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ORIGINAL SCIENTIFIC REPORT

The Addition of Dexmedetomidine to Analgesia for Patients After Abdominal Operations: A Prospective Randomized Clinical Trial

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Abstract

Background Postoperative pain and anxiety are two common factors influencing patient's recovery. Benefits and safety in the use of sedative agents after abdominal operations to improve recovery are not well known. The present study is to evaluate the efficacy and safety of dexmedetomidine use in this population.

Methods A prospective randomized controlled trial of 145 patients undergoing abdominal operations was conducted in the Surgical Intensive Care Unit of Jinling Hospital between October and December 2015. Thirty-two patients were excluded, and 113 were included and divided into the experimental group (59 patients) receiving dexmedetomidine and analgesics for 72 h after abdominal operations, and the control group (54 patients) receiving only analgesics. Postoperative pain, inflammatory response, recovery of gastrointestinal function, adverse events, and sedation level were analyzed.

Results Pain scores, assessed by Prince Henry Pain Scale (PHPS), in the experimental group were significantly lower than in the control group on the first (1.53 vs. 2.07, $p \leq 0.01$), second (1.07 vs. 1.63, $p \leq 0.01$), and third day (1.08 vs. 1.82, $p = 0.01$). Time to defecation was 0.60 days shorter in the experimental group than the control group (2.51 vs. 3.11, $p = 0.01$). There was no significant difference between inflammatory responses in the two groups ($p > 0.05$). Both groups had similar blood pressure, heart rate, prevalence of bradycardia, and hypotension requiring interventions ($p > 0.05$).

Conclusions The addition of dexmedetomidine to analgesia after abdominal operations is safe and could enhance gastrointestinal function recovery and pain control when monitored carefully. The capacity of dexmedetomidine to attenuate inflammatory responses requires further investigation.

Introduction

Nowadays the concept of surgery is much more than conducting operations, and it requires less stress and faster recovery. Pain and anxiety are two important factors influencing postoperative recovery [1]. Postoperative pain can reduce mobility, cause pulmonary and circulatory complications, increase inflammation, delay intestinal motility, aggravate anxiety, and cause mania, insomnia, and hallucinations, particularly in older patients [2]. When inappropriately treated, pain can also cause tachycardia, immunosuppression, increased catecholamine production,

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and increased oxygen consumption [3]. Pain management in the perioperative setting involves interventions performed before, during, and after operations that are intended to reduce or eliminate postoperative pain before discharge. Multimodal management can achieve the best results and improve patient outcomes [4–6]. However, many patients still experience pain, anxiety, and insomnia in the postoperative period. Potent analgesics applied to reduce these symptoms can cause adverse effects, for example, opioid use is associated with respiratory depression, intestinal paralysis, increased risk of coma and delirium [7–9]. These symptoms can retard patient recovery after operations, and for these reasons, only analgesic use may not be enough for achieving fast recovery.

Sedation is often used to improve comfort and to reduce anxiety and stress, simplifying postoperative nursing care [9]. Sedation can shorten the time spent in the intensive care unit (ICU) and the length of time that the patient requiring mechanical ventilation [10, 11]. Guidelines suggest that sedative strategies using non-benzodiazepine sedatives (either propofol or dexmedetomidine) may be preferable to benzodiazepines, more substantially improving clinical outcomes of mechanical ventilated adult patients [12]. Despite the well-known benefits of sedation in critically ill patients [13], the role of postoperative sedation in patients undergoing abdominal operations is not well understood. Whether sedation is beneficial in these cases remains to be determined.

After abdominal operations, procedures applied to shorten recovery time include extensive preoperative counseling, short-acting anesthetics, effective opioid-sparing postoperative pain and nausea control, avoidance of unnecessary invasive monitoring, and early ambulation and oral nutrition [14]. Dexmedetomidine, a new sedative, can cause analgesia and induce a sedative state similar to physiologic sleep, without causing respiratory depression, by acting on α-2 receptors in the locus ceruleus [15–17]. When used to sedate critically ill patients, dexmedetomidine can shorten time on ventilator and length of ICU stay, and reduce risk of delirium and hypertension [3, 18]. However, cases of severe bradycardia and unexpected deaths have been reported [19, 20], and the risks and benefits of applying dexmedetomidine to patients after abdominal operations remain uncertain. We conducted this prospective study to evaluate the efficacy and safety of addition of dexmedetomidine to analgesia in patients after abdominal operations, and compared administration of dexmedetomidine and analgesics with administration of analgesic medication alone.

Materials and methods

Study design

This study was conducted in the Surgical Intensive Care Unit (SICU) of Jinling Hospital, Medical School of Nanjing University in Nanjing, China. Between October and December 2015, 145 eligible patients were randomized and 113 patients were included in the study population. Patients were divided in two groups. The experimental group, comprising 59 patients, received dexmedetomidine and analgesics after abdominal operations. The control group, comprising 54 patients, received only analgesics. Both groups were followed until discharge from hospital. The protocol was approved by the Institutional Review Board of Jinling Hospital, and all patients or legally authorized representatives provided written informed consent. Data were collected and analyzed by the investigators.

Study population

Inclusion criteria were: (1) aged between 16 and 85 years of age, (2) undergoing abdominal operations, including intestinal resection, gastrectomy, hepatectomy, and pancreatectomy, (3) undergoing surgical procedures lasting at least 2 h. Exclusion criteria included: (1) participation in other clinical trials, (2) use of quinolone antibiotics within the 4 preceding weeks, (3) use of non-steroidal anti-inflammatory drugs (NSAIDS) within the preceding month, (4) a history of peptic ulcers, respiratory insufficiency, renal insufficiency, acute hepatitis, or severe liver disease (Child–Pugh class C), (5) pregnancy or lactation, (6) clinically significant electrocardiogram abnormalities, (7) uncontrolled hypotension, (8) bleeding tendency or hematological diseases, (9) untreated mechanical intestinal obstruction, (10) inability to express, or any mental disease, (11) mechanical ventilation or clinical deterioration requiring other procedures.

Randomization and baseline data collection

Patients and all study personnel, except the investigative pharmacist at each site, were blinded to treatment assignment. All eligible patients were centrally randomized 1:0.92 using a random number table into the experimental and control group. Detailed medical history, including sedative and analgesic therapy prior to initiation of the study, baseline demographics, and severity of illness were obtained at the time of enrollment after consent was signed.

Study drug administration

Each patient in the experimental group received dexmedetomidine by venous pump for at least 72 h after abdominal operations. Sedatives used before study enrollment were discontinued prior to the initiation of the study drug, which was administered when patients were within the Richmond Agitation and Sedation Scale (RASS) target range of −2 to +1. The starting maintenance infusion dose of dexmedetomidine was 0.8 μg/kg per hour. Dexmedetomidine dosing was adjusted by the managing clinical team based on RASS sedation assessment every 6 h. Patients not adequately sedated by the study drug titration received dexmedetomidine until adequate sedation was achieved with a maximum dose of 4 mg in 8 h. If over sedation (RASS range, −3 to −5) did not respond to decreasing infusion rate, the infusion was stopped until patients returned to the goal sedation range.

All patients received the analgesics tramadol and flurbiprofen. No other sedatives or analgesics were allowed during the follow-up. Study drug infusion was stopped after a maximum of 7 days. No other sedatives or analgesics were allowed during the period. Any opioids used afterwards were kept records of.

Outcome measures

The primary and secondary outcomes were established a priori. The primary outcomes were Prince Henry Pain Scale (PHPS) score, time to defecation, inflammatory response level (white blood cell, WBC, counts and C-reactive protein, CRP) and length of hospital stay. Secondary outcomes included percentage of time within targeted RASS range, risk of bradycardia or hypotension requiring interventions, and use of opioids or benzodiazepines. PHPS scores were assessed by investigators at 8:00 am the day after operations to assess adequate sedation level in patients of experimental group and until discharge from the ICU. A daily arousal assessment was performed during the treatment period, while patients were within the RASS range of −2 to +1. Patients were asked to perform 4 tasks (open eyes to voice command, track investigator with eyes, squeeze hand, and stick out tongue). Patients were considered awake with successful completion of the assessment when they could perform 3 of 4 tasks. If the patient RASS score was not between −2 and +1, maneuvers described to set the goal sedation score were performed and then the arousal assessment was conducted. Time to defecation was the period from abdominal operation to the first flatus or defecation, which represented recovery of gastrointestinal function.

Safety was assessed by monitoring laboratory test results, vital signs, electrocardiogram findings, physical examination. Adverse events were assessed and monitored by the principal investigator and were recorded from first dose of study drug until 48 h after study drug discontinuation. Adverse events include systolic blood pressure <80 mmHg or >180 mmHg, diastolic blood pressure <50 mmHg or >100 mmHg, heart rate <40/min or >120/min. A change greater than 30 % from baseline heart rate or blood pressure was also considered an adverse event.

Interventions for bradycardia, tachycardia, and hypertension included titration or interruption of dexmedetomidine or administration of medication; interventions for hypotension included titration or interruption of dexmedetomidine, intravenous fluid bolus or drug therapy.

Length of hospital stay was recorded from admission to discharge.

Statistical analysis

Sample size determination

To address the multiple objectives of comparing efficacy and safety during exposure to dexmedetomidine sedation, the sample size determination considered drug exposure, efficacy, and safety parameters. In a previous study, the response within each subject group was normally distributed with standard deviation 1.02. If the true difference in the experimental and control means is 0.6, 48 experimental subjects and 44 control subjects will be needed to reject the null hypothesis that the population means of the dexmedetomidine and control groups are equal with probability (power) 0.8. The type I error probability associated with this test of this null hypothesis is 0.05. Based on this, we planned a study of a continuous response variable from independent control and experimental subjects with 0.92 control per experimental subject.

Efficacy and safety analysis

A Chi-square test was used to identify differences in categorical variables, and analysis of variance (ANOVA) was used to compare differences in categorical variables. Cumulative overall survival rates were determined using the Kaplan–Meier test and compared using the log-rank test. All statistical analyses were performed using SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL), and statistical significance was accepted if $p \leq 0.05$.

Results

Studied population

A total of 128 eligible patients were randomized, and 113 patients were included in the primary analysis study

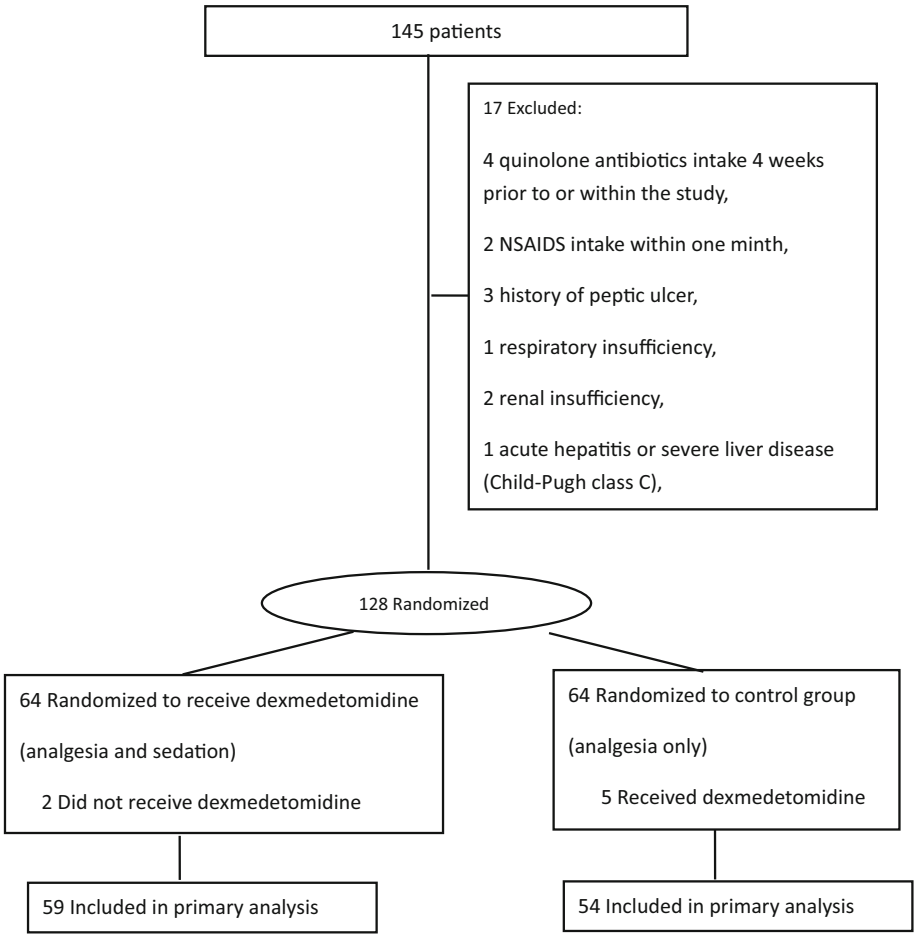

Fig. 1 Patient enrollment, randomization, and treatment flow

Table 1 Baseline characteristics and demographics of study population

Characteristic	Experimental	Control	*p* value
Number	59	54	
Age, mean (SD)	56.98 (13.40)	59.09 (13.91)	0.41
Men (%)	36 (61.2)	32 (59.3)	0.50
Surgical spot			
Gastric tumor	13 (22.0)	13 (24.1)	0.48
Small intestine	15 (25.4)	11 (20.4)	0.34
Colon tumor	12 (20.3)	12 (22.2)	0.49
Rectal tumor	7 (11.9)	3 (5.6)	0.19
Constipation	4 (6.8)	5 (9.3)	0.44
Hepatobiliary diseases	6 (10.2)	4 (7.4)	0.42
Pancreatic diseases	2 (3.4)	4 (7.4)	0.29
Underlying diseases			
Hypertension	11 (18.6)	10 (18.5)	0.59
Diabetes mellitus 2	4 (6.8)	8 (14.8)	0.14
Coronary heart disease	2 (3.4)	2 (3.7)	0.65

population (59 patients received dexmedetomidine, 54 not). Two patients randomized in the dexmedetomidine group did not receive the drug, and five patients randomized in the control group received dexmedetomidine because of intolerable pain or mania. Mechanical ventilation patients were excluded because it is difficult to evaluate pain level by PHS (Fig. 1). Baseline characteristics did not differ significantly between groups (Table 1).

Primary outcomes

Postoperative analgesia

On the first day, median PHPS score was 0.54 lower in the experimental group than the control group (1.53[95 % CI, 1.28–1.77] vs. 2.07[95 % CI, 1.79–2.35]; $p = 0.004$). On the second day, median PHPS score was 0.56 lower in the experimental group (1.07[95 % CI, 0.76–1.38] vs. 1.63[95 % CI, 1.23–2.02]; $p = 0.0023$). On the third day, median PHPS score was 0.74 lower in the experimental

Table 2 Efficacy outcomes in patients treated with/without dexmedetomidine

Outcome	Experimental group	Control group	*p* value
PHS			
1d	1.53 (0.95)	2.07 (1.02)	0.00**
2d	1.07 (0.82)	1.63 (0.92)	0.02*
3d	1.08 (0.88)	1.82 (0.49)	0.01**
Time to defecation	2.51 (1.02)	3.11 (1.59)	0.01**
WBC(10^9/L)			
1d	11.476 (4.18)	12.117 (4.40)	0.43
2d	10.283 (4.26)	11.375 (3.91)	0.34
3d	9.794 (4.23)	8.620 (3.86)	0.45
CRP(mg/L)			
1d	63.916 (50.68)	55.293 (44.64)	0.35
2d	99.180 (57.30)	131.958 (57.87)	0.04*
3d	103.153 (58.81)	112.500 (47.36)	0.64
Oxycodone–aceta	10 (16.9)	8 (14.8)	0.48
Minophen tablets			
BZD	1 (1.69)	1 (1.85)	0.73
Fentanyl(Opioids)	1 (1.69)	2 (3.70)	0.46
LOS(d)	8.51 (4.41)	11.04 (8.12)	0.04*

PHPS Prince Harry Pain Scale, *WBC* white blood cell, *CRP* C-reactive protein, *BZD* benzodiazepines, *LOS* length of hospital stay

* $p < 0.05$; ** $p \leq 0.01$

group (1.08[95 % CI, 0.78–1.38] vs. 1.82[95 % CI, 1.37–2.28]; $p = 0.011$) (Table 2, Fig. 2b).

Recovery of gastrointestinal function

Time to defecation was 0.60 days shorter in the experimental group than the control group (2.51[95 % CI, 2.24–2.78] vs. 3.11[95 % CI, 2.67–3.55]; $p = 0.018$) (Table 2, Fig. 2a).

Inflammatory response

On the first day, the WBC count in the experimental group was 0.64 × 10^9/L lower than in the control group; however, this difference was not significant (11.47[95 % CI, 10.38–12.56] vs. 12.11 [95 % CI, 10.91–12.32]; $p = 0.43$; Table 2). On the second day, the WBC count in experimental group was 1.09 × 10^9/L lower than in the control group, but again this difference was not significant (10.28[95 % CI, 8.66–11.90] vs. 11.37 [95 % CI, 9.72–13.02]; $p = 0.34$; Table 2, Fig. 2c). CRP levels in the experimental group were 8.32 mg/L higher (63.61[95 % CI, 50.40–76.82] vs. 55.29 [95 % CI, 43.10–67.47]; $p = 0.35$). However, CRP in experimental group on the second day was 33.77 mg/L lower (99.18[95 % CI, 77.78–120.57] vs. 131.95 [95 % CI, 107.52–156.39]; $p = 0.043$) (Table 2, Fig. 2d).

Length of hospital stay (LOS)

Dexmedetomidine administration significantly shortened patients' LOS (Table 2). Patients in the experimental group were hospitalized for 2.53 fewer days than those in the control group (8.51[95 % CI, 7.36–9.66] vs. 11.04[95 % CI, 8.22–13.26]; $p = 0.040$).

Secondary outcomes

Safety

The blood pressure and heart rates of patients did not differ significantly between the two groups ($p > 0.05$), and neither did the prevalence of bradycardia nor hypotension requiring interventions (Table 3).

Discussion

Traditional sedative agents may have unpredictable and prolonged duration of action in critically ill patients, due to the redistribution and accumulation of active metabolites [21]. Benzodiazepines have also been reported to be associated with increased risk of coma, delirium, and respiratory depression [7, 8, 22]. Dexmedetomidine proved to be safer by causing fewer adverse effects, and to reduce cardiac output and hepatic blood flow, potentially increasing its action duration in critically ill patients [13]. Thus we presume dexmedetomidine to be more applicable than traditional sedative drugs for postoperative sedation.

Pain and anxiety are two of the most common factors influencing recovery from operation [1]. When inappropriately treated, pain can cause immunosuppression, tachycardia, increased oxygen consumption, and increased catecholamine production [3]. To hasten discharge and recovery, postoperative treatments should minimize physiological and psychological stress [9]. Postoperative analgesia has been reported to be a key contributor to postoperative management of gastrointestinal operation and in Enhanced Recovery After Surgery (ERAS) programs, while the role of sedation is still controversial [23].

Dexmedetomidine is a highly selective α-2 adrenoreceptor agonist providing sedative and anxiolytic activity via receptors within the locus ceruleus, analgesia via receptors in the spinal cord, and attenuation of the stress response with no significant respiratory depression [19]. These properties could explain our results, with reduced pain levels. Thus sedation with dexmedetomidine could

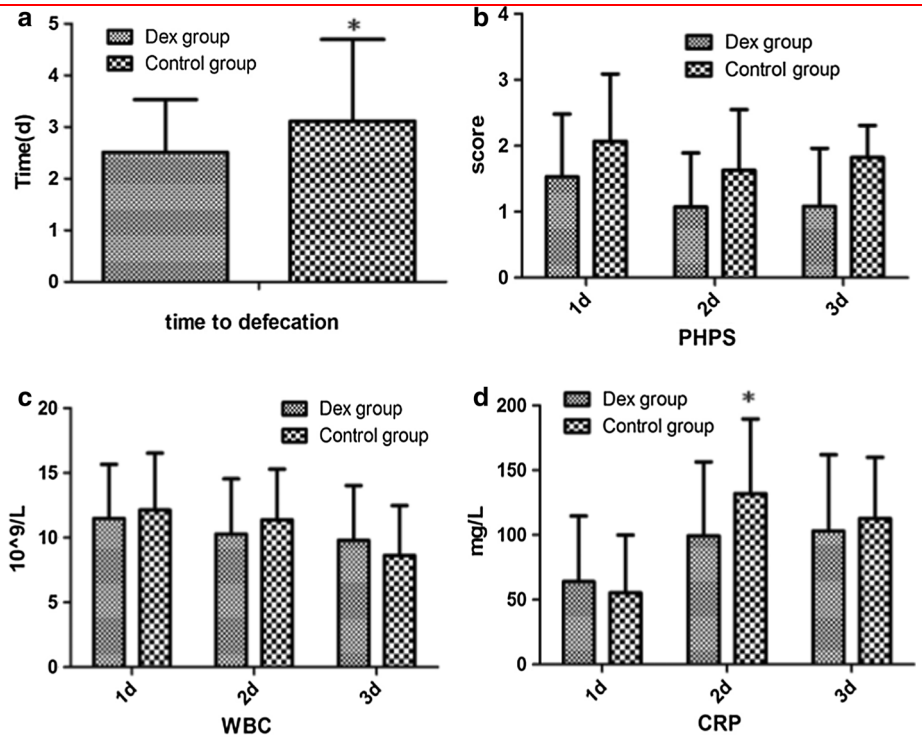

Fig. 2 Results of main outcomes. **a** Time to defecation was counted from surgeries to the first defecation. The median time was 0.60 days shorter in the experimental group than the control group. **b** PHPS scores were assessed at 8:00 am for 3 days after surgeries. On the first day, median score was 0.54 lower in the experimental group than the control group (1.53[95 % CI, 1.28–1.77] vs. 2.07[95 % CI, 1.79–2.35]; $p = 0.004$). On the second day, median score was 0.56 lower in the experimental group (1.07[95 % CI, 0.76–1.38] vs. 1.63[95 % CI, 1.23–2.02]; $p = 0.0023$). On the third day, median PHPS score was 0.74 lower in the experimental group (1.08[95 % CI, 0.78–1.38] vs. 1.82[95 % CI, 1.37–2.28]; $p = 0.011$). **c** WBC was collected for 3 days after surgeries. There was no significant difference between groups ($p > 0.05$). **d** CRP was collected for 3 days after surgeries. There was no significant difference between groups except the second day (99.18[95 % CI, 77.78–120.57] vs. 131.95 [95 % CI, 107.52–156.39]; $p = 0.043$). *$p < 0.05$, **$p \leq 0.01$. *PHPS* Prince Henry Pain Scale, *WBC* white blood cell, *CRP* C-reactive protein

Table 3 Safety outcomes during treatment with/without dexmedetomidine

Outcome	Experimental group	Control group	*P* value
Blood pressure (mmHg)			
1d	113.8/63.5	120.0/65.7	0.01*/0.17
2d	116.4/62.9	115.1/62.6	0.71/0.88
3d	125.7/67.9	122.6/65.3	0.60/0.45
Heart rate			
1d	76.9 (12.71)	75.6 (11.51)	0.56
2d	73.1 (13.47)	72.2 (10.65)	0.78
3d	73.2 (13.03)	73.1 (13.57)	0.97
Hypotension requiring interventions	7 (11.9)	4 (7.4)	0.31
Bradycardia requiring interventions	5 (8.4)	2 (3.7)	0.89

* $p < 0.05$; ** $p \leq 0.01$

reduce the use of analgesics like opioids, avoiding the associated adverse effects.

Operation can have adverse effects on gastrointestinal motility and cause inflammatory response. After abdominal operations, patients usually experience a period of lower motility, mucosa edema, inflammation or even dysfunction of the gastrointestinal system [24, 25]. Time to flatus or defecation is commonly taken to indicate recovery of

gastrointestinal function. In our study, patients sedated with dexmedetomidine had earlier flatus or defecation. This effect could be attributed to several factors. Firstly, sedated patients complained less pain and had better sleep, indicating that these patients experienced less stress. Secondly, previous studies have indicated that dexmedetomidine had anti-inflammatory effects [13], and could potentially alleviate the inflammation caused by surgical stress or gastrointestinal dysfunction. Thirdly, decreased use of analgesics, like opioids, could reduce the associated adverse effects, like inhibition of intestinal smooth muscle and motility, which could delay recovery of gastrointestinal function.

In this study, we did not detect any significant differences in CRP and WBC levels on the first or third day after operations between the two groups, and on the second day only CRP levels were significantly lower in the sedation group. These findings are not consistent with those of previous researches [26, 27]; however, median levels of both WBC and CRP were lower in the sedation group. Many other factors were likely to influence the results. First, postoperative inflammation peaks over 3 days after operations, our observation period may have not included the period in which inflammation is more problematic [28]. Second, antibiotic use may conceal the primary postoperative inflammation levels. Third, different surgical methods can cause different levels of damage to the gastrointestinal tract and as our sample size was relatively small, differences between the individual operations in each group may have concealed significant differences in outcomes. We assumed that sedation with dexmedetomidine had the potential to attenuate postoperative inflammatory responses, but further larger studies assessing more inflammatory responses, such as IL-6 and IL-10 levels, will be required to determine this issue.

Our results indicate that dexmedetomidine did not increase the risk of adverse effects. Within the first 3 days after operations, blood pressure and heart rate of patients in the sedation group did not differ significantly from that in the control group. Unexpectedly, the prevalence of bradycardia and hypotension requiring intervention did not differ between groups. While previous studies have indicated that these adverse effects were associated with dexmedetomidine, most previous work was carried out among critically ill or mechanically ventilated patients, who were in much more severe conditions than the patients in our study [3, 8, 26]. In this study, dexmedetomidine was administered by venous pump. Dose and speed were adjusted based on vital sighs at least every 6 h to ensure that the patients' blood pressures and heart rates were stable. These factors may account for our different results.

In previous studies, dexmedetomidine could reduce the use of opioids in mechanical ventilated patients. In our study, all patients received tramadol and flurbiprofen as analgesics. Study drugs infusion was stopped after a maximum of 7 days. No other sedatives or analgesics were allowed during the period. Any opioids used afterwards were kept records of. According to our data, fentanyl patch was the only opioids used. There are 3 patients (1 in dexmedetomidine group and 2 in control group) who received fentanyl patch on least 7 days after operations. All 3 patients regained defecation and flatus before the use of fentanyl patch. Besides this, pain scores and inflammation levels were assessed for the first 3 days after operations. So we assume that these 3 patients would not affect our results and did not exclude them.

Lastly, the present study showed that patients in the dexmedetomidine group had a shorter hospital stay of over 2.5 days. It is worth noticing that there were two patients in the control group who had severe complications after operations, which resulted in delayed discharge from hospital. Of the two patients, one experienced postoperative bleeding and had a second operation, the other patient had anastomotic fistula, which caused severe infection and sepsis. Both patients had complications beyond 72 h after operations, so we included them in the statistical analysis. As there is no patients in the dexmedetomidine group had complications, we assume that severe complications risk might play a much more important role in the reduction in LOS than the use of dexmedetomidine.

The efficacy and safety of postoperative sedation is still controversial, but our study suggests that for abdominal operations, postoperative sedation could alleviate pain and enhance recovery of gastrointestinal function. These results suggest that dexmedetomidine might attenuate postoperative inflammatory responses. We thus assume that dexmedetomidine is safe and beneficial when applied for postoperative sedation following abdominal operations.

The concept of ERAS was first introduced by Kehlet in 2001 to describe earlier consciousness and recovery after operations [29]. ERAS programs aim to minimize physiological and psychological stress and achieve faster recovery [9]. In clinical practice, application of the theory has achieved great benefits [23], enabling patients to get out of bed earlier, and reducing the rate of complications and hospital expenses [30–32]. Our results indicate that addition of dexmedetomidine to analgesia could be useful to ERAS programs, particularly for abdominal operations. However, larger trials will be required to investigate the effects of postoperative sedation for other operations, such as subtotal gastrectomy.

Our conclusions are limited by the scope of this study. First, the relatively small number of patients treated with dexmedetomidine did not allow us to draw any definitive conclusion. Second, our ICU is specially attached to general surgery department, admitting surgical patients only.

More than half of our patients are postoperative patients and not intubated. Baseline conditions were stable, and delirium risk was very low. The levels of sedation and delirium were similar, and most patients reached the target range. So we chose not to address it. Third, we did not analyze length of ICU stay, because most postoperative patients stayed in the ICU for no more than 3 days. Last, we administered dexmedetomidine by venous pump. In the future, if postoperative sedation becomes a routine practice, other routes of administration, like oral administration, may be more effective and convenient.

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