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Dexmedetomidine improves gastrointestinal motility after laparoscopic resection of colorectal cancer

A randomized clinical trial

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Abstract

Background: To investigate the effects of intraoperative application of dexmedetomidine (Dex) on early gastrointestinal motility after laparoscopic resection of colorectal cancer.

Methods: In this prospective, randomized double-blind investigation, 60 patients who underwent laparoscopic resection of colorectal cancer were randomly allocated to receive Dex (DEX group, n = 30) or saline (CON group, n = 30). In the DEX group, Dex was loaded (1 μg/kg) before anesthesia induction and was infused (0.3 μg/kg/h) during surgery. Time to postoperative first flatus (FFL) and first feces (FFE), and time to regular diet were recorded. Serum diamine oxidase (DAO) activity and intestinal fatty acid-binding protein (I-FABP) were detected.

Results: Both the time to the FFL (44.41 ± 4.51 hours vs 61.03 ± 5.16 hours, $P = 0.02$) and the time to the FFE (60.67 ± 4.94 hours vs 82.50 ± 6.88 hours, $P = 0.014$) were significantly shorter in the DEX group than the CON group. Furthermore, the time to regular diet of the DEX group was shorter than that of the CON group (76.15 ± 4.11 hours vs 91.50 ± 5.70 hours, $P = 0.037$). Both DAO and I-FABP increased significantly from beginning of surgery to postoperative day 1 in the CON group (2.49 ± 0.41 ng/mL vs 4.48 ± 0.94 ng/mL for DAO, $P = 0.028$, 1.32 ± 0.09 ng/mL vs 2.17 ± 0.12 ng/mL for I-FABP, $P = 0.045$, respectively), whereas no significant change was observed in the DEX group. Furthermore, patients in the DEX group had stable hemodynamics and shorter hospital stay than those in the CON group.

Conclusion: Dex administration intraoperatively benefits recovery of gastrointestinal motility function after laparoscopic resection of colorectal cancer with stable hemodynamics during surgery though further studies are needed to explore the mechanisms of Dex on gastrointestinal motility.

Abbreviations: ANOVA = one-way analysis of variance, ASA = American Society of Anesthesiology, CO = cardiac output, DAO = serum diamine oxidase, DBP = diastolic blood pressure, Dex = dexmedetomidine, FFE = first feces, FFL = postoperative first flatus, HR = heart rate, I-FABP = intestinal-type FABP, I/R = ischemia reperfusion, I-FABP = intestinal fatty acid binding protein, L-FABP = liver-type FABP, MBP = mean blood pressure, OAA/S = observer's assessment of alertness/sedation scale, PCIA = patient-controlled intravenous analgesia, POD = postoperative day, PONV = postoperative nausea and vomiting, SBP = systolic blood pressure, SVV = stroke volume variation, VAS = visual analogue scale.

Keywords: dexmedetomidine, gastrointestinal motility, laparoscopy

1. Introduction

With the expansion of indications, laparoscopy has been widely used in colorectal cancer resection.[1,2] Compared with open approach, laparoscopy showed several advantages including limited postoperative pain and more rapid recovery with equivalent recurrence rates.[3] However, pneumoperitoneum during laparoscopic surgery would also impair intestinal function which was associated with high postoperative mortality rate.[4] Impaired intestinal function by pneumoperitoneum during the surgery might be attributed to oxidative stress, ischemia, and hypoxia of intestinal mucosa resulted from high intra-abdominal pressure.[5] Besides, blood pressure and heart rate variation during surgery would also worsen intestinal ischemia reperfusion (I/R) injury. In patients who underwent laparoscopy, impaired intestinal function are mainly manifested as delayed gastrointestinal transit and prohibited intestinal peristalsis with bacterial overgrowth in the digestive tract.[6]

As a highly selective α2 receptor agonist, dexmedetomidine (Dex) has been proved to possess sedative, analgesic, anxiolytic, and sympatholytic properties without respiratory depression.[7,8]

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CC and PH contributed equally to this work.

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Earlier reports demonstrated that patients benefit a lot from perioperative application of Dex, such as reduced stress response during incubation and operation, and hemodynamic stability.[9,10] However, the effects of Dex on gastrointestinal function remain controversial. Some researchers demonstrated that Dex could protect intestine from injury caused by intestinal I/R and endotoxemia,[11,12] whereas others found that Dex would prolong the gastric emptying and gastrointestinal transit in the rat.[13]

The effects of Dex on postoperative intestinal function in patients who underwent laparoscopy remained largely unknown though clinical study showed that epidural Dex administration would improve gastrointestinal motility after colonic resection.[14] Therefore, the present clinical trial was designed to investigate the effects of intraoperative application of Dex on postoperative gastrointestinal motility function after laparoscopic resection of colorectal cancer.

2. Methods

2.1. Study subjects

This randomized, double-blinded, prospective, controlled study was performed in accordance with the Declaration of Helsinki, approved by the Institutional Review Board of the third affiliated hospital of Sun Yat-Sen University (approval number:[2015] 2-95) and registered with the Chinese Clinical Trial Registry at www.chictr.org on June 7, 2015 (registration number: ChiCTR-IOR-15006518).

All patients undergoing elective laparoscopic colorectal resection in the hospital were considered for inclusion. The following were the inclusion criteria: aged >18 years; American Society of Anesthesiology (ASA) Physical Status I/II/III; stage T1 without distant metastasis; partial colorectal resection; and obtained written consent. Patients who met any of the following criteria were excluded: gastrointestinal motility disorder based on medical history; prior abdominal surgery; pre-existing heart disorders including sick sinus syndrome, atrioventricular block, or sinus bradycardia; long-term use of sedative drugs; neurologic or psychiatric illness; renal or hepatic insufficiency; and bone metastasis or distant metastasis. Patients who were transferred to open surgery during the operation and those who fail to follow up were excluded from the final analysis.

Using a computer-generated random number table, patients were randomly assigned to the Dex group (DEX group) or the control group (CON group). This step was conducted by Shaoli Zhou.

Patients received standardized care during the perioperative period, and were allowed to ingest small amounts of water orally 24 hours after surgery. Patients were not allowed to ingest any type of food until first flatus occurred.

2.2. Sample size

On the basis of retrospective data from our institution in the same surgical group (mean time of first flatus 69.5 hours, standard deviation (SD) 9.3 hours), a power analysis was performed using mean time of first flatus as the primary variable. Twenty-five patients were required in each group to detect a 9-hour difference in the exhaust time between the groups, at a α level of 0.05, with a power of 90%, expecting a SD of 9.3 hours. Considering 20% lost up, 30 patients were enrolled in each group.

With written consent, 62 ASA I/II/III patients were enrolled between June 2015 and December 2015.

2.3. Procedure

To eliminate any possible effects of surgical technique, all procedures were undertaken by the same surgical group. The standard approach for laparoscopic colorectal resection was performed as previously described.[15]

All surgical procedures were performed under general anesthesia. To maintain blinding, the anesthetist who prepared and performed the anesthesia was not involved in management or assessments until emergency occurred. The investigators (Chaojin Chen and Lifei Lai) and patients were blind to the intervention.

Anesthesia was induced with intravenous midazolam (0.1 mg/kg), fentanyl (2–4 μg/kg), propofol (1–2 mg/kg), cisatracurium (0.2 mg/kg), and maintained with end-tidal sevoflurane (2%–2.5%). In the DEX group, Dex was loaded (1 μg/kg) before anesthesia induction for 10 minutes and was infused (0.3 μg/kg/h) during surgery. The patients in the CON group were given the same dose of saline instead of Dex during the operation. A FloTrac/Vigileo system was used to administer the perioperative fluid infusion and keep hemodynamic stability. Ten minutes before the end of surgery, patients were given 2 mg morphine and then connected to a patient-controlled intravenous analgesia (PCIA) delivery system that was programmed to deliver sufentanil (0.04 μg/kg/h) with boluses (1 μg/time) on demand with a lockout interval of 15 minutes.

2.4. Demographics and perioperative variables

The demographics and baseline measurements including age, gender, height, weight, heart rate, blood pressure, evaluation of cardiopulmonary function, history of smoking, and drinking were recorded. The intraoperative and postoperative clinical variables included the pneumoperitoneum time and pressure, the duration of anesthesia and operation, the perioperative circulatory change, the volume of infusion (RBC, plasma, colloid, and crystalloid solution), and loss. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and heart rate (HR) values were recorded at the beginning (T1), immediately after administration of Dex (T2), immediately after anesthesia induction (T3), 1 minute after induction (T4), intubation (T5), 1 minute after intubation (T6), 5 minutes after intubation (T7), at the initial time of surgery (T8), 1 minute after the start of surgery (T9), 10 minutes after the start of surgery (T10), at the initial time of pneumoperitoneum (T11), 1 minute after the start of pneumoperitoneum (T12), 5 minutes after the start of pneumoperitoneum (T13), 15 minutes after the start of pneumoperitoneum (T14), 60 minutes after the start of pneumoperitoneum (T15), 90 minutes after the start of pneumoperitoneum (T16), 120 minutes after the start of pneumoperitoneum (T17), at the time when pneumoperitoneum ended (T18), 1 minute after pneumoperitoneum ended (T19), 5 minutes after pneumoperitoneum ended (T20), 15 minutes after pneumoperitoneum ended (T21), and at the time when the surgery ended (T22).

Cardiac output (CO) and stroke volume variation (SVV) were also recorded. Side effects potentially related to Dex, such as bradycardia, and hypotension were recorded. Hypotension was defined as the mean arterial pressure <30% from baseline for 60 seconds, and bradycardia was defined as HR <50 beats per minute. Follow-up evaluations were performed on postoperative day (POD) 1, 2, and 3.

2.5. The outcomes

The primary outcomes included the time to postoperative first flatus (FFL) and first feces (FFE), time to regular diet, and the duration of postoperative hospitalization stay.

The secondary outcomes included postoperative pain scores (visual analogue scale (VAS)), postoperative nausea and vomiting (PONV), the modified observer's assessment of alertness/sedation scale (OAA/S), sleep quality score, as well as serum diamine oxidase (DAO) activity, and intestinal fatty acid-binding protein (I-FABP).

The total dose of analgesic was recorded.

2.6. Statistical analysis

SPSS 19.0 software (SPSS Inc., Chicago, IL) was used to perform statistical analyses. The one-sample Kolmogorov–Smirnov test was used to test the normality of quantitative data and quantitative variables of normal distribution were presented as mean ± standard error (SE), followed by T test to compare the difference between groups. Qualitative data were presented as percentage/composition ratio, and Pearson χ^2-square test or Fisher's exact probabilities was used to compare the difference. For continuous variables, one-way analysis of variance (ANOVA) and repeated measures of ANOVA were used to evaluate changes between the groups. Repetitive measurement deviation analysis was performed to compare the level of DAO and I-FABP at different postoperative time points, as well as the perioperative circulatory variables. Differences were considered significant when the 2-tailed P values were <0.05.

3. Results

A total of 62 patients were randomly assigned to DEX or CON groups. After excluding 2 patients whose operation method was changed during surgery, 60 patients were included for final analyses (n = 30 per group, flow diagram). Demographics and surgical aspects did not differ significantly between the 2 groups (Table 1).

3.1. Primary and secondary outcomes

Both the time to the FFL (44.41 ± 4.51 hours vs 61.03 ± 5.16 hours, $P = 0.02$, Table 2) and the time to the FFE (60.67 ± 4.94 hours vs 82.50 ± 6.88 hours, $P = 0.014$, Table 2) were significantly shorter in the DEX group than in the CON group. Furthermore, the time to regular diet of the DEX group was shorter than that of the CON group (76.15 ± 4.11 hours vs 91.50 ± 5.70 hours, $P = 0.037$, Table 2).

The patients in the DEX group had better postoperative sleep quality (3.52 ± 0.308 vs 5.78 ± 0.415, $P < 0.001$) and shorter postoperative hospital stay (8.15 ± 0.37 days vs 9.70 ± 0.63 days, $P = 0.045$, Table 2) than those in the CON group.

However, the postoperative pain score and patient-controlled analgesia sufentanil requirements on POD1 and POD2 were not statistically different between the 2 groups. Concerning the MOAA/S score and PONV, the incidence did not differ between the 2 groups.

DAO increased significantly from beginning of surgery to POD1 in the CON group (2.49 ± 0.41 ng/mL vs 3.47 ± 0.50 ng/mL vs

Table 1

Preoperative and intraoperative baseline demographic and clinical variables.

Variables	Control group	DEX group	*P* value
Preoperative characteristics			
Age, y	60.17 ± 1.644	56.67 ± 2.705	0.263
Height, cm	160.07 ± 1.115	162.22 ± 1.682	0.291
Weight, kg	59.05 ± 1.398	59.57 ± 2.221	0.843
Male, n (%)	15 (50)	14 (46.7)	0.796
Smoke and drink, n (%)	6 (20)	7 (23.3)	0.754
ASA Grade, n (%)			0.059
1	1 (3.3)	3 (10)	
2	22 (73.3)	23 (76.7)	
3	7 (23.3)	4 (13.3)	
Heart function, n (%)			0.396
1	17 (56.7)	18 (60)	
2	12 (40)	11 (36.7)	
3	1 (3.3)	1 (3.3)	
MBP, mm Hg	96.8 ± 2.119	93 ± 2.563	0.255
SBP, mm Hg	132.47 ± 3.208	126.7 ± 3.72	0.243
HR, bpm	72.13 ± 2.138	73.3 ± 2.233	0.708
Intraoperative variables			
Anesthesia time, min	230.2 ± 12.14	221.19 ± 12.30	0.605
Operation time, min	186.7 ± 8.882	177.59 ± 11.02	0.519
Pneumoperitoneum time, min	96.13 ± 6.25	103.2 ± 9.13	0.522
Pneumoperitoneum pressure, Pa	13 (12.5–13.0)	13 (12.0–13.0)	0.098
Total infusion, mL	2015 ± 85.47	1964.81 ± 112.27	0.720
Crystal, mL	1200 (1100–1525)	1100 (1000–1500)	0.175
Colloidal, mL	500 (500–1000)	500 (500–1000)	0.718
Blood loss, mL	50 (50–100)	50 (40–100)	0.534
Urine output, mL	400 (300–762)	350 (250–550)	0.257
Blood transfusion, n (%)	2 (6.7)	3 (10)	1.000
PCIA, n (%)	28 (93.3)	27 (90)	1.000
Hypotension, n (%)	3 (10)	6 (20)	0.47
Hypertension, n (%)	3 (10)	2 (6.7)	1.000
Bradyarrhythmia, n (%)	9 (30)	10 (33.3)	0.781

ASA = American Society of Anesthesiology, DEX = dexmedetomidine, HR = heart rate, MBP = mean blood pressure, PCIA = patient-controlled intravenous analgesia, SBP = systolic blood pressure.

Table 2

Primary and secondary outcome variables.

Variables	Control group	DEX group	*P* value
FFL, h	61.03 ± 5.16	44.41 ± 4.51	0.020
FFE, h	82.50 ± 6.88	60.67 ± 4.94	0.014
Time to regular diet, h	91.50 ± 5.70	76.15 ± 4.11	0.037
Length of postoperative hospital stay, d	9.70 ± 0.63	8.15 ± 0.37	0.045
Time to the first analgesic, h	10.44 ± 1.78	13.46 ± 1.81	0.102
Total dose of analgesic, μg	121.57 ± 8.71	103.43 ± 4.59	0.335
Sleep quality score*	5.78 ± 0.415	3.52 ± 0.308	<0.001
MOAA/S			1.000
Level 4	4 (13.3)	3 (10)	
Level 5	26 (86.7)	27 (90)	
PONV			0.991
Level 1	24 (80)	24 (80)	
Level 2	4 (13.4)	3 (10)	
Level 3	1 (3.3)	2 (6.7)	
Level 4	1 (3.3)	1 (3.3)	
VAS in postoperative 24 h	3.22 ± 0.335	2.81 ± 0.302	0.224

Values are presented as mean ± SE or number (%).

For PONV, the severity of nausea and vomiting was graded according to verbal rating scale scores. The VAS score was defined as the length in millimeters from 0 (no pain) to 10 (the worst pain imaginable.

DEX = dexmedetomidine, FFL = postoperative time to first flatus; FFE = postoperative time to first feces, MOAA/S = observer's assessment of alertness/sedation scale, MOAA/S Level 4 = lethargic response to name spoken in normal ton), MOAA/S Level 5 = responds readily to name spoken in normal tone, awake/alert), PONV = postoperative nausea and vomiting, PONV Level 1 = no,0, PONV Level 2 = mild, 1–3, PONV Level 3 = moderate, 4–6, PONV Level 4 = severe, 7–10, VAS = visual analogue scale.

* Sleep quality score, was defined as the length in millimeters from 0 (no awakening, deep sleep) to 10 (frequent awakening during the whole night, awake almost all the night, no sleep time).

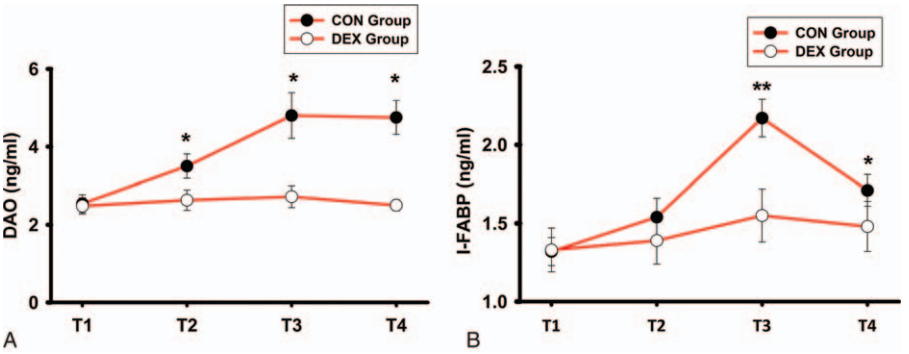

Figure 1. The serum DAO activity and I-FABP of different time points ($^{*}P<0.05$, $^{**}P<0.001$).

4.48±0.94 ng/mL, $P=0.028$, Fig. 1A), whereas no significant increase was observed in the DEX group (2.30±0.22 ng/mL vs 2.27±0.25 ng/mL vs 2.71±0.39 ng/mL, $P=0.25$, Fig. 1A). Of note, the DEX group had lower DAO level after the operation at each observed time-point, though the change was only statistically significant at the end of the operation (3.47±0.50 ng/mL vs 2.27±0.25 ng/mL, $P=0.032$, Fig. 1A).

With regard to the serum I-FABP, the expression also showed a significant increase from initial surgery to POD1 in the CON group (2.17±0.12 ng/mL vs 1.32±0.09 ng/mL, $P=0.045$, Fig. 1B), but not in the DEX group. The differences between the 2 groups on POD1 and POD3 were statistically significant (2.17±0.12 ng/mL vs 1.41±0.11 ng/mL, $P<0.001$, 1.71±0.96 ng/mL vs 1.35±0.97 ng/mL, $P=0.012$, respectively, Fig. 1B).

3.2. Perioperative hemodynamic changes

CO and SVV were used to guide the stability of perioperative hemodynamics, and they did not differ significantly between the 2 groups (Fig. 2A and B).

Compared with the CON group, perioperative MAP values in the DEX group varied less violently (Fig. 2C), especially at the time of induction (T5–T3, 2.63±3.15 mm Hg vs 17.4±2.80 mm Hg, $P=0.001$), intubation (T6–T5, 2.85±2.93 mm Hg vs 14.07±3.41 mm Hg, $P=0.006$), initial surgery (T10–T8, 8.78±3.06 mm Hg vs 25.7±2.62 mm Hg, $P<0.001$), and so was the HR at the time of induction (T3–T5, 2.93±1.25 bpm vs 9.80±1.60 bpm, $P=0.001$), the initial time of surgery (T10–T8, 2.59±1.24 bpm vs 8.67±1.49 bpm, $P=0.003$), and the initial time of pneumoperitoneum (T13–T11, 8.84±1.61 bpm vs 4.74±1.12 bpm, $P=0.046$, Fig. 2D).

Although the HR and MAP values were lower in the DEX group than those in the CON group immediately after administration of Dex, the differences were not statistically significant (T2, 67.52±2.563 bpm vs 72.80±2.062 bpm, $P=0.111$, 90.78±2.696 mm Hg vs 95.79±2.406 mm Hg, $P=0.17$, respectively, Fig. 2C and D). There were no statistical differences with regard to the proportion of patients with bradycardia and hypotension between DEX group and CON group (Table 1).

4. Discussion

The present study demonstrated that Dex administration in patients undergoing laparoscopic resection of colorectal cancer benefited early postoperative gastrointestinal motility function as reflected by shorter time to FFL and FFE compared with saline.

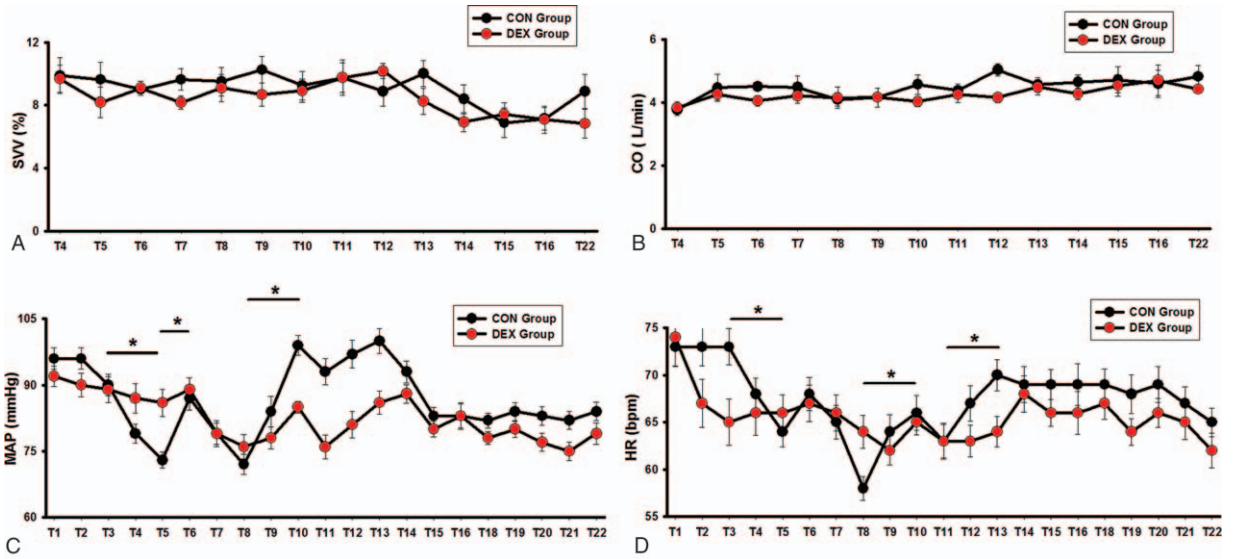

Figure 2. Hemodynamics of different time points ($^{*}P<0.05$).

These results might be attributed to that the usage of Dex was associated with less gastrointestinal injury reflected as lower serum expressions of DAO and IFABP. Furthermore, the Dex produced stable hemodynamic effects, improved the sleep quality, and shortened hospital stay.

Laparoscopic resection of colorectal cancer leads to the anatomical abnormality and deficient intestinal function because of removing the intestinal tissue in surgery. In addition, ischemia and hypoxia of intestinal mucosa resulting from the establishment of pneumoperitoneum during the surgery would impair the function of intestinal mucosa barrier, probably resulting in intestinal bacterial translocation and causing multiple organ failure syndrome.[16,17] Early postoperative defecate, feeding of patients are of great significance to accelerate the recovery of their clinical gastrointestinal function and shorten the length of hospital stay. The present study found that perioperative Dex administration could improve postoperative gastrointestinal motility function and shorten hospital stay which is consistent with previous study.[18]

Dex is a highly selective α2 receptor agonist that can be used as sedation in intensive care units. Dex offers hemodynamic stability, pain alleviation, and improved stress response without respiratory depression.[19,20] Thus, Dex has been widely used as anesthetic adjutant during surgery. Of note, previous studies demonstrated that epidural Dex administration could improve the postoperative gastrointestinal motility function and shorten the time to FFL of patients who underwent colonic resection.[14] It was verified by animal study that Dex could augment the contraction of rat ileum.[21] In line with the previous studies, the results of the present study demonstrate that intraoperative Dex administration could shorten time to FFL and FFE compared with control. However, the effect of Dex on gastrointestinal function was controversial. Dex would inhibit peristalsis in in vitro and it could also inhibit gastric empty and gastrointestinal transit in rats.[13,22] In healthy volunteer, the inhibitory effect of Dex on gastrointestinal function was consistent with that in animals.[23]

The contradictory results might be explained by differences of the research objects. On physiological conditions, Dex might inhibit the motility of gastrointestinal by an action on enteric neurons.[22,23] Whereas on pathological conditions, Dex would rather benefit the gastrointestinal function for it attenuates the intestinal injury induced by I/R.[11,12] Either in vitro or in vivo study, Dex offered protective effect against the gastrointestinal I/R injury.[12,24] Besides, it was demonstrated that Dex could reduce the surgical stress and pain stimulation which yield global hemodynamics stability and prevent the violent alteration of intestinal microcirculation.[25] Of note, the hemodynamic stability, alleviated pain, and reduced stress responses offered by Dex might help patients quickly recover early postoperative walking which contributes to recovery of postoperative gastrointestinal motility.[26] Furthermore, as a α2 receptor adrenoreceptor agonist, Dex is able to accelerate intestinal wound healing by increasing intestinal epithelial cell proliferation.[27]

In the present study, Dex could alleviate intestinal injury which mainly reflected as the decreased DAO and I-FABP expression. DAO is a kind of endocellular enzyme, existing in almost all tissues and organs. Cytoplasm of upper chorion cells of intestinal mucosa possessed highly reactive DAO.[28,29] Activity of the DAO in the peripheral blood is stable. After the epithelial cells of intestinal mucosa were damaged, DAO released by cells would enter into the intercellular space of intestinal cells and blood, leading to the increased DAO expression in blood. Therefore, the DAO was a plasma marker reflecting the integrity of the epithelial cells of intestinal mucosa. Studies have demonstrated that activity of DAO in plasma is a marker measuring intestinal I/R injury.[30–32] Like DAO, FABP is a kind of small-molecule cytochrome protein with 2 types, liver-type FABP (L-FABP) and intestinal-type FABP (I- FABP) which was secreted by small intestinal epithelial cells. I- FABP was proven to be a sensitive marker of ischemia in intestine disorders.[33] Researches have proved that I-FABP was quickly released into the blood when the intestinal epithelial cells were damaged and suffered from I/R injury.[33,34] Therefore, DAO and I- FABP levels could reflect the intestinal I/R injury. The present study found that in comparison with saline, Dex administration perioperatively decreased the postoperative DAO and I-FABP expression significantly, indicating that Dex might benefit the intestinal mucosa barrier function. However, further studies are needed to explore the mechanisms of Dex in gastrointestinal function.

This study had some limitations. Firstly, the study was a single-center clinical trial. The results need to be confirmed by large samples of multicenter study. Secondly, the parameters used to determine the gastrointestinal motility are clinical assessment. The golden standard, scintigraphic recording should be used in the future to confirm the results. Thirdly, the present study only tested the dose recommended by instruction. Therefore, dose-depended effects of Dex on gastrointestinal motility function and the underlying mechanisms should be explored in the near future.

In summary, our results provide a new insight for the clinical use of Dex, showing that Dex administration during laparoscopic resection of colorectal cancer is beneficial for recovery of gastrointestinal motility function after surgery. These effects might be attributed to Dex-induced reduction of gastrointestinal injury and stability of hemodynamics.

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