil PCA and pain intensity were recorded at 1, 2, 4, 8, 16, 24, 48, and 72 hours after surgery. LOS was evaluated on extubation and 30 minutes, 1 hour, 2 hours, and 4 hours after surgery. BCS scores were recorded 1, 3, and 7 days after surgery.

Statistical Analysis

The sample size was calculated on the basis of an expected difference of 25% in i.v. sufentanil PCA consumption. For a study power of 80% ($\alpha = 0.05$, $\beta = 0.2$), the required sample size per group was calculated to be 26, with a total of 78 patients (PASS 11.0; NCSS Statistical Software, Kaysville, UT).[8,16] Assuming a dropout rate of 15%, the final sample size was determined to be 30 patients each group. Therefore, a sample size of 90 was chosen to allow for adequate data collection.

The Kolmogorov–Smirnov test was used to assess the distribution of variables. Homogeneity of variance was determined using Levene tests. Quantitative data were expressed as mean and standard deviation or median and interquartile range. Intergroup comparisons were performed using repeated-measures analysis of variance. The Bonferroni correction was used for post hoc multiple comparisons. Categorical data were expressed as frequency and percentage, and analyzed using χ^2 tests or Fisher exact tests when appropriate. Probability (P) values of <0.05 were considered statistically significant. Statistical analysis was performed with SPSS for Windows Version 16.0 (SPSS Inc, Chicago, IL).

TABLE 1. Clinical Characteristics of Patients in the C, D1, and D2 Groups

	Group C	Group D1	Group D2	*P*
Age, y	52.8 ± 5.4	53.9 ± 5.01	54.6 ± 6.1	0.876
Body weight, kg	60.1 ± 6.1	58.3 ± 5.23	57.3 ± 5.2	0.782
BMI, kg/m^2	21.11 ± 1.6	22.7 ± 2.2	23.1 ± 2.5	0.324
ASA I to II, n	16/11	17/11	17/10	0.826
Intraoperative data				
Durations of surgery, min	108.3 ± 16.8	112.7 ± 13.9	110.5 ± 14.6	0.839
Durations of anesthesia, min	127.7 ± 15.8	130.3 ± 16.5	125.5 ± 11.7	0.357
Estimated blood loss, mL	102.5 ± 23.3	95.0 ± 20.1	103.41 ± 17.7	0.231
Fluids, mL	1164.1 ± 79.4	1125.0 ± 69.2	1169.3 ± 84.0	0.276
Urine output, mL	307.5 ± 89.4	339.8 ± 73.5	302.2 ± 85.3	0.235
Recovery time at PACU, min	37.7 ± 7.2	40.2 ± 8.6	38.5 ± 8.6	0.723

Variables presented as mean ± SD or number of patients n. Group C = sufentanil (0.02 μg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 μg/kg/h, each); Group D2 = sufentanil (0.02 μg/kg/h) plus dexmedetomidine (0.05 μg/kg/h). ASA = American Society of Anesthesiology, BMI = body mass index, PACU = postanesthesia care unit. None showed any statistical significance ($P > 0.05$).

RESULTS

Baseline Characteristics

Figure 1 was the CONSORT diagram of patient recruitment. Among the 90 patients enrolled, 8 were excluded. All the 3 groups were similar in terms of patient characteristics, duration of surgery and anesthesia, intraoperative blood loss, infusion, urine output, and recovery time at PACU (Table 1).

Intraoperative Outcomes

HR in Groups D1 and D2 was lower than that in Group C at T(post-int) and T(pre-inc) ($P < 0.05$) (Figure 2A). Furthermore, the MBP in Groups D1 and D2 was also lower than that in Group C after T0 ($P < 0.05$) (Figure 2B). The intraoperative consumption of sufentanil, cisatracurium, and propofol did not differ in the 3 groups, whereas the sevoflurane requirement in Groups D1 and D2 was approximately30% less than that in Group C (Table 2).

Postoperative Efficacy Outcomes

The postoperative requirement of sufentanil in the Groups D1 and D2 remained lower than that in Group C during the first 3 days of the surgery ($P < 0.05$); however, it was greater in Group D1 than in Group D2 at 24, 48, and 72 hours after surgery ($P < 0.05$) (Figure 3). The severity of pain, in terms of the VAS_r and VAS_m, was lower in Groups D1 and D2 than in Group C throughout the first 3 postoperative days ($P < 0.05$). Compared with Group D1, Group D2 had lower VAS_r during the first 2 hours of surgery ($P < 0.05$) and lower VAS_m during the first 3 postoperative days ($P < 0.05$) (Figure 4A and B).

During the first postoperative hour, the LOS was higher in Groups D1 and D2 than in Group C ($P < 0.05$) (Figure 5A). Group D2 had higher BCS score than Group C until the third postoperative day ($P < 0.05$), whereas it had higher BCS scores than Group D1 only on the first day after surgery ($P < 0.05$). Furthermore, the BCS score in Group D1 was higher than that in Group C on the first day after surgery ($P < 0.05$) (Figure 5B).

Postoperative Tolerance Outcomes

The main adverse events are shown in Table 3. Compared with Groups C and D1, Group D2 had lower overall incidence of nausea and vomiting ($P < 0.05$). There was no instance of serious respiratory depression or need for any of the following interventions: physical stimulation of the patient, naloxone administration, and positive pressure ventilation at the end of this study. None of the patients required any adjunctive analgesia, and none of the adverse events warranted termination of PCA use.

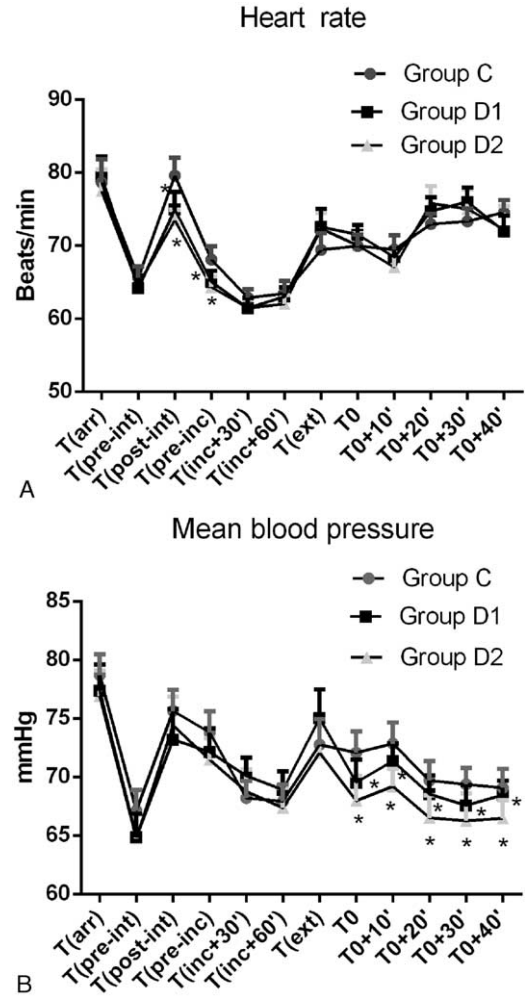

FIGURE 2. (A) Comparison of heart rates (HR) (beats/min) among the 3 groups at different time points: HR in Groups D1 and D2 was lower than that in Group C at T(post-int) and T(pre-inc) ($P < 0.05$). (B) Comparison of mean blood pressure (MBP) (mm Hg) in the 3 groups at different time points: MBP in Group D2was also lower than that in Groups C and D1 at T0, T0+10′, T0+20′, T0+30′, T0+40′ ($P < 0.05$). The whisker caps correspond to the fifth and 95th confidence interval. $^{*}P < 0.05$ versus Group C. $^{\#}P < 0.05$ versus Group D1.

DISCUSSION

In this study, we found that i.v. infusion of a combination of dexmedetomidine (0.05 μg/kg/h) and sufentanil as PCA during the initial 72 hours after abdominal hysterectomy could minimize analgesic consumption, maximize the analgesic effect, improve patient satisfaction, and reduce the coexisting sufentanil-induced nausea and vomiting, without the occurrence of clinically relevant bradycardia, oversedation, or respiratory depression.

It is widely believed that approximately 5% to 30% of patients undergoing abdominal hysterectomy experience severe postoperative pain,[1] and this pain is recognized as an important predictive factor for chronic pain.[15,17,18] Postoperative pain is most severe during the first 3 postoperative days. Morphine is the most commonly used opioid for postoperative pain, and it is much cheaper and easier to manage than other opioids. However, several recent meta-analyses of randomized controlled trials have shown the benefits of using sufentanil, especially with respect to the adverse effects.[19,20] We found that compared with the group treated with only sufentanil, those administered dexmedetomidine before intubation had a significantly lower HR after intubation and before incision, without any change in the MBP. However, the hemodynamic changes noted in our surgeries were not consistent with the findings of Lin et al.[8] This may be attributed to the low doses of dexmedetomidine (0.5 μg/kg for 10 minutes used before intubation, 0.3 μg/kg/h during the operation) used in this study. Our findings are in agreement with those of Ickeringill et al,[21] who reported that dexmedetomidine infusion without the administration of the loading dose avoided the undesirable hemodynamic effects reported previously. Because of the synergistic effect of dexmedetomidine with narcotic drugs, we found that

TABLE 2. Consumptions of Drugs During Operation Among the 3 Groups

	Group C	Group D1	Group D2	*P*
Sevoflurane (MAC)	1.2 ± 0.6	0.8 ± 0.4*	0.8 ± 0.5*	0.000
Sufentanil, μg	41.8 ± 3.2	41.1 ± 2.5	40.6 ± 2.5	0.263
Propofol, mg	134.0 ± 8.6	130.3 ± 8.9	130.0 ± 9.1	0.122
Cisatracurium, mg	19.7 ± 2.5	20.1 ± 2.2	20.3 ± 2.2	0.590
Atropine	2 (7.4%)	3 (10.7%)	2 (7.4%)	1.000
Ephedrine	2 (7.4%)	2 (7.1%)	4 (14.8%)	0.722

Variables presented as mean ± SD or number of patients n (%). Group C = sufentanil (0.02 μg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 μg/kg/h, each); Group D2 = sufentanil (0.02 μg/kg/h) plus dexmedetomidine (0.05 μg/kg/h); MAC = minimum alveolar concentration.

* $P < 0.05$ versus Group C.

the intraoperative requirement of sevoflurane was 30% lesser in Groups D1 and D2 than in Group C.

In our study, the dexmedetomidine groups received intraoperative infusion of sufentanil and dexmedetomidine, whereas the sufentanil group received sufentanil alone during the surgery. Although we believe that postoperative i.v. infusion of dexmedetomidine can significantly improve pain relief, further investigations are required to confirm this. Moreover, the antihyperanalgesic effect of dexmedetomidine continued throughout the study period (72 hours). Consistent with the findings of previous study, we found that adding dexmedetomidine to PCA reduced sufentanil consumption by about 25%.[16] A previous study revealed that i.v. morphine administered in combination with dexmedetomidine (continuous dose of 0.05 μg/kg/h) for postoperative analgesia during general anesthesia could provide satisfactory analgesia from 4 to 24 hours after surgery.[8] Recently, Nie et al[16] showed that the administration of i.v. sufentanil with dexmedetomidine (continuous dose of sufentanil 0.015 μg/kg/h and dexmedetomidine 0.045 μg/kg/h, and a bolus dose of sufentanil 0.023 μg/kg/h and dexmedetomidine 0.07 μg/kg/h) was associated with lower sufentanil consumption and better analgesic effect and patient's satisfaction than sufentanil PCA alone, in postdelivery cases. Accordingly, in our study, patients in each group received sufentanil at a continuous dose of 0.02 μg/kg/h and a bolus dose of 0.02 μg/kg. Consistent with the findings of Nie et al, we found that the group treated with the combination of the higher dose of dexmedetomidine and sufentanil (Group D2) had better analgesia and better patient satisfaction than the other 2 groups, without any increase in the frequency of adverse events. This may be attributed to the blocking of α2-adrenoceptors in the spinal cord and in the locus coeruleus, which produces an analgesic and a sedative effect, respectively. However, the scope of this study did not allow for the determination of whether the analgesic and sedative effects were responsible for the reduced opioid requirement observed in this study. Nevertheless, we believe that because the sedation levels were similar in all the 3 groups after the postoperative 1 hour, the analgesic action rather than sedative effect was more likely to have contributed to the sufentanil-sparing action of dexmedetomidine. We noted differences in the VAS_r and VAS_m scores within the 3 groups. The reasons for this remain elusive, but it may be partly attributed to the differences in the mechanism underlying the generation of the postoperative pain during rest and movement. Further research is necessary to elucidate the reasons for the discrepancies in the effect of dexmedetomidine on pain during rest and movement.

Our study has some limitations. First, dexmedetomidine was administered at a rate of 0.5 μg/kg for 10 minutes before

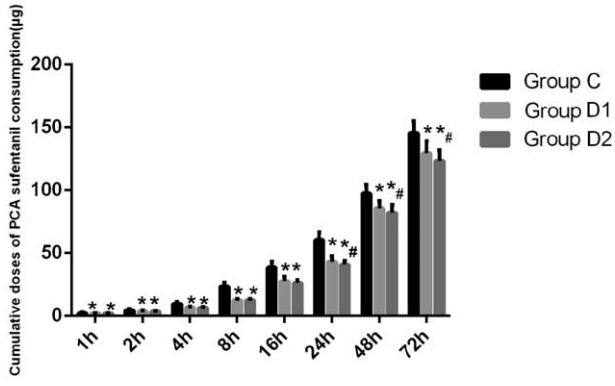

FIGURE 3. Postoperative consumption of PCA sufentanil in the 3 groups. * $P < 0.05$ versus Group C. # $P < 0.05$ versus Group D1.

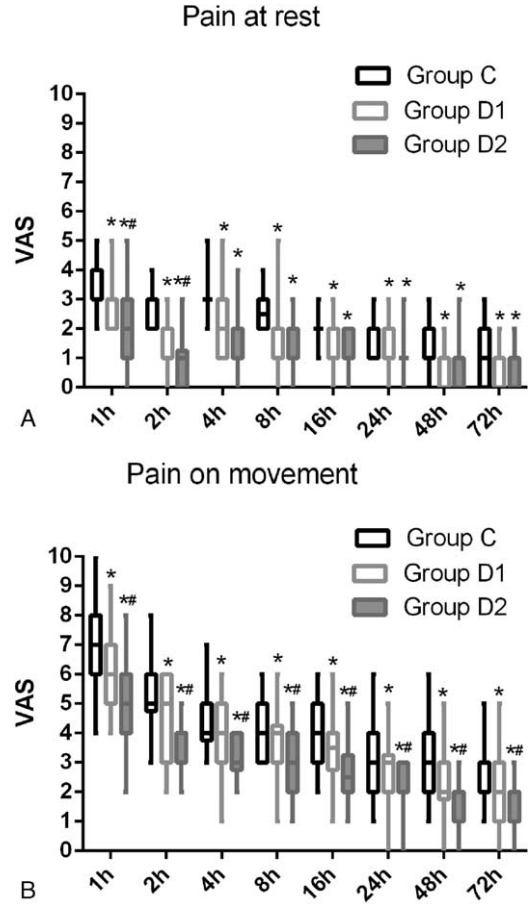

FIGURE 4. Time course of postoperative pain (at rest/movement) expressed as scores on a visual analogue scale (VAS) out of 10 in the 3 groups: (A) the VAS_r (postoperative pain [at rest]) and (B) the VAS_m (postoperative pain [at movement]). * $P < 0.05$ versus Group C; # $P < 0.05$ versus Group D1.

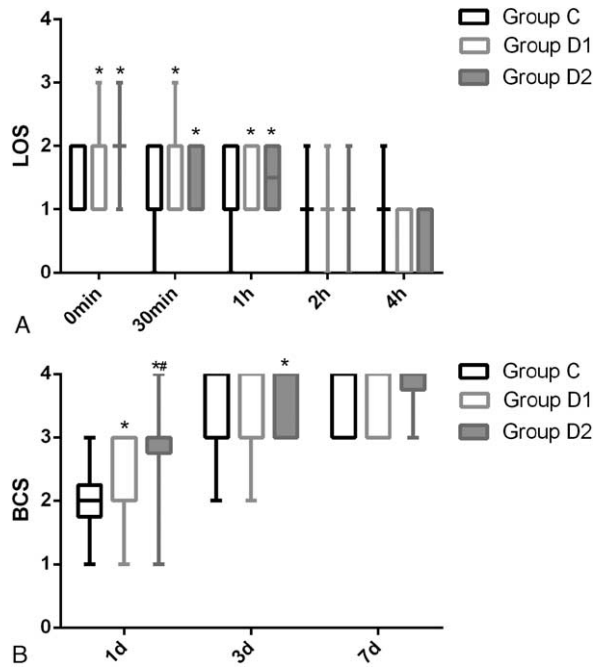

FIGURE 5. (A) Comparison of patients' sedation among the 3 groups. LOS = level of sedation (0, fully awake; 1, drowsy/closed eyes; 2, asleep/easily aroused with light tactile stimulation or a simple verbal command; 3, asleep/arousable only by strong physical stimulation; 4, unarousable). (B) Comparison of patients' satisfaction (BCS) among the 3 groups. BCS = Bruggemann comfort scale (0, persistent pain; 1, severe pain while deep breathing or coughing; 2, mild pain while deep breathing or coughing; 3, no pain while deep breathing; 4, no pain while coughing). $^{*}P < 0.05$ versus Group C; $^{\#}P < 0.05$ versus Group D1.

intubation and then at a rate of 0.3 μg/kg/h during the operation. Rather than using a fixed rate, adjusting the infusion rate according to the patient's condition may further improve hemodynamic stability. Furthermore, we did not measure the concentration of dexmedetomidine in this study at any time point. Moreover, the study included a heterogeneous group of patients aged between 35 and 65 years. Although the incidence of the acute postoperative pain may differ with age, as the composition of all the 3 groups was the same with respect to the age groups, we believe that the effect of this broad age range would be negligible. Lastly, this study was performed at a single center. Investigations of more diverse populations from different centers and using different surgical techniques would furnish more conclusive results.

In conclusion, the use of the combination of sufentanil (0.02 μg/kg/h) and dexmedetomidine (0.05 μg/kg/h) was found to be associated with less PCA requirement, better analgesic effect within the initial 72 hours, and better patient satisfaction compared with the use of sufentanil (0.02 μg/kg/h) plus a lower dose of dexmedetomidine (0.02 μg/kg/h) or sufentanil (0.02 μg/kg/h) alone.

TABLE 3. Postoperative Adverse Events in Patients Among the 3 Groups

	Group C	Group D1	Group D2
Nausea	10 (37.0%)	12 (42.9%)	7 (25.9%)*,†
Vomiting	6 (22.2%)	5 (17.9%)	2 (7.4%)*,†
Pruritus	3 (11.1%)	2 (7.1%)	2 (7.4%)
SRD	0 (0%)	0 (0%)	0 (0%)
Bradycardia	4 (14.8%)	5 (17.9%)	4 (14.8%)
Dizziness	3 (11.1%)	4 (14.3%)	3 (11.1%)

Variables presented as number of patients n (%). Group C = sufentanil (0.02 μg/kg/h); Group D1 = sufentanil plus dexmedetomidine (0.02 μg/kg/h, each); Group D2 = sufentanil (0.02 μg/kg/h) plus dexmedetomidine (0.05 μg/kg/h); SRD = serious respiratory depression.

$^{*}P < 0.05$ versus Group C.

$^{\dagger}P < 0.05$ versus Group D1.

REFERENCES

1. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology.* 2000;93:1123–1133.
2. Joshi GP. Multimodal analgesia techniques and postoperative rehabilitation. *Anesthesiol Clin North America.* 2005;23:185–202.
3. Wu CL, Raja SN. Treatment of acute postoperative pain. *Lancet.* 2011;377:2215–2225.
4. White PF, Raeder J, Kehlet H. Ketorolac: its role as part of a multimodal analgesic regimen. *Anesth Analg.* 2012;114:250–254.
5. De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. *Anesth Analg.* 2012;114:424–433.
6. Kulo A, van de Velde M, van Calsteren K, et al. Pharmacokinetics of intravenous ketorolac following caesarean delivery. *Int J Obstet Anesth.* 2012;21:334–338.
7. Remerand F, Le Tendre C, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesth Analg.* 2009;109:1963–1971.
8. Lin TF, Yeh YC, Lin FS, et al. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth.* 2009;102:117–122.
9. Zheng Y, Cui S, Liu Y, et al. Dexmedetomidine prevents remifentanil-induced postoperative hyperalgesia and decreases spinal tyrosine phosphorylation of N-methyl-d-aspartate receptor 2B subunit. *Brain Res Bull.* 2012;87:427–431.
10. Grosu I, Lavand'homme P. Use of dexmedetomidine for pain control. *F1000 Med Rep.* 2010;2:90.
11. 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.
12. Dahmani S, Brasher C, Stany I, et al. Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies. *Acta Anaesthesiol Scand.* 2010;54:397–402.
13. Jakob SM, Ruokonen E, Grounds RM, et al., Dexmedetomidine for long-term sedation investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA.* 2012;307:1151–1160.
14. Blaudszun G, Lysakowski C, Elia N, et al. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology.* 2012;116:1312–1322.
15. Schnabel A, Meyer-Friessem CH, Reichl SU, et al. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A

meta-analysis of randomized controlled trials. *Pain.* 2013;154: 1140–1149.

16. Nie Y, Liu Y, Luo Q, et al. Effect of dexmedetomidine combined with sufentanil for post-caesarean section intravenous analgesia: a randomised, placebo-controlled study. *Eur J Anaesthesiol.* 2014;31:197–203.
17. 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.
18. Katz J, Clarke H, Seltzer Z. Review article: preventive analgesia: quo vadimus? *Anesth Analg.* 2011;113:1242–1253.
19. Youssef N, Orlov D, Alie T, et al. What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery?: a meta-analysis of randomized controlled trials. *Anesth Analg.* 2014;119:965–977.
20. Popping DM, Elia N, Marret E, et al. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomized trials. *Pain.* 2012;153:784–793.
21. Ickeringill M, Shehabi Y, Adamson H, et al. Dexmedetomidine infusion without loading dose in surgical patients requiring mechanical ventilation: haemodynamic effects and efficacy. *Anaesth Intensive Care.* 2004;32:741–745.