—Original—

Optimal Dose of Dexmedetomidine for Preemptive Analgesia Combined with Transversus Abdominis Plane Block after Colon Cancer Surgery

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Background: Pain after colon cancer surgery can be effectively relieved by transversus abdominis plane (TAP) block. We aimed to determine the optimal dose of dexmedetomidine for preemptive analgesia when combined with TAP block after colon cancer surgery.

Methods: A total of 120 patients undergoing laparoscopic resection for colon cancer from March 2018 to October 2019 were randomly assigned to control (group C), low-dose (group L, 0.5 μg/kg), moderate-dose (group M, 1 μg/kg), and high-dose groups (group H, 1.5 μg/kg) (n=30 each). After puncture under ultrasound guidance, the designated dexmedetomidine dose and 0.25% ropivacaine were injected on both sides (20 mL each side). Mean arterial pressure (MAP), heart rate (HR), numeric rating scale (NRS) score, and Ramsay score were compared at 2 h (T0), 4 h (T1), 8 h (T2), 12 h (T3), 24 h (T4), and 48 h (T5) after surgery. The area sensitive to mechanical stimulation-induced pain at the incision was measured at T4, T5, and 72 h after surgery (T6). Adverse reactions were compared.

Results: MAP and HR were lower in the dexmedetomidine groups, especially groups M and H, than in group C ($P<0.05$). NRS scores at T0-T5 and pain-sensitive areas at T4-T6 were lower in the dexmedetomidine groups than in group C ($P<0.05$), but Ramsay scores were similar ($P>0.05$). Compared with group L, groups M and H had lower NRS scores and pain-sensitive areas ($P<0.05$). The incidence rates of adverse reactions were lower in the dexmedetomidine groups than in group C ($P<0.05$).

Conclusions: Dexmedetomidine 1 or 1.5 μg/kg is effective and did not increase adverse reactions. A dose of 1 μg/kg is recommended as an adjuvant to ropivacaine for TAP block.

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Key words: dexmedetomidine, transversus abdominis plane block, colon cancer, analgesia

Introduction

Postoperative pain, a common complication after colon cancer surgery, is mainly caused by stimuli affecting the peripheral nerve receptors of patients during surgery[1]. Pain can alter the blood supply to the myocardium if not relieved, thus reducing immunity and slowing postoperative recovery[2]. Transversus abdominis plane (TAP) block is a regional block, that is, local anesthetic is injected into the fascial plane between the obliquus internus abdominis and transversus abdominis to block afflux of noxious stimuli through sensory nerves innervating the anterior abdominal wall, thereby relieving pain after colon cancer surgery[3]. Dexmedetomidine, an α2 receptor agonist, exerts sedative and analgesic effects by activating α2 receptors in the central nerve and spinal cord[4]. A study reported that dexmedetomidine can serve as an adjuvant to local anesthetics. Because it prolongs the action of TAP block and reduces the required dose of local anesthetics, it may prove valuable in clinical practice[5]. This study investigated the dose of dexmedetomidine, when combined with TAP block, that achieved the best clinical outcomes after colon cancer surgery.

Materials and Methods

Baseline Clinical Data

This study was approved by the ethics committee of Ji-

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aozuo People's Hospital (approval No. 2018030012). A total of 120 patients undergoing elective laparoscopic radical resection for colon cancer in our hospital from March 2018 to October 2019 were selected, including 72 men and 48 women aged 34-65 years, with a mean age of 45.81 ± 9.43 years and a mean body mass index (BMI) of 21.02 ± 1.36 kg/m^2.

Inclusion criteria: 1) Patients who received a diagnosis of colon cancer and consented to laparoscopic radical resection for colon cancer; 2) those classified as having an American Society of Anesthesiologists (ASA) physical status of I or II; and 3) those who gave written informed consent.

Exclusion criteria: 1) Patients allergic to anesthesia; 2) those with a history of abdominal surgery; 3) those with dysfunction of a vital organ; 4) those receiving long-term treatment with sedative or analgesic drugs; and 5) those with incomplete case data.

Group Assignment

All 120 patients enrolled were evenly assigned to the control group (group C) or the dexmedetomidine low-dose group (group L), moderate-dose group (group M), or high-dose group (group H). The patients in groups L, M, and H received dexmedetomidine (Jiangsu Hengrui Medicine Co., Ltd., China) 0.5, 1.0, and 1.5 μg/kg, respectively, while those in group C were given the same volume of normal saline (Guangdong Kelun Pharmaceutical Co., Ltd., China).

Anesthesia Methods

All patients were routinely deprived of water and food for 6 h before surgery. Upon entering the operating room, blood pressure, heart rate (HR), electrocardiography, blood oxygen saturation, and Narcotrend (NT) anesthesia depth were monitored. The surgery was performed under general anesthesia with tracheal intubation and maintenance of anesthesia through TAP block. General anesthesia was induced with sufentanil 0.4 μg/kg, propofol 2 mg/kg, and cis-atracurium 0.15 μg/kg. Tracheal intubation was conducted after patients were unconsciousness, and an anesthesia machine was connected. Anesthesia was maintained by continuous intravenous injection of propofol 4-6 mg/kg・h, remifentanil 0.15-0.2 μg/kg・min, and cis-atracurium 2 μg/kg・min. During surgery, NT anesthesia/consciousness depth was maintained at stage D (index: 37-64). After surgery, bilateral TAP block was performed under ultrasound guidance. The skin of patients in supine position was routinely disinfected and covered with a towel. Then, the midaxillary line of the anterior abdominal wall between the upper margin of the iliac crest and lower margin of the costal arch was positioned, on which a high-frequency (5-10 Hz) ultrasound probe (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China) was placed to identify the obliquus externus abdominis, obliquus internus abdominis, and transverses abdominis from the superficial layer to the deep layer, in that order. After that, under ultrasound guidance, the fascial plane between the obliquus internus abdominis and transverses abdominis was punctured with a 0.7 mm × 80 mm sterile injection needle (Zhejiang Kangdelai Medical Instrument Co., Ltd., China) using in-plane technology. When pumpback revealed no blood or gas, the designated dexmedetomidine dose and 0.25% ropivacaine (AstraZeneca AB, Sweden) were injected on both sides (20 mL each side) in each group. A fusiform space between the obliquus internus abdominis and TAP shown on ultrasonic scanning images indicated successful puncture.

Baseline Data and Surgical Variables

The baseline data of patients in the four groups were collected, including age, gender, weight, BMI, and ASA grade. In addition, data for surgery-related variables, such as surgical time, anesthesia time, intraoperative infusion volume, intraoperative urine volume, and blood loss, were recorded.

Hemodynamic Variables

Mean arterial pressure (MAP) and HR were detected and recorded at 2 h (T0), 4 h (T1), 8 h (T2), 12 h (T3), 24 h (T4), and 48 h (T5) after surgery.

Scoring of Pain and Sedation

A numeric rating scale (NRS) score ranging from 0 to 10 points was used to assess pain severity of patients at T0-T5, with 1-4 points for mild pain, 5-6 points for moderate pain, and 7-10 points for severe pain.

The sedative effect on patients was assessed using the Ramsay scale with a score range of 1 to 6 points, including insufficient sedation (1-2 points), satisfactory sedation (3-4 points) and oversedation (5-6 points).

Calculation of Pain-sensitive Area

In a previous study[6], the skin around the incision was mechanically stimulated at T4-T6 with a fine, soft brush, while moving gradually from a painless area to the incision site. Then, the areas where the patient reported slight pain, pain, and sharp pain were marked, and the distance between the pain area and incision was measured, after which the pain-sensitive area was calculated.

Observation of Adverse Reactions

The postoperative adverse reactions of patients included dizziness, nausea and vomiting, respiratory de-

Table 1 Baseline clinical data

Index	Group C (n=30)	Group L (n=30)	Group M (n=30)	Group H (n=30)	F/χ^2	P
Age (years)	45.94±8.24	46.01±8.21	45.67±8.35	46.57±9.04	1.396	0.817
Gender [male/female (n)]	12/18	13/17	12/18	11/19	0.278	0.964
Weight (kg)	62.85±6.28	63.12±7.02	63.26±6.86	63.53±7.29	0.934	0.910
BMI (kg/m^2)	23.89±2.14	24.47±2.32	25.02±2.08	24.63±2.05	1.223	0.822
ASA Grade I/II (n)	17/13	20/10	23/7	19/11	2.779	0.427
Operation time (min)	165.1±34.2	161.2±32.7	165.1±34.2	163.52±32.3	6.15	0.431
Anesthesia time (min)	212.8±44.3	221.3±43.2	217.8±42.7	220.8±41.9	2.55	0.726
Intraoperative infusion volume (L)	2.13±0.51	2.08±0.43	2.11±0.51	2.07±0.43	8.67	0.134
Intraoperative urine volume (mL)	407.93±38.4	403.2±42.3	408.93±38.5	405.14±39.2	3.71	0.625
Hemorrhage volume (mL)	159.63±25.31	160.26±25.18	162.63±25.31	161.34±24.68	4.68	0.608

Table 2 Hemodynamic indices ($\bar{\chi} \pm s$)

Index	Time	Group C (n=30)	Group L (n=30)	Group M (n=30)	Group H (n=30)
MAP (mm Hg)	T0	95.4±5.6	91.5±5.4*	88.6±5.2*#	87.4±5.3*#
	T1	93.2±4.8	90.1±4.7*	86.9±4.6*#	86.7±4.2*#
	T2	92.3±5.2	88.7±4.9*	85.4±5.1*#	85.2±5.2*#
	T3	91.2±4.9	87.2±4.9*	84.7±4.6*#	84.5±4.9*#
	T4	90.6±4.6	86.6±4.8*	84.2±4.1*#	84.1±4.3*#
	T5	87.3±4.7	84.4±4.5*	83.5±5.0*	83.1±4.8*
HR (beats/min)	T0	85.2±6.5	82.8±6.9	79.2±5.9*#	79.3±6.0*#
	T1	84.5±6.8	80.5±7.2*	76.5±7.1*#	76.0±6.9*#
	T2	84.1±7.0	79.3±6.3*	75.8±6.5*#	75.3±6.7*#
	T3	83.2±6.4	78.4±7.0*	74.4±6.7*#	73.6±7.2*#
	T4	80.7±6.7	77.2±6.5*	73.7±6.8*#	73.1±6.9*#
	T5	78.3±6.6	75.1±6.2	71.8±6.5*#	71.2±6.4*#

*P<0.05 *vs.* group C, #P<0.05 *vs.* group L.

pression, shivering, hypotension (systolic blood pressure <90 mm Hg), bradycardia (HR <60 beats/min), and drowsiness. The numbers of patients with these adverse reactions were recorded.

Statistical Analysis

All data were analyzed with SPSS 19.0 software. Quantitative data were subjected to homogeneity of variance and normal distribution tests. Those with a normal distribution are expressed as mean ± standard deviation. Pairwise comparisons were conducted by the t test, and multigroup comparisons were carried out with one-way analysis of variance. Numerical data are reported as frequencies or rates, and intergroup comparisons were performed with the χ^2 test. A two-tailed P value of <0.05 was considered statistically significant.

Results

Baseline Clinical Data

The general characteristics of the four groups were compared. There was no significant difference in age, gender, weight, BMI, ASA classification, operation time, anesthesia time, intraoperative infusion volume, intraoperative urine volume, or hemorrhage volume among the four groups (P>0.05) (**Table 1**).

Hemodynamic Variables

MAP and HR were compared among the four groups at each time point. MAP was significantly lower at T0-T5 in groups L, M, and H than in group C (P<0.05), HR was significantly lower at T1-T4 in group L than in group C (P<0.05), and HR at T0-T5 was significantly lower in groups M and H than in group C (P<0.05). In groups M and H, MAP at T0-T4 was significantly lower than in group L (P<0.05) and HR at T0-T5 was significantly lower than in group L (P<0.05). No significant difference between groups M and H was observed in MAP or HR at any time point (P>0.05), suggesting that dexmedetomidine stabilized the postoperative hemodynamics of the patients (**Table 2**).

NRS and Ramsay Sedation Scores

The NRS and Ramsay sedation scores were compared

Table 3 NRS and Ramsay sedation scores at each time point (point, $\bar{\chi} \pm s$)

Index	Time	Group C (n=30)	Group L (n=30)	Group M (n=30)	Group H (n=30)
NRS score	T0	3.9±0.6	3.6±0.5*	3.3±0.6*#	3.2±0.7*#
	T1	3.8±0.5	3.5±0.4*	3.2±0.6*#	3.1±0.5*#
	T2	3.6±0.5	3.3±0.6*	3.0±0.5*#	2.9±0.4*#
	T3	3.4±0.4	3.1±0.6*	2.8±0.5*#	2.6±0.6*#
	T4	3.1±0.7	2.8±0.4*	2.5±0.7*#	2.4±0.8*#
	T5	2.9±0.6	2.5±0.6*	2.1±0.7*#	2.0±0.6*#
Ramsay sedation score	T0	3.8±0.6	3.6±0.6	3.5±0.8	3.6±0.7
	T1	3.7±0.5	3.5±0.7	3.4±0.6	3.4±0.5
	T2	3.6±0.5	3.4±0.6	3.4±0.7	3.5±0.6
	T3	3.4±0.4	3.3±0.6	3.5±0.6	3.4±0.5
	T4	3.2±0.7	3.1±0.7	3.3±0.7	3.3±0.7
	T5	3.1±0.6	3.2±0.6	3.2±0.5	3.3±0.6

*P<0.05 *vs.* group C, #P<0.05 *vs.* group L.

Table 4 Pain-sensitive areas during mechanical irritation of incision of patients at different time points after surgery (cm^2, $\bar{\chi} \pm s$)

Time	Group C (n=30)	Group L (n=30)	Group M (n=30)	Group H (n=30)
T4	31.9±4.3	20.1±3.2*	15.67±2.5*#	12.5±2.1*#
T5	55.4±5.6	36.3±3.6*	26.3±3.1*#	25.7±3.5*#
T6	50.2±4.8	33.2±3.2*	23.6±2.6*#	23.3±2.9*#

*P<0.05 *vs.* group C, #P<0.05 *vs.* group L.

among the four groups at each time point. The NRS score was significantly lower at T0-T5 in groups L, M, and H than in group C (P<0.05), and the decline was significantly greater in groups M and H at T0-T5 than in group L (P<0.05). There was no significant difference in NRS score between groups M and H at any time point (P>0.05). No significant difference was found in Ramsay sedation score among the four groups (P>0.05) (**Table 3**). These results suggest that dexmedetomidine enhances pain tolerance without over-sedating patients.

Pain-sensitive Areas during Mechanical Irritation of the Incision

The pain-sensitive area during mechanical irritation of the incision was compared at 24, 48, and 72 h after surgery among the four groups. The pain-sensitive area at T4-T6 was significantly smaller in groups L, M, and H than in group C (P<0.05) and significantly smaller in groups M and H than in group L (P<0.05). However, the difference was not significant between groups M and H (P>0.05) (**Table 4**).

Postoperative Adverse Reactions

Comparison of postoperative adverse reactions among the four groups of patients showed that the total incidence rates of adverse reactions were 33.3%, 10%, 10%, and 6.67% in the four groups. Incidence rates of adverse reactions were significantly lower in the dexmedetomidine groups than in group C (P<0.05) and there were no significant differences among dexmedetomidine groups. No dizziness occurred postoperatively in groups M and H, and the incidence rate was significantly lower in these groups than in group C (P<0.05). Moreover, the incidence rates of hypotension and bradycardia were slightly higher in groups M and H than in groups C and L, but no significant differences were observed (**Table 5**).

Discussion

Postoperative pain is a frequent complication of surgery. Although postoperative pain usually resolves naturally, recent studies reported that postoperative pain may accelerate consumption of oxygen and aggravate myocardial ischemia, further affecting patient recovery[7]. Therefore, studies of methods of alleviating postoperative pain may aid in the recovery of surgical patients. Ultrasound-guided transversus abdominis plane (TAP) block has a precise analgesic effect and can help postoperative recovery. The most commonly used local anesthetic for TAP block, ropivacaine, can effectively alleviate postoperative pain but has a short duration of action and can cause adverse reactions, including nausea and vomiting[8]. Dexmedetomidine, an α2 receptor agonist with high se-

Table 5 Postoperative adverse reactions [n (%)]

Adverse reaction	Group C (n=30)	Group L (n=30)	Group M (n=30)	Group H (n=30)	χ^2	P
Dizziness	5 (13.33)	1 (3.33)	0 (0)*	0 (0)*	11.930	0.008
Nausea/vomiting	3 (10.00)	1 (3.33)	0 (0)	0 (0)	6.207	0.102
Respiratory depression	2 (6.67)	1 (3.33)	1 (3.33)	0 (0)	2.069	0.558
Hypotension	0 (0)	1 (3.33)	2 (6.67)	1 (3.33)	2.069	0.558
Bradycardia	0 (0)	0 (0)	0 (0)	1 (3.33)	3.025	0.388
Total	10 (33.3)	3 (10.00)*	3 (10.00)*	2 (6.67)*	10.719	0.013

*P<0.05 *vs.* group C.

lectivity and specificity, can inhibit sympathetic excitability, has obvious sedative and analgesic effects, and does not cause respiratory depression. A study confirmed that dexmedetomidine can serve as an ancillary drug to prolong the action time of local anesthetics and enhance their analgesic effect[9].

Although most studies of dexmedetomidine have confirmed its effectiveness for postoperative analgesia, the conclusion was ambiguous because the dose used varied. One study found that dexmedetomidine 1 μg/kg improved the effect of paravertebral analgesia and led to fewer complications in patients undergoing radical mastectomy[10]. Another study showed that addition of dexmedetomidine 0.5 μg/kg to ropivacaine enhanced the analgesic effect on patients undergoing hysterectomy through TAP block[11]. Therefore, on the basis of previous studies and clinical experience, the present study used low (0.5 μg/kg), moderate (1 μg/kg), and high (1.5 μg/kg) doses of dexmedetomidine for preemptive analgesia, which were separately diluted with normal saline containing 0.25% ropivacaine to 20 mL, to study the analgesic effect of each dose after surgery for colon cancer.

The stress caused by surgical trauma and postoperative pain may increase oxygen consumption and cardiac work and induce arrhythmia and other adverse reactions[12]. One study suggested that dexmedetomidine helped maintain stable cardiovascular function during intubation[13]. In the present study, postoperative MAP and HR were observed to evaluate the postoperative hemodynamic status of patients. MAP and HR were differentially reduced postoperatively in all dexmedetomidine groups. Additionally, MAP and HR were higher in the low-dose group than in the moderate-dose and high-dose groups, and there was no significant difference between the moderate-dose and high-dose groups. These results suggest that moderate-dose and high-dose dexmedetomidine can stabilize postoperative hemodynamics, an effect that may be related to catecholamine release when the stress response of the body is decreased.

In this study, the sedative and analgesic effects of different doses of dexmedetomidine were evaluated by NRS score, Ramsay sedation score, and postoperative area of pain sensitivity during mechanical irritation of the incision. Pain scores at different postoperative time points for all dexmedetomidine groups were lower than those for the control group, pain-sensitive areas were smaller at 24, 48, and 72 h postoperatively, and no significant difference was found in sedation scores, indicating that the use of dexmedetomidine based on ropivacaine yielded a stronger analgesic effect, without oversedation or other adverse reactions. Pain scores at each time point were lower in the dexmedetomidine groups, while pain-sensitive areas were smaller in the moderate-dose and high-dose groups than in the low-dose group. However, there was no significant difference between the moderate-dose and high-dose groups, indicating that the analgesic effect was better in the moderate-dose and high-dose groups than in the low-dose group.

Previous studies showed that dexmedetomidine combined with opioids decreased incidence rates of adverse reactions, including dizziness, nausea and vomiting, respiratory depression, and shivering, in postoperative analgesia[14]. However, when resisting sympathetic excitability, dexmedetomidine may induce adverse reactions such as hypotension and bradycardia[15]. Therefore, postoperative adverse reactions were compared among all the groups in this study. The incidence rates of adverse reactions were clearly lower in all dexmedetomidine groups than in the control group, and there was no significant difference among the dexmedetomidine groups. The incidence rates of hypotension and bradycardia were slightly higher in the moderate-dose and high-dose groups than in the control group and low-dose group, but the difference was not significant. Some researchers maintain that dexmedetomidine inhibits the emetic center via direct action on the α2 receptor located at the central site and that

its therapeutic effect on shivering may be associated with reduction of thresholds of systolic blood pressure and shivering. However, hypotension and bradycardia caused by dexmedetomidine can be recovered by stopping the analgesia pump immediately and administering an appropriate dose of vasoactive drugs. The above findings also suggest that, to reduce the incidence rates of adverse reactions, patients should be carefully monitored when receiving moderate-dose and high-dose dexmedetomidine.

This study has limitations. It was a single-center study with a small sample size, so the results may be biased. Further multicenter studies with larger sample sizes are ongoing in our group. Additionally, to determine drug safety, patients must undergo long-term follow-up.

In conclusion, the present results show that dexmedetomidine 1 μg/kg and 1.5 μg/kg had a good analgesic effect and that there was no significant difference in the incidence rates of adverse reactions between the two groups. Therefore, dexmedetomidine 1 μg/kg appears to be safe and effective as an ancillary drug with ropivacaine for TAP block in patients undergoing colon cancer surgery.

Conflict of Interest: None declared.

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