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Intraoperative Administration of Dexmedetomidine Improved Moderately Postoperative Analgesia of Laparoscopic Colorectal Surgery: A Prospective, Randomized, Controlled Trial

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Abstract

Purpose: Although laparoscopic surgery is generally considered minimally invasive, some patients have difficulty in postoperative analgesia. This study investigated the possibility of improving postoperative analgesia by intraoperative dexmedetomidine infusion.

Methods: This study was a two-arm, single-blind, randomized, intergroup trial. A total of 64 patients having undergone laparoscopic colorectal surgery were included, which were randomly divided into two: dexmedetomidine administration (DEX group) *vs.* no-administration (control group), with the former received DEX at 0.5 μg/kg/h. The primary endpoint was the maximum Numerical Rating Scale (NRS) pain score at rest within 4 hours after returning to the High Care Unit (HCU). The secondary endpoints included the NRS pain score at rest on the following morning, the doses of analgesics and antiemetics, The Quality of Recovery (QoR) score, intraoperative circulatory dynamics, and postoperative respiratory status.

Results: DEX group, compared with control group, showed the followings; 1) significantly smaller maximum NRS pain score at rest within 4 hours after returning to the HCU (mean of 2.4 (SD of 2.0) *vs.* 4.2 (1.7)); 2) significantly smaller NRS pain score at rest on the following morning (1.9 (1.4) *vs.* 3.1 (1.6)); 3) significantly smaller doses of patient-controlled analgesia (PCA) fentanyl and acetaminophen; 4) smaller doses of pentazocine and flurbiprofen; and 5) more QoR score (86 *vs.* 80). There was no significant difference in postoperative nausea and vomiting or antiemetic use.

Conclusion: Intraoperative administration of dexmedetomidine significantly improved pain scores at rest within 4 hours after returning to the HCU in the present study population. Intraoperative dexmedetomidine also significantly improved pain scores at rest of the following morning, which played a role of "prophylactic analgesia" beyond expectation.

Keywords: Dexmedetomidine • Postoperative analgesia • iv-PCA • Prophylactic analgesia • Quality of recovery

Introduction

Postoperative analgesia is an important challenge in the perioperative period, as postoperative pain and discomfort can affect postoperative recovery. At our hospital, epidural anesthesia is the first choice for postoperative analgesia in laparotomy, whereas intravenous patient-controlled analgesia (iv-PCA) is the main choice in laparoscopic surgery. Laparoscopic surgery is generally said to be minimally invasive and to cause less postoperative wound pain; however, in practice, there are some patients experiencing inadequate postoperative analgesia. In a pilot study conducted at our hospital, 20 patients who returned to the High Care Unit (HCU) after undergoing laparoscopic surgery with general anesthesia had the mean Numerical Rating Scale (NRS) pain score at rest of 4 to 5 (moderate pain) during the night to the following morning despite therapeutic intervention.

The disposable PCA device used in our hospital delivers a continuous flow rate of 2 mL/h (fixed), a bolus dose of 1 mL/20 min (fixed), and a total volume of 100 mL. Fentanyl to be filled in the infusion device is diluted to 10-15 μg/mL in consideration of the adverse drug reactions of respiratory depression, nausea, and vomiting. The continuous dose of fentanyl is 20-30 μg/h, and the bolus dose is 10-15 μg/dose (lockout time of 20 minutes and maximum hourly dose of 30-45 μg/3 mL). Although this device is effective in many cases, it is often observed that when the patient's blood concentration of fentanyl is far from the minimum effective analgesic concentration at that point, the bolus dose does not reach the effective analgesic concentration and sufficient analgesic effect cannot be obtained.

Dexmedetomidine which we focused on in this study is familiar to anesthesiologists. It has been used for many years for sedation in ICUs and operating rooms because it provides sedation without affecting respiration. It has been reported that the use of dexmedetomidine as an adjuvant to general anesthesia during surgery reduces the doses of intraoperative anesthetics and analgesics required [1,2] and those of postoperative analgesics [3–7]. Dexmedetomidine has recently attracted attention as one of the drugs that play a role in multimodal postoperative analgesia and opioid sparing anesthesia [8-11]. It is expected to have potential to act as an adjunct to postoperative analgesia. Although the analgesic effect of dexmedetomidine is not as strong as that of opioids, postoperative analgesia in laparoscopic surgery may be improved by using dexmedetomidine in combination with opioids, NSAIDs, and acetaminophen.

By the way the appropriate timing of initiation for postoperative analgesia has not been clarified. The first possible timing is after a patient complains of pain in the postoperative period. However, if administration of dexmedetomidine is initiated at maintenance dose (0.2-0.7 μg/kg/h) after a patient complains, it will take hours for the analgesic effect to appear. Another possible method is to perform the initial loading when a patient complains. However, when

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initial loading (6 μg/kg/h × 10 min) is performed, the adverse drug reactions of bradycardia, decreased blood pressure associated with bradycardia, and elevated blood pressure associated with vasoconstriction (bimodal changes of blood pressure) are likely to occur due to the rapid increase in the blood concentration of the drug [11].

The method we adopted in this study was to administer dexmedetomidine at a maintenance dose (0.2-0.7 μg/kg/h) intraoperatively. This method reduces the risk of bradycardia and blood pressure fluctuations; and allows for immediate response of an anesthesiologist during surgery even if hemodynamic changes occur. At the completion of the surgery, a certain blood concentration of dexmedetomidine will be reached and the postoperative analgesic effect can be expected.

Materials and Methods

This study was approved by the Clinical Research Review Board (CRB) of Kobe City Medical Center General Hospital (approval number: CRB5190001) and registered in the University Hospital Medical Information Network Clinical Trials Registry (registration number: 000039944). The study protocol approved by the CRB was also registered in the Japan Registry of Clinical Trials (jRCT) (registration number: jRCTs051200056).

This study included 64 patients who underwent elective laparoscopic surgery of the colorectum under general anesthesia between November 2020 and September 2021. We explained preoperatively to patients who met the eligibility criteria using the CRB-approved explanatory document. We enrolled patients who consented in the Research Electronic Data Capture (REDCap) system and assigned them into two groups, intervention group and control group, by simple randomization procedure. This study was a two-arm, single-blind, randomized, intergroup trial in which only patients were blinded. That is, the HCU nurses who evaluate NRS pain from night to the following morning after surgery and the patients who fill out the NRS pain score sheet on the following morning are not informed of the assignment of the research groups.

According to previous studies [3,4] and a pilot study conducted at our hospital, when the difference in the NRS pain scores between the two groups is set at 1.5 points with a standard deviation of 2 points, an unpaired t-test can detect the difference with a two-tailed significance level of 5% and a power of 80% in 30 cases per group. Based on the above, the target number of cases was set to 60 (30 dexmedetomidine-administered cases and 30 non-administered cases) as efficacy analysis cases. Enrollment was terminated when the efficacy analysis reached 60 cases, except for cases of dropout, such as a case of withdrawal of consent after assignment or a case of intraoperative change of surgical technique from laparoscopic surgery to laparotomy (Figure 1).

The inclusion criteria were as follows: (1) patients scheduled to undergo laparoscopic surgery under general anesthesia without the combined use of epidural anesthesia and nerve block, (2) patients undergoing surgery in which the expected anesthesia time exceeds 3 hours (due to the administration of dexmedetomidine for more than 3 hours), (3) men and women aged over 20 and under 80 years, and (4) patients with the ability to understand the written explanations and provide consent on their own. Regarding inclusion criteria (2), the condition that the administration of dexmedetomidine exceeds 3 hours is based on a report indicating that when dexmedetomidine is administered continuously for more than 3 hours, the elimination half-life after discontinuation becomes constant in the range of 3 to 4 hours [12].

Exclusion criteria were as follows: (1) patients with history of hypersensitivity to any of the components of dexmedetomidine, (2) patients with known decreased cardiac function (e.g., history of ischemic heart disease, heart failure, severe valvular disease), (3) patients whose heart rate was less than 50 beats/min or greater than 90 beats/min on preoperative electrocardiogram (ECG), (4) patients whose systolic blood pressure was less than 90 mmHg or greater than 160 mmHg in the preoperative outpatient clinic, (5) patients with the following abnormalities on preoperative ECG (QT prolongation, left and right bundle branch block, 2nd and 3rd degree atrioventricular block, frequent ventricular extrasystoles), (6) patients with severe anemia (hemoglobin of less than 8 g/dL) on preoperative blood sampling, (7) patients with hepatic dysfunction (Child-Pugh classification of B or higher or liver enzymes (AST, ALT, and gamma-GTP) exceeding twice the upper limit of normal) on preoperative examination, (8) patients with impaired renal function (dialysis due to renal failure or estimated GFR of less than 30) according to preoperative examination, (9) patients with decreased respiratory function (preoperative SpO2 of 94% or less in room air) or receiving oxygen therapy, and other patients who are expected to be difficult to extubate in the operating room, (10) patients with a body mass index(BMI) of 35 (kg/m^2) or more, (11) patients with known drug abuse, heavy alcohol consumption, or drug dependence (e.g., sleeping pills), and (12) patients deemed unlikely to provide valid responses to the postoperative NRS pain assessment and quality of recovery (QoR) questionnaire.

Anesthesia was induced with propofol 1-2 mg/kg, rocuronium 6-8 mg/kg, fentanyl 100-200 μg, and remifentanil 0.1-0.4 μg/kg/min. Anesthesia was maintained with either propofol, sevoflurane, or desflurane, with a target BIS range of 35-50 according to the discretion of the anesthesiologist in charge. Intraoperative vital signs were monitored to ensure that the heart rate did not fall below 45 bpm; and that the systolic blood pressure was in the range of 85-150 mm Hg. As needed, vasopressors (atropine, ephedrine, and phenylephrine), antihypertensive agents (nicardipine), and colloid solution (hydroxyethyl starch 130,000) were administered. Muscle relaxants were added as needed, and for reversal after the completion of surgery, either sugammadex or neostigmine was used to antagonize. If inhalation anesthetics were selected, droperidol 0.5-1.0 mg was administered intravenously as a prophylactic antiemetic at the completion of surgery.

As a transitional opioid for postoperative analgesia, 8-12 mL (400-600 μg) of fentanyl was administered intraoperatively in divided doses, targeting an effect site concentration of around 1.0 ng/mL by Shafer's simulation at the completion of surgery. At the time of wound closure, 1,000 mg of acetaminophen was administered. The iv-PCA device was filled with 30 mL of fentanyl for patients aged 50-60 years, 25 mL for patients aged 60-70 years, and 20 mL for patients aged 70-80 years, considering age and weight, and 2 mL (5 mg) of the antiemetic droperidol, together with 0.9% saline to make a total volume of 100 mL, and started at 2 mL/h at the time of wound closure.

In the DEX group, dexmedetomidine was initiated at 0.5 μg/kg/h after confirming the hemodynamic stability after induction of anesthesia. Dexmedetomidine was reduced at the completion of surgery and discontinued after the patient was awakened from anesthesia and extubated.

The primary endpoint was the maximum NRS pain score at rest within 4 hours after returning to the HCU. The secondary endpoints included the NRS pain score at rest on the following morning of surgery, the amount of analgesics and antiemetics administered in the HCU, the quality of recovery (QoR) score (20 items on a 100-point scale), intraoperative circulatory dynamics (intraoperative mean heart rate, mean blood pressure, and mean BIS values), doses of cardiovascular agonists (ephedrine, phenylephrine, and atropine) and colloid solution (hydroxyethyl starch 130,000), and respiratory depression (respiratory rate <8 breaths/min, SpO2 <92%) after extubation and returning to the HCU.

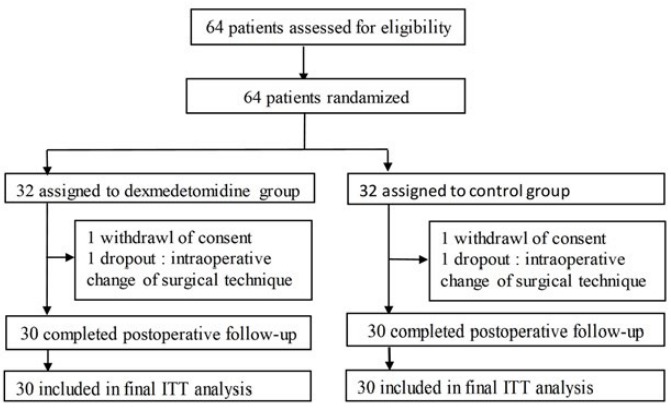

Figure 1. Flowchart of the study. ITT=Intention-to-treat.

From the time of returning to the HCU to the following morning of surgery, pain assessments were assessed by HCU nurses every 2 hours using NRS pain score and recorded in electronic medical records. When we examined patients on the following morning, patients were asked to fill in the NRS pain evaluation form. Regarding analgesics and antiemetics administered in HCU, the doses of pentazocine (mg), acetaminophen (g), flurbiprofen (mg), and metoclopramide (mg) were recorded by the HCU nurses in an electronic medical records, which we referred on the following morning. As for the bolus usage (ml) of iv-PCA, the bolus dose at night was calculated by reading the scale of the remaining amount when we examined the patient on the following morning.

Patients were also asked to fill in the quality of recovery (QoR) score form when we examined patients on the following morning. The QoR score (20-item multidimensional postoperative assessment score on a 100-point scale) (Table 1) was created by selecting 20 items that are suitable for assessment of the postoperative day (POD) 1, from four domains, including physical comfort, emotion, physical ability, and pain, of the Quality of Recovery-40 (QoR-40) [13], a conventionally used scale.

The study design was a single center, two-arm, single-blind, randomized, intergroup trial with a target number of 60 patients (30 patients of DEX group and 30 patients of control group) for efficacy analysis. Patient background and intraoperative information (Table 2), the primary endpoint, and the secondary endpoints were obtained for each group to determine the median and interquartile range, mean and standard deviation, number of cases, and percentage (%) for comparison between the two groups. Comparisons between the two groups were made by Student's t test or Mann-Whitney U test for continuous variables and Fisher's exact probability test or Pearson's chi-square test for categorical variables. All tests were two-tailed tests, and a p-value of less than 0.05 was considered statistically significant. The data of the present study were statistically analyzed using the JMP14.0 software.

Results

Sixty-four patients who provided a written consent were randomly assigned through REDCap. There were two cases of withdrawal of consent after assignment. In addition, there were two cases of dropout due to intraoperative change of surgical technique from laparoscopic surgery to laparotomy. 60 patients (30 patients of DEX group and 30 patients of control group) were completed the postoperative examination on POD1 and follow-up observations (Figure 1).

DEX group, compared with control group, showed significantly smaller maximum NRS pain score at rest within 4 hours after returning to the HCU (mean of 2.4 (SD of 2.0) *vs.* 4.2 (1.7)) (unpaired t-test: p <0.001). DEX group, compared with control group, also showed significantly smaller NRS pain

Table 1. Quality of Recovery (QoR) questionnaires.

Physical Comfort (6 items, 30 points)	I was able to relax, I slept well during the night, I felt nauseous, I vomited, I felt dizzy, I felt cold and shaky
Emotional State (6 items, 30 points)	I felt calm, I felt good, I felt anxious, I felt depressed, I felt isolated, I had hallucinations/nightmares
Physical Ability (3 items, 15 points)	I could breathe easily, I could move my body easily, I could talk normally
Pain (5 items, 25 points)	I felt pain at rest, I felt pain with movement, I needed painkillers, I had pain in my back/hip, I had pain in my throat

We selected 20 items from the Quality of Recovery(QoR-40 developed by Myles, et al. and partially modified.
We scored on a Likert scale (5 points each × 20 items on a 100-point scale).

Table 2. Demographic data and Intraoperative information.

Parameters	Control group n = 30	DEX group n = 30	P value
Age (year)	66 [60,72]	69 [58,74]	0.62
Gender (male/female) (n)	14 /16	12/18	0.61
BMI (kg/m^2)	23 [19,26]	22 [20,24]	0.90
Preoperative medical history			
Cardiac disease (n)	2 (6%)	1 (3%)	0.56
Cerebrovascular disease (n)	0 (0%)	0 (0%)	1.0
Impaired renal function (eGFR <45) (n)	1 (3%)	0 (0%)	0.32
Preoperative Hb level (g/dL)	13 [12,14]	13 [12,14]	0.63
ASA-PS I/II/III (n)	0/29/1	1/29/0	0.16
Surgery duration (min)	273 [216,388]	283 [224,405]	0.87
Anesthesia duration (min)	370 [300,504]	369 [316,522]	0.82
Anesthesia maintenance (SEV/DES/propofol) (n)	15/6/9	12/7/11	0.74
End-tidal sevoflurane concentration (%)	1.1 (0.1)	1.1 (0.1)	0.26
End-tidal desflurane concentration (%)	3.5 (0.4)	3.4 (0.4)	0.72
Propofol effect site concentration (μg/mL)	2.7 (0.3)	2.5 (0.4)	0.19
Total intraoperative fentanyl dose (μg)	550 [440,650]	52 [450,650]	0.84
Total intraoperative remifentanil dose (μg)	4000 [2880,7000]	4000 [2900,6100]	0.78
Fentanyl dose contained in PCA (mL/ total 100 mL)	25 [25,30]	25 [25,30]	0.96
Intraoperative dexmedetomidine dose (μg)	0	140 [104,204]	–

Data are presented as median [interquartile range], mean(standard deviation) or number of patients (%).
BMI=Body Mass Index; eGFR= estimated Glomerular Filtration Rate ; Hb=Hemoglobin; ASA-PS=American Society of Anesthesiologists-Physical Status; SEV=Sevoflurane; DES=Desflurane; PCA= Patient-controlled Analgesia

score at rest on the following morning (1.9 (1.4) *vs.* 3.1 (1.6)) (unpaired t-test: p = 0.005) (Table 3).

The distribution of maximum NRS pain score at rest within 4 hours after returning to the HCU was as follows: mild pain (NRS 0-3) in 24 patients in the DEX group and 13 in the control group, moderate pain (NRS 4-6) in four patients in the DEX group and 14 in the control group, and severe pain (NRS 7-8) in two patients in the DEX group and three in the control group (Figure 2).

The distribution of the NRS pain score at rest on the following morning of surgery was as follows: mild pain (NRS 0-3) in 27 patients in the DEX group and 23 in the control group, moderate pain (NRS 4-6) in three patients in the DEX group and six in the control group, and severe pain (NRS 7-8) in zero patients in the DEX group and one in the control group (Figure 3).

The quality of recovery (QoR) scores, the frequency of postoperative nausea and vomiting, the doses of analgesics and antiemetics administered from the time of return to the HCU to the following morning, the number of patients administered, and the amount of iv-PCA bolus used and the number of patients who used it were as shown in Table 4.

For safety evaluation, the intraoperative circulatory dynamics (intraoperative mean heart rate (HR), mean MAP, and mean BIS values), the doses of cardiovascular agonists (ephedrine, phenylephrine, and atropine) and colloid solution (hydroxyethyl starch 130,000), and the presence or absence of respiratory depression after extubation and returning to the HCU were as shown in Table 5.

Discussion

Table 3. Maximum resting NRS pain score within 4 hours after returning to HCU and Resting NRS pain score on the following morning of surgery.

Parameters	Control Group n = 30	DEX Group n = 30	Mean Difference (95%CI)	P-Value
Maximum NRS pain score at rest within 4 hours after returning to the HCU	4.2 (1.7)	2.4 (2.0)	-1.8 (-2.8, -0.9)	<0.001
The NRS pain score at rest on the following morning of surgery	3.1 (1.6)	1.9 (1.4)	-1.2 (-1.9, -0.4)	0.005

Data are presented as mean (standard deviation).

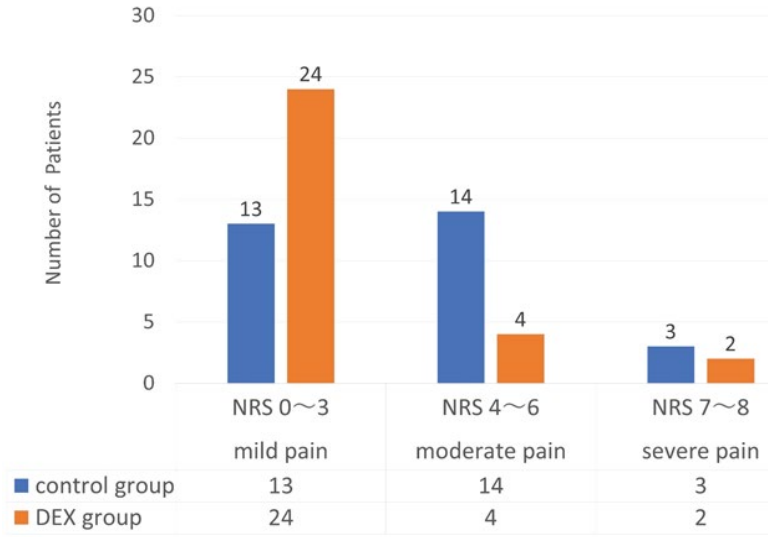

Figure 2. Maximum NRS pain score at rest within 4hours after returning to HCU.

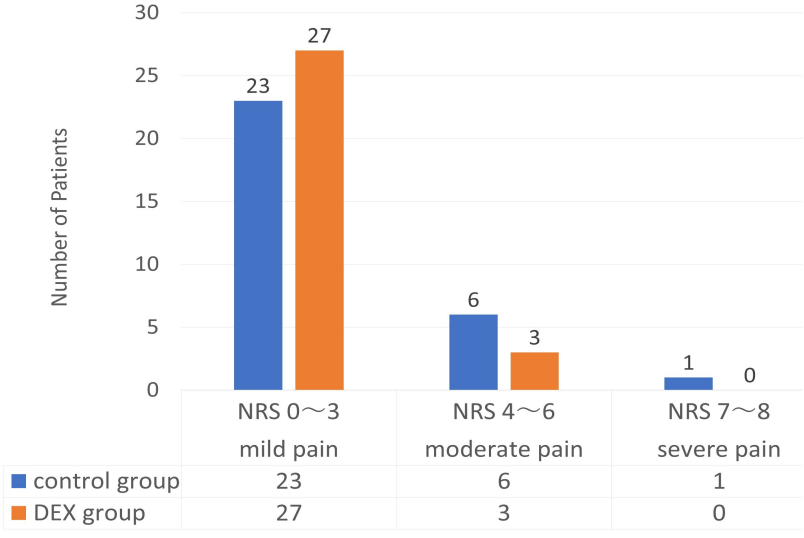

Figure 3. The NRS pain score at rest on the following morning of surgery.

Table 4. Quality of recovery (QoR) scores, nausea and vomiting, Rescue analgesics and antiemetics after returning to the HCU.

Parameters	Control Group n=30	DEX Group n=30	Mean Difference (95%CI)	P-Value
Physical comfort (Maximum 30 points)	25 [23,27]	25 [23,26]	0.03 (-1.4, 1.4)	0.96
Emotional state (Maximum 30 points)	25 [22,27]	26 [23,28]	0.67 (-1.3, 2.7)	0.51
Physical ability (Maximum 15 points)	13 [9,14]	14 [13,15]	1.9 (0.7, 3.1)	0.003
Pain (Maximum 25 points)	20 [17,21]	22 [19,23]	1.9 (-0.03, 3.8)	0.05
Total (Maximum 100 points)	80 [75,86]	86 [82,90]	4.4 (-0.4, 9.2)	0.07
Nausea (n)	5 (17%)	5 (17%)	0 (-0.2, 0.2)	1.0
Vomiting (n)	3 (10%)	3 (10%)	0 (-0.16, 0.16)	1.0
Pentazocine administration(mg) (n)	0 (0,30) 8 (26%)	0 (0, 15) 3 (10%)	-3.0 (-6.4, 0.38)	0.08
Acetaminophen administration(g) (n)	2 [1,3] 25 (83%)	1 [0,2] 20 (67%)	-0.6 (-1.2, -0.04)	0.04
Flurbiprofen administration(mg) (n)	0 (0,100) 5 (17%)	0 (0, 50) 2 (7%)	-6.7 (-1.7, 3.3)	0.19
PCA bolus dose of fentanyl(μg) Bolus users (n)	80 (90) 22 (73%)	35 (45) 15 (50%)	-45 (-80, -7.3)	0.02
Metoclopramide administration(mg) (n)	0 (0, 20) 4 (13%)	0 (0, 10) 5 (17%)	0.3 (-2.8, 2.1)	0.79

Data are presented as median [interquartile range], median (minimum, maximum), mean (standard deviation), or number of patients (%).

Table 5. Intraoperative circulatory dynamics, use of cardiovascular agonists, postoperative respiratory status.

Parameters	Control Group (n=30)	DEX Group (n=30)	P-value
Intraoperative mean HR (bpm)	64 [61,68]	59 [54,67]	0.02
Intraoperative mean MAP (mmHg)	81 [75,84]	79 [78,86]	0.77
Intraoperative mean BIS	44 [41,46]	41 [40,44]	0.03
Intraoperative ephedrine dose used (mg)	14 [11,25]	12 [10,21]	0.43
Intraoperative phenylephrine dose used(μg)	50 [0,650]	0 [0,63]	0.053
Intraoperative colloid solution dose(mL)	125 [0,350]	105 [0,400]	0.90
Intraoperative atropine users (n)	2 (7%)	4 (13%)	0.36
Postoperative respiratory depression (n)	0	0	1.0

Data are presented as median [interquartile range] or number of patients (%).
HR=Heart Rate; MAP=Mean Arterial Pressure; BIS= Bi Spectral Index

DEX group, compared with control group, showed significantly smaller maximum NRS pain score at rest within 4 hours after returning to the HCU (mean of 2.4 (SD of 2.0) *vs.* 4.2 (1.7)) (unpaired t-test: $p < 0.001$) (Table 3). How can we interpret this difference?

Postoperative pain due to surgery in the acute phase has been associated with the surgical technique [14]. In a pilot study conducted at our hospital, the mean NRS score at rest within 4 hours after returning to the HCU from laparoscopic surgery (non-DEX administration, n=30, use of iv-PCA for postoperative analgesia without combined use of epidural anesthesia and nerve block) were 5.4 for abdominal surgery (upper and lower abdomen), 4.5 for urology (prostate, bladder, and kidney), and 3.0 for gynecology (uterus). Postoperative pain in upper abdominal laparoscopic surgery tends to be severe. Postoperative pain in lower abdominal and urological laparoscopic surgery is often moderate. Postoperative pain in gynecological laparoscopic surgery is often mild. Lower abdominal laparoscopic surgery, the target of this study, was expected to result in moderate postoperative pain, and the intraoperative administration of dexmedetomidine was shown to be effective overall.

In the distribution of the maximum NRS pain score at rest within 4 hours after returning to the HCU (Figure 2), severe pain (NRS 7-8) was observed in two patients in the DEX group and three patients in the control group, indicating that there are a certain number of patients who are difficult to treat with intravenous opioid administration, even though the same surgical technique was performed and equivalent doses of analgesics were administered intraoperatively. The amount of fentanyl administered intraoperatively (8-15 mL of fentanyl) and the amount of fentanyl filled in the iv-PCA device (20-30 mL) in the five patients who complained of severe pain (NRS 7-8) did not differ significantly from those in the moderate pain (NRS 4-6) group and mild pain (NRS 0-3) group. Five patients of severe pain (NRS 7-8) were initially given an iv-PCA bolus (30-45 μg of fentanyl dose) after returning to the HCU, but did not achieve analgesia. In patients for whom the analgesic effect of the main analgesic, fentanyl is inadequate, the efficacy of dexmedetomidine is insufficient. All of five patients were subsequently treated with the weak opioid, pentazocine (15-30 mg).

Within 4 hours after returning to the HCU, four patients in the DEX group and 14 patients in the control group complained of moderate pain (NRS 4-6). 24 patients in the DEX group and 13 patients in the control group complained of mild pain (NRS 0-3) (Figure 2). Intraoperative administration of dexmedetomidine is presumed to be useful in relieving moderate pain. In the literature [15], the analgesic effect of dexmedetomidine is intermediate between that of acetaminophen and NSAIDs, based on the degree of decreases in morphine consumption and Visual Analogue Scale pain score at 24 hours postoperatively. The present finding that dexmedetomidine has moderate analgesic effect is consistent with the point made by Blaudszun G, et al [16]. Overall, intraoperative administration of dexmedetomidine was effective in targeting a group of postoperative patients with moderate pain in the acute phase after laparoscopic colorectal surgery.

Next, we discuss the sustaining effects of dexmedetomidine. In this protocol dexmedetomidine was administered only intraoperatively. We wondered how much analgesic effect dexmedetomidine would retain on the following morning of the surgery. After overnight therapeutic intervention in the HCU, DEX group, compared with control group, showed significantly smaller NRS pain score at rest on the following morning (1.9 (1.4) *vs.* 3.1 (1.6)) (unpaired t-test: $p = 0.005$) (Table 3).

In the present study, dexmedetomidine was administered at a maintenance dose of 0.5 μg/kg/h for a median of 6 hours intraoperatively (interquartile range of 4-8 hours), thus resulting in a sedative concentration of dexmedetomidine after returning to the HCU. According to the literature [11], dexmedetomidine at low concentrations in the blood has a mild analgesic effect with a sedative effect that the patient responds to being called normally while circulatory and respiratory status is maintained, which were observed in each patient of the DEX group. However, before starting this study we didn't expect there would be a significant difference in pain scores between the two groups on the following morning of surgery, because the blood concentration of dexmedetomidine would have decreased.

A study in healthy volunteers reported that the elimination half-life of dexmedetomidine was 2-3 hours, which is a relatively long half-life compared to that of propofol [17]. In the literature [18], simulations using published pharmacokinetic parameters for dexmedetomidine present even longer disappearance time. The disappearance time of 50% in plasma after the completion of the infusion is 4 hours 44 minutes for dexmedetomidine, and the disappearance time of 90% is 28 hours. In other words, even on the following morning of surgery, 14-18 hours after returning to the HCU, dexmedetomidine administered intraoperatively seems to maintain a certain level of blood concentration with mild analgesia.

There is also a study that claims that prophylactic analgesia results in a longer than expected duration of analgesic effect [5]. The sedative effects of dexmedetomidine are mediated by elevation of noradrenergic pathways in the locus coeruleus, whereas the analgesic effects involve suppression of nociceptive signals transmitted via the posterior horn of spinal cord and enhancement of α2-adrenoceptor-dependent descending pathways in the spinal cord. Basic research by Funai Y, et al. reported that systemic administration of dexmedetomidine at doses below the range for sedation enhanced descending noradrenergic inhibitory pathways and facilitated inhibitory synaptic transmission in the posterior horn of spinal cord [19]. The results of the present study may be interpreted as indicating that the intraoperative administration of dexmedetomidine served as a "prophylactic analgesic" since the blood concentration of dexmedetomidine was maintained, albeit at a relatively low level, even after the completion of administration, contributing to the mitigation of postoperative pain and the reduction of analgesic use [20,21]. Intraoperative administration of dexmedetomidine at a maintenance dose was initially planned in order to avoid adverse drug reactions (bradycardia and increased blood pressure) associated with rapid administration; however, intraoperative administration of dexmedetomidine may lead to "prophylactic analgesia".

Next, we discuss the quality of recovery (QoR) score (20 items on a 100-point scale) (Tables 1 and 4). Among the four domains, the "physical ability" domain (satisfaction in moving freely, taking deep breaths, and talking) of DEX group, compared with that of control group, were significantly higher (median of 14 *vs.* 13) (unpaired t-test: $p = 0.003$). The "pain" domain of DEX group, compared with that of control group, were higher (median of 22 *vs.* 20). This result was consistent with the lower NRS pain score in the DEX group on the following morning of surgery although not significant (unpaired t-test: $p = 0.05$).

As for the "physical comfort" domain (e.g., being able to relax at night, sleeping well), few patients in both groups responded positively. Conversely, few patients in both groups responded negatively to the "emotional state" domain (e.g., feeling anxious or depressed, feeling isolated). There were no significant differences between the two groups in the "physical comfort" and "emotional state" domains. The overall QoR score of DEX group, compared with that of control group, were higher (median of 86 *vs.* 80) (unpaired t-test: $p = 0.07$). From the night of the surgery to the following morning, the overall quality of recovery tended to be better and more satisfactory in the DEX group although not significant.

In a study by Bekker *A,* et al. [22], dexmedetomidine was administered at 0.5 μg/kg/h intraoperatively for spinal surgery under general anesthesia and the quality of recovery after surgery (QoR-40, 40 items on a 200-point scale) was assessed. DEX group showed higher QoR score compared with control group from POD1 to POD2, and showed significantly higher QoR score only on POD3, indicating that intraoperative administration of dexmedetomidine moderately improved the quality of recovery after surgery. In a study by Li Q, et al. [23], they administered dexmedetomidine intraoperatively to female patients undergoing thoracic surgery and added dexmedetomidine to postoperative sufentanil-based iv-PCA, which improved postoperative analgesia, reduced the incidence of postoperative nausea and vomiting, and increased satisfaction.

In the present study, it can also be inferred that intraoperative administration of dexmedetomidine moderately reduced the perioperative stress of patients and improved the quality of recovery, mainly because of the analgesic effect that continued mildly after the completion of administration. Moreover, a systematic review by Flanders CA, et al. found that administration of dexmedetomidine reduced inflammatory cytokines associated with surgery [24]. The anti-inflammatory effects dexmedetomidine, together with the moderate analgesic effects of dexmedetomidine, may contribute to improve quality of recovery after surgery.

Lastly, we discuss the safety evaluation. In the present study, dexmedetomidine was administered intraoperatively at a maintenance dose of 0.5 μg/kg/h. Although there were some cases of transient bradycardia and blood pressure fluctuations associated with this administration, all were within the range that could be managed with regular drug administration. There was no significant difference in the administration of ephedrine, phenylephrine, atropine, and colloid solution between the two groups. There were no cases of hypoxic events ($SpO2<92\%$) or respiratory depression (respiratory rate <8 breaths/min) after extubation in an operating room and after returning to HCU (Table 5).

The present study has several limitations. First, NRS pain score at rest on the following morning of surgery of DEX group was significantly smaller compared with that of control group, but it remains unclear at what concentrations dexmedetomidine is effective for postoperative analgesia. Second, the analgesic effect of dexmedetomidine is not strong, so it is a future topic to investigate what analgesic combinations are suitable for multimodal analgesia. Third, in the present study we have shown that the quality of recovery (QoR) tended to be better in the DEX group. Another study is needed with the quality of recovery as the primary endpoint.

Conclusion

We could safely administer dexmedetomidine at a maintenance dose starting intraoperatively without significant hemodynamic changes during surgery or postoperative respiratory depression. Intraoperative administration of dexmedetomidine significantly improved pain scores at rest within 4 hours after returning to the HCU, which was effective in targeting a group of postoperative patients with moderate pain after laparoscopic colorectal surgery. Intraoperative dexmedetomidine also significantly improved pain scores at rest of the following morning, which played a role of "prophylactic analgesia" beyond expectation.

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Conflict of Interest Statement

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