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Intraoperative Dexmedetomidine Promotes Postoperative Analgesia and Recovery in Patients after Abdominal Colectomy

A CONSORT-Prospective, Randomized, Controlled Clinical Trial

Dong-Jian Ge, MD, Bin Qi, MD, Gang Tang, MD, and Jin-Yu Li, MD

Abstract: Surgery-induced acute postoperative pain and stress response may lead to prolonged convalescence. The present study was designed to investigate the effects of intraoperative dexmedetomidine on postoperative analgesia and recovery after abdominal colectomy surgeries.

Sixty-seven patients scheduled for abdominal colectomy under general anesthesia were divided into two groups, which were maintained using propofol/remifentanil/dexmedetomidine (PRD) or propofol/remifentanil/saline (PRS).

During surgery, patients in the PRD group had a lower bispectral index value, which indicated a deeper anesthetic state and a higher sedation score right after extubation, than patients in the PRS group. During the first 24 hours after surgery, PRD patients consumed less morphine in patient-controlled analgesia, and had a lower score in visual analog scale, than their controls from the PRS group. The global 40-item quality of recovery questionnaire and 9-question fatigue severity score both showed a higher recovery score from day 3 after surgery in the PRD group.

Intraoperative administration of dexmedetomidine seems to promote the analgesic property of morphine-based patient-controlled analgesia, and speed recovery from surgery in patients after abdominal colectomy.

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Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, BMI = body mass index, DEX = dexmedetomidine, HR = heart rate, MBP = mean blood pressure, PACU = postanesthesia care unit, PCA = patient-controlled analgesia, VAS = visual analog scale.

INTRODUCTION

Postoperative pain and fatigue are 2 of the key causes of prolonged convalescence after abdominal surgery.[1–3] Opioid-based patient-controlled analgesia (PCA) is well established and widely used in postoperative analgesia.[4] Currently, the main challenge in PCA is to reduce opioid consumption and related side effects like nausea, vomiting, itch, and so on. Since surgery-induced fatigue is less understood than postsurgical pain, more investigations are necessary to dissect the underlying mechanisms to develop novel drugs or to find effective therapeutics from the currently available drugs.

Anesthesia management may modulate surgery-induced pain, stress responses, and fatigue.[1,5] Recent clinical studies reported that the highly selective alpha-2 adrenergic receptor (α2-AR) agonist dexmedetomidine (DEX) promotes the analgesic effect, and prolongs the analgesic time of local anesthetics even to 24 hours after dental and osteopathic surgeries.[3] Most of these studies investigated the synergic action of intraoperative DEX with local anesthetics on surgery-induced acute pain during or after surgeries.[3] However, more evidence is needed to support its potential analgesia-promoting effect in PCA after general-anesthetized surgeries. Few studies have indicated that DEX has an active influence on recovery,[6,7] even at a single dose.[8] The evidence above suggested that patients with surgery-induced pain and fatigue may benefit from perioperative DEX administration. However, side effects, including hypotension and bradycardia, have limited its clinical application under conditions without professional monitoring. Therefore, in the present study, we hypothesized that intraoperative DEX may improve the analgesic effect of morphine-based PCA, and promote the recovery from surgery in patients after abdominal colectomy.

METHODS

Participants

This study was approved by the Institutional Medical Ethics Committee of Nanjing Medical University, and was in accordance with the approved guidelines. Informed consent was obtained from all the participants. The sample size of the study was calculated according to the previous studies,[9,10] and was based on a pilot study. Twenty-one patients in each group were required to detected a difference of "1 over 10" in the visual analog scale (VAS) score, with a power of 0.8 and type I error of 0.05.[9] Sixty-seven patients were assigned to the propofol/remifentanil/saline (PRS) (n = 32, 3 patients from the PRS group were lost because of noncooperation) and the propofol/remifentanil/dexmedetomidine (PRD) (n = 35, 1 patient from the PRD group was lost because of noncooperation) groups using

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From the Department of Anesthesiology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an, Jiangsu, P.R. China (D-JG, BQ, GT, J-YL).
Correspondence: Jin-Yu Li, Department of Anesthesiology, Huai'an First People's Hospital, Nanjing Medical University, 6 Beijing Road West, Huai'an, Jiangsu, 223300, P. R. China (e-mail: jin-yuli@outlook.com).
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computer-generated randomized table (Fig. 1). The PRS and PRD patients received propofol, remifentanil, and saline or DEX for general anesthesia maintenance, respectively (Fig. 2). The maintenance syringe pumps were prepared by a different anesthesiologist to make this study a randomized, double-blinded investigation. Postoperative evaluations were performed by another different anesthesiologist. Patients matching the following criteria were included in this study: between 35 and 75 years old; American Society of Anesthesiologists (ASA) grade I or II; weight 50 to 80 kg; and height 145 to 185 cm. Patients were excluded if they had ischemic heart diseases; opioid addiction, long-term alcohol abuse, long-term smoking history, sedative–hypnotic drug(s); obesity (BMI > 30); postoperative nausea and vomiting history; or neuropsychiatric diseases and related treatment history. Patients were instructed to the use of the VAS (0, no pain; and 10, worst pain possible) and the intravenous (i.v.) PCA pump (50 mg morphine and 8 mg ondansetron in 100 mL saline, every pump press leads to a 2 mL of infusion). There were no important changes in the methods after the trial commencement. Full details of the trial protocol can be found in the supplementary appendix.

Anesthesia

On arrival, electrocardiography, blood pressure, oxygen saturation, and the bispectral index (BIS) were monitored every 5 minutes. A BIS value of <60 was used to adjust the titration of anesthetics on the basis of amnesia. For induction, patients from both the groups received midazolam (0.05 mg/kg), remifentanil (2–5 μg/kg), propofol (1.5–2 mg/kg), and cisatracurium (0.2 mg/kg). Immediately after intubation, patients were ventilated with an oxygen and air mixture ($FiO_2 = 0.4$), with a $PetCO_2$ at 30 to 35 mm Hg, and intravenous infusion was switched to maintenance syringe pump at a rate of 50 to 80 μg/kg/minute for propofol, 0.15 to 0.2 μg/kg/minute for remifentanil, and 0.4 μg/kg/hour for DEX. As a control, patients from the PRS group received the same volume of saline which allows all the patients receive all other drugs at the same velocity; thus, patients from these 2 groups received the same treatments except for DEX. Cisatracurium (0.05 mg/kg) was intermittently used for muscle relaxation. Patients were woken up and extubated followed by sedation evaluation using the Ramsay sedation scale.

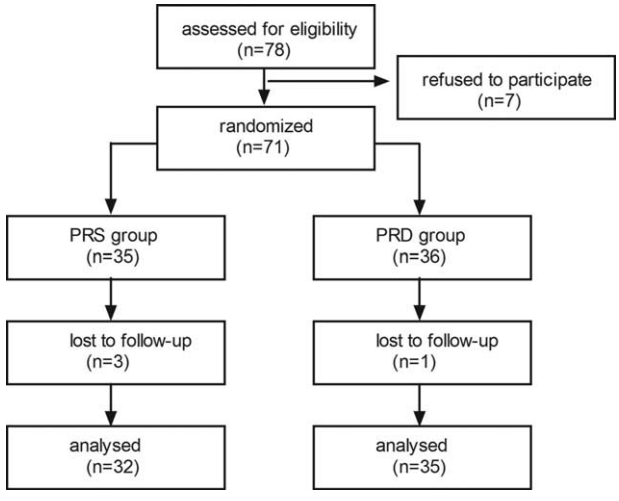

FIGURE 1. Consort flow diagram.

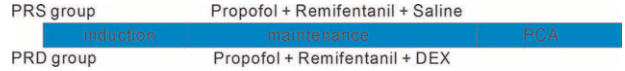

FIGURE 2. Schematic of anesthesia and postoperation analgesia. Patients received same treatments for induction and PCA (see "Methods" section). Patients in both the groups received anesthesia maintenance with propofol, remifentanil, and saline (PRS group), or dexmedetomidine (PRD group). PCA = patient-controlled analgesia, PRD = propofol/remifentanil/dexmedetomidine, PRS = propofol/remifentanil/saline.

Data Collection

Patient demographic information was collected on admission. Hemodynamic indexes and BIS were recorded during surgery every 5 minutes, and data from selected time points were used for analysis. Postoperative pain at rest and on movement were evaluated with VAS, and the global 40-item quality of recovery questionnaire[11,12] and 9-question fatigue severity score[1] were used to evaluate the recovery and fatigue level at different time points after surgery (all time points see figure legends). Participants who received rescue morphine in the postanesthesia care unit (PACU) had the rescue morphine included in the total consumption of postoperative PCA morphine. PCA pump pressing number and adverse effects after surgery were noted.

Statistics

All data in the present study were analyzed with GraphPad Prism 5.0 software. Parameters like age, weight, operation time, anesthesia time, and PACU stay time, pump-press number and morphine consumption were compared between the 2 groups by unpaired Student *t* test. Heart rate (HR), mean blood pressure (MBP), VAS, and BIS at different time points were compared between the two groups with 2-way analysis of variance (ANOVA), followed by Bonferroni post-test. ASA grade and postoperative adverse effects were analyzed with Fisher test. All data with $P < 0.05$ were considered significant.

RESULTS

Demographic Data and Surgery/Anesthesia-related Information

Patients from both the groups had comparable demographic and surgery/anesthesia-related variables, including age, weight, BMI, ASA class, operation time, anesthesia time, and PACU stay time (Table 1).

The 2 groups were also comparable with respect to their baseline MBP and HR, followed by a decrease induced by induction and sharp increase evoked by intubation. Subsequently, the MBP and HR were maintained at a lower level than baseline to extubation. Additionally, 24 hours after surgery, the MBP and HR returned to the baseline level (Fig. 3A and B).

Anesthesia Depth Evaluation

Anesthesia depth was monitored with BIS. Significantly, patients from the PRD group had a lower BIS value when compared to the PRS group (Fig. 3C, $^{*}P < 0.05$, $^{**}P < 0.01$,

TABLE 1. Basic Demographic Data and Surgery/Anesthesia-related Information

	PRS Group (n = 32)	PRD Group (n = 35)	*P* Value
Age (y)	53.17 ± 1.29	52.77 ± 1.88	0.8637
Sex (F/M)	15/17	18/17	0.8083
Weight (kg)	70.52 ± 1.55	68.44 ± 0.96	0.2494
BMI (kg/m^2)	23.93 ± 0.87	24.08. ± 0.75	0.8960
ASA I/II	21/11	25/10	0.6034
Operation time (min)	127.50 ± 7.68	133.77 ± 9.54	0.6145
Anesthesia time (min)	162.10 ± 6.77	173.13 ± 8.37	0.3148
PACU stay time (min)	42.13 ± 2.30	40.15 ± 3.15	0.6189

Data shown as mean ± standard error of mean (SEM). ASA = American Society of Anesthesiologists, BMI = American Society of Anesthesiologists, PACU = postanesthesia care unit.

$^{***}P < 0.0001$), which indicated a deeper anesthesia state. The PRD group also had a higher immediate Ramsay sedation score after extubation when compared to their controls in the PRS group (Fig. 3D, $^{*}P < 0.05$).

Postoperative PCA Evaluation

After surgery, the patients received a morphine-based PCA pump. Postoperation pain was assessed with VAS, and the pain-induced pump press number and morphine consumption were noted. During the first 24 hours, patients from the PRD group had a lower VAS score both at resting (Fig. 4A, at time point of 8, 12, and 24 h after surgery, $^{*}P < 0.05$) and movement states (Fig. 4B, at time point of 8 and 24 h after surgery, $^{*}P < 0.05$) compared with the PRS group. Patients from the PRS group also had a higher pump press number and more morphine consumption than those in the PRD group (Fig. 4C and D, $^{*}P < 0.05$).

Postoperative Recovery and Fatigue Evaluation

The global 40-item quality of recovery questionnaire scores showed lower values for the both groups on day 1 after surgery as compared with baseline. On day 3 after surgery, patients in the PRD group had a significantly higher score as compared with the PRS group (Fig. 5A, $^{*}P < 0.05$), but maintained lower values than their baseline numbers. Patients in the PRD group showed a lower fatigue severity score than those from the PRS group on day 3 and day 7 (Fig. 5B, $^{*}P < 0.05$) after surgery; however, the score still remained higher than their baselines.

Postoperative Adverse Effects

No difference was observed in the postoperative adverse effects between the 2 groups during the first 24 hours. PRD patients had a trend of suffering from less adverse effects like nausea and vomiting than those from the PRS group (Table 2).

DISCUSSION

In the present study, we found that intraoperative administration of DEX promoted the analgesic property of morphine-based PCA and speed of recovery from surgery of patients after abdominal colectomy.

Opioids, especially morphine-based, patient-controlled analgesia, were widely used for pain control after abdominal surgeries.[13–15] To combat the side effects such as nausea, vomiting, itch, and so on, there has been a pursuit for novel drugs, or more information regarding combining currently available drugs, to reduce the morphine consumption. Alpha-2 receptor (α2R) agonists, like clonidine (α2R:α1R ratio is 200:1), has been used as pain treatment for decades.[16,17] A

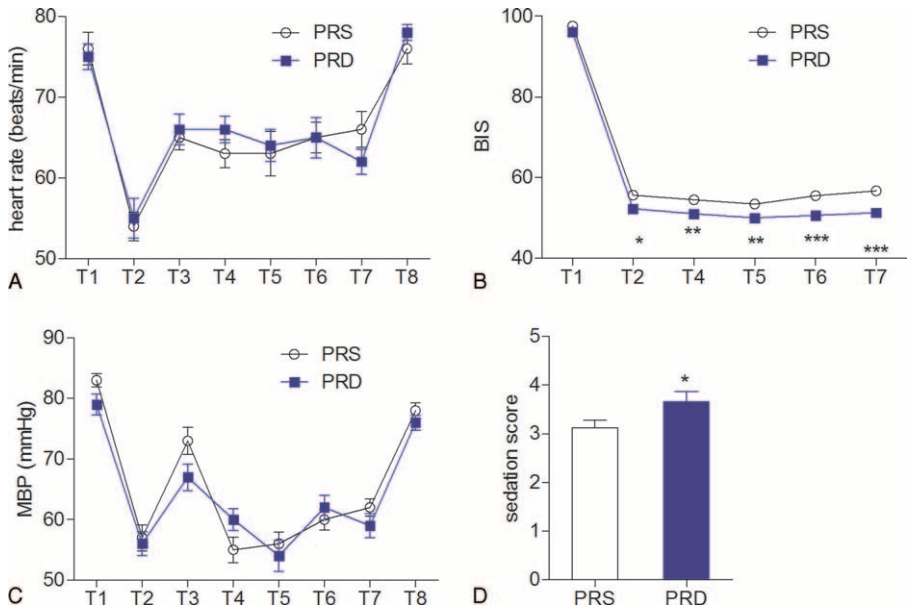

FIGURE 3. Heart rates, MBP, BIS value, and Ramsay sedation score. A, Heart rates at different time points. B, MBP at different time points. C, BIS values at different time points ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.0001$). D, Ramsay sedation scale score right after extubation ($^{*}P < 0.01$). For A–C: T1: baseline, T2: induction, T3: intubation, T4–T7: 10, 30, 60, and 90 minutes after intubation, T8: 24 hours after surgery. BIS = bispectral index, MBP = mean blood pressure.

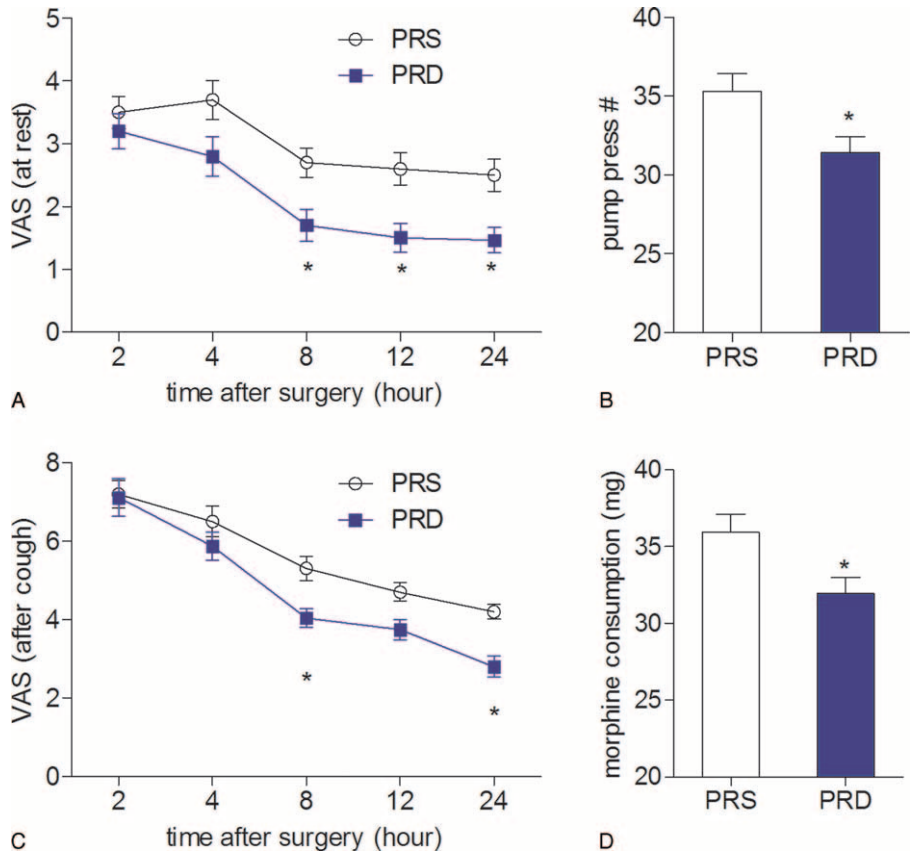

FIGURE 4. The 24-hour PCA evaluation and morphine consumption. A, VAS pain score at rest at different time points in the 2 groups ($^{*}P < 0.05$). B, VAS pain score on movement at different time points in the 2 groups ($^{*}P < 0.05$). C and D, The pump-press numbers and morphine consumption during the first 24 hours after surgery are shown ($^{*}P < 0.05$).

recent study reported that α1 receptor activation encountered α2R-related analgesia, which suggested that an agonist with a higher α2R selectivity would show a more potent analgesic effect and would be more suitable for pain treatment.[18] DEX is a α2R agonist developed in the 1990s, and was first used for a short-term sedative in the intensive care unit.[5] Clinical studies have confirmed its potential as an adjuvant for pain treatment, mostly during the acute perioperative settings. This suggests that DEX might act as a new drug in surgery-induced acute pain control.[13] DEX has been implicated in general anesthesia maintenance at different infusion rates, from 0.2 to 2.0 μg/kg/hour.[5,10,19] In the present study, we combined DEX at a relatively slow infusion rate of 0.4 μg/kg/hour, which has been used for general anesthesia maintenance in Asian patient population,[6] with propofol and remifentanil to maintain the general anesthesia in patients undergoing abdominal colectomy surgery, and found that intraoperative DEX is helpful to relieve both the resting and moving postoperative acute pain. However, patients from the PRD group who received intraoperative DEX had lowered pump-press numbers and consumed less morphine than those from the PRS group. The analgesic and opioid-sparing effect of DEX have been well described in previous studies, both in adult and children.[7,20,21] Similar to the present data, these studies reported significantly lower VAS, morphine consumption, and morphine demands. Together with these findings, the present study indicated that intraoperative

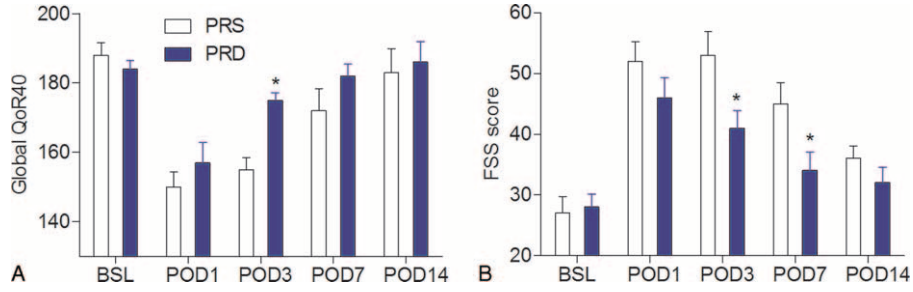

FIGURE 5. Recovery quality evaluation in the 2 groups. A, Global 40-item quality of recovery questionnaire score ($^{*}P < 0.05$). B, Nine-question fatigue severity scores ($^{*}P < 0.05$). BSL = baseline before surgery, POD = postoperation day.

TABLE 2. Postoperative Side Effects From Patients in the Two Groups

	PRS group	PRD group	*P* Values
Nausea	13/32 (40.63%)	8/35 (22.86%)	0.1869
Vomiting	9/32 (28.13%)	4/35 (14.23%)	0.1230
Itch	2/32 (6.25%)	3/35 (8.57%)	1.0000
Respiratory depression	0/32 (0.00%)	0/35 (0.00%)	–
Dizziness	3/32 (9.38%)	3/35 (8.57%)	1.0000
Bradycardia	2/32 (6.25%)	4/35 (11.43%)	0.6747

Data shows the positive number and percentage of patients. PRD = propofol/remifentanil/dexmedetomidine, PRS = propofol/remifentanil/saline.

administration of DEX is a potential way to be used to promote morphine-based PCA after abdominal surgery.

The most common treatment-related adverse events associated with DEX were hypotension (~30%), hypertension (~12%), bradycardia (9%), and dry mouth, according to a preliminary result from a phase III study.[22] Continuous infusion, single injection, and loading dose injection, followed by continuous infusion, are 3 accepted manners to use DEX in general anesthesia patients.[6] Overdose during a short period, such as single-loading dose injection, is one of the key causes of adverse events[1]; thus, loading dose injection and loading dose followed by continuous injection normally showed more adverse effects than only continuous infusions, because of a brief overdose. During operations, DEX induces hemodynamic changes like hypertension, hypotension, and bradycardia, especially after a bolus dose. Thus, in this present study, we administrated a continuous infusion without a loading dose. Using this continuous infusion, we did not see significant difference in HR and MBP between the two groups, which indicated a stable anesthesia statement. BIS value has been widely accepted and well used as an index of sedation measurement in different kinds of sedative and anesthesia techniques,[23,24] and it was significantly correlated with commonly used subjective clinical scales,[23] for example, the Ramsay sedation scale we used in this study. Interestingly, we observed significant lower BIS values in the PRD group during anesthesia, and higher sedation score right after extubation, which was consistent with the previous studies and indicates that intraoperative DEX provided a more stable anesthesia, without changing the hemodynamic characters.[25] In the present study, BIS values were kept between 40 and 60, which indicated an appropriate sedation level during operations.

So far, the mechanisms underlying the long-lasting analgesic effects of DEX are still unknown. DEX was first introduced into clinical use as a short sedative since it is a fast-metabolized chemical with a short plasmatic half-time of 2 to 2.5 hours.[13] There are several possibilities responsible for the long-lasting analgesic effect: unlike the sedation effect, DEX is using a different α2AR-dependent downstream mechanism to act as an analgesic; another reason might be that DEX prolongs the analgesic time and the analgesic effect of other analgesics. Although an animal study reported that its analgesic property could be neutralized by α2AR antagonist,[26] we can not completely exclude the remote possibility that DEX is also using α2AR-independent mechanisms to show its analgesic effects.

Surgery-induced fatigue was another factor that prolonged convalescence from surgery.[1,14,16,17] In the present study, all patients reported higher fatigue level after surgery, but on day 3 and day 7 after surgery, patients in the PRD group had significantly lower score of fatigue than their control, which is consistent with the findings from a recent study from the New York University Medical Center.[14] Using a global 40-item questionnaire, the present study found the Global QoR-40 score was significantly improved in the PRD group on day 3 after surgery. Few other studies reported intraoperative infusion of DEX had active effects on recovery in patients after different surgeries,[14,16,17] like major spinal surgery and nasal surgery. Together with these previous studies, this study indicated that intraoperative DEX is helpful to alleviate surgery-induced fatigue in the early postoperative period. Multiple factors are responsible for the slow recovery from surgery, including pain, fatigue, and surgery-induced metabolic, endocrine, and immune changes, known as ''stress responses.'' There is no existing evidence showing the relationship among these factors. We believe that there is a vicious circle among these 3 factors: acute postoperative pain will reduce movement motivation and keep the patient at a relatively ''comfortable position'' even for hours, which will deteriorate fatigue and impair the ability of responding to stress physically and mentally; fatigue might be a result of multisystem disorder induced by response stress, and will possibly worsen response stress and acute pain after surgery; and at molecular level, stress response induced multisystem changes, including inflammatory factors, such as cytokine interleukins,[14] which are widely accepted mediators in the pain process (Fig. 6). Also, more investigations need to be done to verify this hypothesis in the future.

We found that DEX induced sedation and analgesia without increasing the risks of opioid-related side effects, like respiratory depression, which is consistent with the previous studies. We also saw a decreasing trend of postoperative nausea and vomiting. Future large sample studies should be done to verify its effects on morphine and surgery-related side effects, like nausea and vomiting.

The present study might have a limitation: some patients took nonopioid analgesics before their surgery for abdominal pain, like nonsteroidal anti-inflammatory drugs, which might affect the VAS results after surgery.

Taken together, maintenance with DEX (0.4 μg/kg/h) provided a more stable anesthesia without changing the hemodynamic characters, and is useful to promote the morphine-based PCA, alleviate fatigue, and promote patient recovery after abdominal colectomy. This study indicated that intraoperative

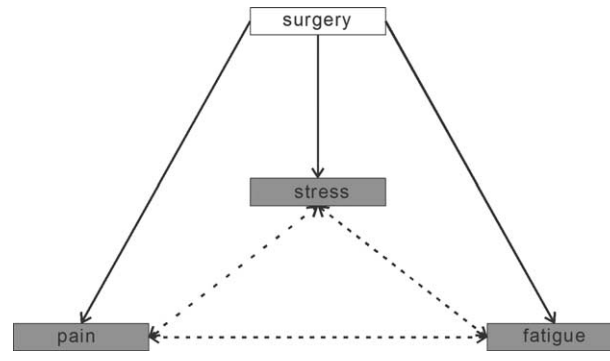

FIGURE 6. Schematic showing potential relationships among surgery-induced pain, stress, and fatigue.

administration of DEX benefited the female patients, at least those who experienced abdominal surgeries.

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D-JG and J-YL conceived this study; QB, GT, and D-JG conducted the experiments; and J-YL and D-JG analyzed the results and wrote the manuscript. All authors reviewed the manuscript.

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