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Original Article

Postoperative Continuous Infusion of Dexmedetomidine Did Not Improve Recovery of Gastrointestinal Function in Laparoscopic Colorectal Surgery: A Randomized Clinical Trial

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Abstract:

Objectives: To explore the effects of postoperative infusion of dexmedetomidine on the recovery of gastrointestinal function among patients undergoing laparoscopic colorectal surgery.

Methods: 130 participants aged 18 to 75 years who were scheduled to receive laparoscopic colorectal surgery were enrolled. Dexmedetomidine infusion was conducted as a loading dose of 0.5 μg/kg over 15 minutes before skin scuffing followed by a dose of 0.05 μg/kg per hour at the end of surgery lasting 48h in dexmedetomidine group, while patients in the control group only received loading dose of 0.5 μg/kg. The primary outcome was time to first flatus. Secondary outcomes were postoperative gastrointestinal function measured by the I-FEED (intake, feeling nauseated, emesis, physical examination, and duration of symptoms) scoring system, time to first oral feeding, incidence of delirium, pain scores, sleep quality, postoperative anxiety states, postoperative nausea and vomiting and length of stay in hospital. Plasma samples were collected to test concentrations of C-reactive protein.

Results: Among 130 patients enrolled, 60 were randomized to receive intraoperative dexmedetomidine, and 60 were randomized to receive placebo. There was no significant difference in time to first flatus (median, 59 hours [IQR, 50.5-66.9 hours] vs 63.5 hours [49.3-81.6 hours], respectively; P= 0.15), time to first feces (median, 86 hours [IQR, 68-115 hours] vs 70.3 hours [IQR, 56.1-95.5 hours]; P =0.43), and time to first oral feeding (median, 77.5 hours [68.1-86.7] vs 79.3 [IQR, (67.6-100.4)] P =0 .29). Postoperative gastrointestinal function (measured by the I-FEED score) and delirium incidence were similar in the dexmedetomidine and control group. Patients in the dexmedetomidine group had longer total sleep time and higher sleep efficiency than those in the control group.

Conclusion: Postoperative continuous infusion of dexmedetomidine could improve the quality of sleep after laparoscopic colorectal surgery. However, postoperative dexmedetomidine infusing continuously after laparoscopic colorectal surgery did not improve recovery of gastrointestinal function.

Key words: dexmedetomidine; postoperative continuous infusion; laparoscopic colorectal surgery; recovery

1. Introduction

Postoperative gastrointestinal dysfunction (POGD), an acute pathophysiological change of the gastrointestinal, is characterized by gastrointestinal mucosal damage, barrier dysfunction and gastrointestinal motility disorders[1]. Clinically, POGD was manifested as nausea and vomiting, abdominal distension, intolerant to solid or semi-liquid diet within 24

hours, abdominal distension and imaging evidence of POI. The occurrence of postoperative gastrointestinal dysfunction has been kept up to 10%-30%, prolonging stay in hospital and increasing readmission and hospital costs[2].

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist, whose characteristic is sedative, analgesic and anti-sympathetic[3]. Dexmedetomidine, widely used in perioperative sedation and postoperative analgesia, decreased incidence of postoperative delirium[4] and NRS score[5]. However, the conclusion of dexmedetomidine on gastrointestinal function have been controversial[6]. Most studies have verified the effect of promoting squirming after colorectal surgery[7], caesarean section[8] and lumbar spinal fusion[9]. However, some researchers have reporter the effect of dexmedetomidine inhibiting gastric emptying[10,11]. Vasoconstriction of dexmedetomidine has been verified by another animal trial, which could influence the micro-perfusion of the colon, jejunum and stomach[12].

High-quality researches that exploring the continuous infusion of dexmedetomidine postoperatively on the gastrointestinal function in laparoscopic colorectal surgery have been less reported. We hypothesized that postoperative continuous infusing dexmedetomidine could accelerate the recovery of gastrointestinal function after laparoscopic colorectal surgery.

Materials Aand Methods

Study Design and Settings

Subjects of this study are patients undergoing laparoscopic colorectal surgery under general anesthesia at the affiliated Suzhou hospital of Nanjing Medical University, China, between January 9,2024 and December 29,2024. This study was approved by the Ethics Committee of the affiliated Suzhou Hospital of Nanjing Medical University (J-2023-070-K01) and was registered at the Chinese Clinical Trial Registry (ChiCRT2400079610).

Participants

Patients aged 18 to 75 who were scheduled to receive elective laparoscopic colorectal surgery with an expected surgical duration of 1 to 6 hours were screened to assess their study eligibility. The exclusion criteria were as follows: allergic to dexmedetomidine, refusal to participate, preoperative cognitive impairment (severe dementia, low cognitive function, mental disorder), inability to cooperate with assessments (language disorder, severe hearing or vision impairment, coma), presence of sick sinus syndrome, severe bradycardia (heart rate<50/min) or more than second degree atrioventricular block, permanent pacemaker implantation, severe heart failure, or ejection fraction<30% of patients Alzheimer's disease, and schizophrenia. A total of

Randomization and Assigned Groups

130 patients were randomized to group dexmedetomidine (Group D) and group normal saline (Group S) through the use of a random number table 65 patients in each group. One hour before the induction of anesthesia, the group assignments were concealed in sequentially numbered opaque envelopes. Two anthologists were in a blinded manner. The first investigator was responsible for enrollment and another one recorded the variables. Both were blinded to each subject's assigned group. Patients were blinded to group assignments throughout the study. In case of an unexpected emergency, the unmasking was activated and the patient was excluded from the final analysis in such case.

Anesthesia and Analgesia Procedures

All participants were administered 0.5 ug/kg dexmedetomidine before skin incision. General anesthesia was conducted with propofol 1.0–1.5 mg/kg, sufentanil 0.4 μg/kg, and cisatracurium 0.2 mg/kg. After 2 min of cisatracurium administration, tracheal intubation was facilitated. Tidal volume was adjusted (6–8) ml/kg and breath frequence was adjusted (10-16) breaths/min to maintain the end-tidal carbon dioxide (EtCO2) level at 35–45 mmHg. Depth of anesthesia maintained by propofol 2-10 mg/kg/h, remifentanil 5–20 μg/kg/h and sevoflurane 1-3% to keep the bispectral index (**BIS**) fluctuating between 40-60. 100mg flurbiprofen axetil and 0.2ug/kg sufentanil were infused before skin scuffing. A heating blanket was used intraoperatively to keep nasopharyngeal temperature higher than 36°C. Patients in group dexmedetomidine received PCA pump of 0.05ug/kg/h dexmedetomidine, 0.6 ug/kg/d sufentanil and 200mg flurbiprofen axetil 48h postoperatively, while patients in control group received 0.6 ug/kg/d sufentanil and 200mg

flurbiprofen axetil in PCA pump. Once the VAS (visual analog scale) (VAS: 0, no pain; 10, severe pain) score was more than 4, 100 mg flurbiprofen axetil was given for acute rescue analgesic. In the first day after the operation, patients were reminded to sit by bedside and early ambulate assisted by family members.

Outcome Measures

The primary outcome was the time to first flatus according to patient self-report. Secondary outcomes were as follows: postoperative gastrointestinal function using the I-FEED (intake, feeling nauseated, emesis, physical examination, and duration of symptoms) scoring system, time to first feces, time to first oral feeding, incidence of delirium (measured twice daily for 2 days using the CAM-3D), sleep quality including total sleep time and sleep efficiency (measured by ActiGraph WGT3X-BT), postoperative pain scores, postoperative anxiety states(measured by self-rating anxiety scale) ,postoperative nausea and vomiting and hospital length of stay.

The I-FEED scoring system consists of 5 components based on clinical presentation, each 0 to 2 points. Scores of 0-2 indicate normal gastrointestinal function, and scores of 3-5 represent gastrointestinal intolerance. Once the score gets up more than 6, it is indicating that POGD. Severity of pain was measured by a 10-point rating scale, with 0 indicating no pain and 10 indicating maximal pain. Subjective and objective sleep measurement was assessed by Pittsburgh Sleep Quality Index (PSQI) and wrist-placed ActiGraph WGT3X-BT respectively. Self-rating anxiety scale consists of 20 items and each item scores 2 points. Scores of SAS 50-59,60-69 and more than 70 represent mild anxiety, moderate anxiety and severe anxiety respectively.

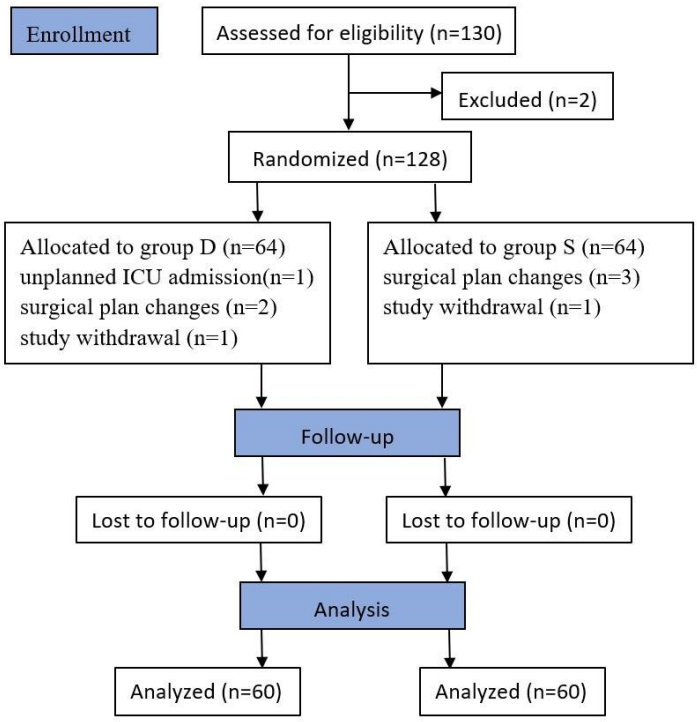
Adverse postoperative events, including bradycardia (<40 beats per minute), cardiac arrest, hypertension (blood pressure >20% higher than baseline or systolic blood pressure >160 mm Hg), hypotension (blood pressure >20% lower than baseline or systolic blood pressure <80 mm Hg) and severe allergic reaction were recorded.

Statistical Analysis

Graphpad Prism 9.0 software was used to perform statistical analyses. Normally distributed datasets were presented as mean ± standard error (SE), followed by unpaired Welch's t-test to compare the difference between groups. Non-normally distributed datasets are summarized as the median and interquartile range by Mann–Whitney U test. Categorical datasets are summarized as frequency (percentage) and were compared using Fisher's exact test. Differences were considered significant when the 2-tailed P values were <0.05.

Results

Of 130 patients screened for eligibility, 2 were excluded, and 128 proceeded to randomization, 64 patients randomized to receive dexmedetomidine and placebo (Figure 1). A total of 4 patients were excluded in dexmedetomidine group (because of 1 patient with unplanned ICU admission, 2 because of surgical plan changes and 1 because of study withdrawal after surgery) and 4 patients were excluded in the control group (3 because of surgical plan changes, 1 because of study withdrawal after surgery). The remaining 120 patients (60 in the dexmedetomidine group and 60 in the placebo group) were included in the per-protocol analysis.



In total, 83 patients (69.2%) were male and 37 (30.8%) were female. Baseline characteristics of the dexmedetomidine and control groups were similar(mean [SD] age, 62.9 [7.6] years vs 65.1 [7.0] years, respectively; men 40[66.7%] VS men 43[71.7%]; mean (SD) height 163[7.0] VS 162.1[7.4];mean [SD] weight 61.9 [7.9] VS 61.3 [9.0]); and there were no significant differences in American Society of Anesthesiologists status (eg, 22 patients [41.5%] vs 31 patients [58.5%] had class 2 status]), anatomical site of surgery (eg, 20 patients [33.3%] vs 25 patients [41.7%] had colon surgery) , surgical time (mean [SD] time, 145.4 [34] years vs 179.5 [43]min), anesthesia duration(mean [SD] time, 165.9 [33.6] years vs 158.7 [42.6]min) or albumin level (mean [SD] concentration, 41.1 [4.3] years vs 42.8 [4.9] g/L). There was no difference in the output of urine between dexmedetomidine group and control group (median, 300 mL [IQR, 200-337.5 mL] vs 250 mL [IQR, 200-300 mL]) (Table 1).

Table 1. Patient Characteristics and Intraoperative Data.

Characteristic	NO. (%)	
	Dexmedetomidine group	Control group
Age, mean (SD), y	62.9 (7.6)	65.1 (7.0)
Height, mean (SD), cm	163(7.0)	162.1(7.4)
Weight, mean (SD), kg	61.9 (7.9)	61.3 (9.0)
BMI, mean (SD)	23.3(2.4)	23.3(2.8)
Sex		
Female	20(33.3)	17(28.3)
Male	40(66.7)	43(71.7)
ASA		
I	38(63.3)	29(48.3)
II	22(36.7)	31(51.7)
Anatomical site of surgery		
left hemicolon	16(26.7)	15
right hemicolon	24	20
rectum	20	25

Time, mean (SD), min		
Anesthetic	165.9 (33.6)	158.7 (42.6)
Surgical	145.4 (34)	179.5 (43)
Sufentanil, mean (SD), μg	37.1(4.7)	36.7(5.4)
Albumin, mean (SD), g/L	41.1(4.3)	42.8(4.9)
Length of stay, mean (SD), d	10.3(2.3)	11.2(2.6)
Urine output, median (IQR), mL	300(200-337.5)	250(200-300)

Primary Outcome

There was no difference in median time of first flatus according to patient self-report between the dexmedetomidine group and the control group: 59 hours (50.5-66.9) vs 63.5 hours (49.25-81.6) (P =0 .15) (Table 2).

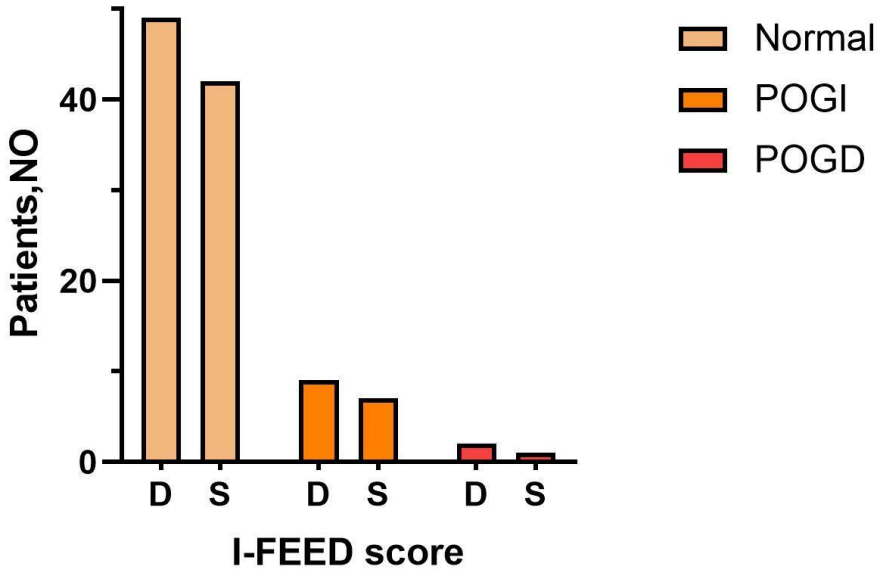
Table 2. Clinical Postoperative Outcomes

	Median (IQR)			
Outcome	Dexmedetomidine group	Control group	z Score or χ^2 value	P value
Primary outcome				
Time to first flatus, h	59(50.5-66.9)	63.5(49.3-81.6)	-	0.15
Secondary outcome				
Time to first feces, h	85(68-115)	70.3(56.1-95.5)	-	0.43
Time to first oral feeding, h	77.5(68.1-86.7)	79.3(67.6-100.4)	-	0.29
Delirium, NO. (%)				
Postoperative 24h	10(16.7)	8(13.3)	0.50	0.62
Postoperative 48h	3(5)	2(3.3)	0.46	0.65
Total sleep time, min				
Postoperative day 1	342(315-401)	288(241-409)	-	0.007
Postoperative day 2	408(358-452)	336(290-413)	-	0.0002
Sleep efficiency, %				
Postoperative day 1	91.3(89.3-94.3)	85.4(81.7-91.8)	-	<0.0001
Postoperative day 2	92.8(89.3-95.3)	90.1(85.3-94)	-	0.0031
VAS				
Postoperative 24h at rest	1(1-2)	2(1-2)	-	0.25
Postoperative 24h at movement	2(2-3)	2(2-3)	-	0.0397
Postoperative 48h at rest	1(1-2)	1(1-2)	-	0.68
Postoperative 48h at movement	2(1-2)	2(1-2)	-	0.50
CRP, mg/L	57.9(45.1-84.5)	82(67.7-97.8)	-	0.0087
SAS, N(%)	-	-	10.88	0.0032
No anxiety	48(80)	30(50)	-	-
Mild anxiety	10(6.1)	18(30)	-	-
Moderate anxiety	2(3.3)	10(16.7)	-	-
Severe anxiety	0(0)	2(3.3)	-	-
Nausea and vomiting, N (%)				
Postoperative 24h	4(6.67)	5(8.33)	0.32	0.75
Postoperative 48h	2(3.33)	1(1.67)	0.58	0.56
hypotension	3(5)	1(1.67)	1.107	0.309
bradycardia	0(0)	0(0)	-	>0.99

Secondary Outcomes

The I-FEED scores between the dexmedetomidine group and the control group were similar (Figure 2). There was no significant difference in time to first oral feeding (77.5 hours [68.1-86.7]vs

79.3[67.6-100.4], P =0 .29) and time to first feces (85hours [68-115] vs 70.3 hours [56.1-95.5], P=0.43). The occurrence of deliriums in dexmedetomidine group and control group was 10(16.7%) and 8(13.3%) at 24h postoperatively, which was 3(5%) and 2(3.3%) at 48h postoperatively.



Patients in the dexmedetomidine group had longer total sleep time and higher sleep efficiency at 24h (TST: 342min [315-401] vs 288min [241-409],P=0.007; EF: 91.3[89.3-94.3] vs 85.4[81.7-91.8], P<0.0001) and 48h (TST:408[358-452] vs 336[290-413],P=0.0002; EF: 92.8[89.3-95.3] vs 90.1[85.3-94],P=0.0031) postoperatively.

Although it is of no difference on VAS score (1[1-2] vs 2[1-2]) at rest at 24h postoperatively, but patients in the dexmedetomidine group had lower VAS scores (2[2-3] vs 2[2-3]) on movement. VAS scores were similar at 48h between the two groups.

Compared to group saline, patients in group dexmedetomidine had lower CRP levels (57.9(45.1-84.5) vs 82(67.7-97.8), p=0.0087). In the dexmedetomidine group, less patients behaved anxious after operation ([10 mild anxiety, 2 moderate anxiety]vs [18 mild anxiety, 10 moderate anxiety, 2 severe anxiety]). There was no difference in PONV, hypertension and bradycardia between the two groups. (Table 2)

Discussion

This randomized trial explored the effects of the postoperative continuous infusion of dexmedetomidine on the recovery of gastrointestinal function. Our findings demonstrated that continuous dexmedetomidine infusing postoperatively did not decrease the time to first flatus, time to first feces and time to first oral feeding. Also, the use of postoperative dexmedetomidine had no effect on the incidence of delirium in the first 2 postoperative days. However, postoperative VAS scores 24h at movement, sleep quality in the first 2 postoperative days, postoperative SAS scores, and CRP levels in the first 48h postoperatively were significantly lower in the dexmedetomidine group compared with the control group.

Our results are not consistent with those of previous studies. In the surgery of laparoscopic colorectal cancer resection, patients who received a loading dose (1 μg/kg) before anesthesia induction and continuous infusing (0.3 μg/kg/h) during surgery, had a shorter time to first flatus (FFL) and first feces[13]. Another clinical trial verified verified a single dose of 0.5 μg kg^{-1}dexmedetomidine administered for 15 min, followed by continuous pumping of 0.2 μg $kg^{-1}h^{-1}$ until 30 min before the end of surgery could not only shortened the time of first flatus, but also decrease the NRS scores 6h postoperatively and the incidence of PONV[14]. However, it was not observed a quicker gastric emptying in critical ill patients who received intraoperative dexmedetomidine[15]. Our trials did not also

observe the beneficial effect of dexmedetomidine on postoperative bowel function, although some patients had a shorter time recovery of first flatus. Dexmedetomidine had definitely decreased the stress response and improved the VAS score, which was assistant with other trials[16].

The following possible explanations may account for the inconsistent data. First, dexmedetomidine, α2-adrenergic receptors agonist, could reduce sympathetic tone and improve gastrointestinal transit in low-dose by acting on central α2-adrenergic receptors, while a high-dose dexmedetomidine may inhibit transit by acting on excitatory cholinergic pathways by inhibiting α2-adrenergic receptors[17,18]. Secondly, although patients got better sleep quality and lower CRP levels by an anti-sympathetic and anti-stress effect of dexmedetomidine, the recovery of intestinal function could be owed to complex pathophysiological mechanism, including pharmacological factors interact, ischemic reperfusion injury, inflammation, ambulation, early diet. The undesired influence of opioid on decreasing gastric motility and and inhibiting bowel propulsion could not be neglected[19]. Recently, new drugs, such as alvimopan and methylnaltrexone, has been verified the potential effect of blocking the peripheral effects of μ-opioid receptor in the gastrointestinal tract and maintaining opioid analgesia in the CNS[20]. Dexmedetomidine may have beneficial effects on the postoperative recovery of gastrointestinal function by decreasing the use of sufentanil and remifentanil medications intraoperatively and postoperatively[21], thus was not observed in our trails. Furthermore, patients in the dexmedetomidine group had a lower level of CRP than those who did not receive dexmedetomidine in the analgesia pump postoperatively, which was due to attenuating ischemic reperfusion injury and inhibit inflammatory response of dexmedetomidine[22]. In addition, the injury of the gastrointestinal was a unneglected factor.

Our study has three limitations. Firstly, it has not been elucidated that the precise effects of dexmedetomidine on gastrointestinal function, so multicenter controlled trials are needed to verify the effect of dexmedetomidine. Secondly, no further analysis was performed according to rectum, left colon or right colon. Thirdly, further studies are needed to investigate the relationship between age and recovery of intestinal function.

Conclusions

Postoperative dexmedetomidine did not improve recovery of gastrointestinal function in laparoscopic colorectal surgery, but could improve the sleep quality postoperatively.

Ethics approval and informed consent

This study was approved by the Ethics Committee of the affiliated Suzhou Hospital of Nanjing Medical University (J-2023-070-K01) and was registered at the Chinese Clinical Trial Registry (ChiCRT2400079610).

Author Contributions

Fei Wang wrote the original draft and analyzed the data. Xiaoqian Liu and Jiaqi Gu were responsible for materials preparation, data collection and project administration. Xian Chen interpreted the data and revised the manuscript. Yumin Zhu designed the study and revised the manuscript.

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Conflict of Interest

The authors report no conflicts of interest in this work.

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