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ABOUT COVER

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ORIGINAL ARTICLE

Randomized Controlled Trial

Impact of intravenous dexmedetomidine on postoperative bowel movement recovery after laparoscopic nephrectomy: A consortprospective, randomized, controlled trial

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Abstract

BACKGROUND

Postoperative ileus is a frequent postoperative complication, especially after abdominal surgery. Sympathetic excitation is the primary factor for postoperative ileus. Sympathetic activation becomes increased by surgical stress, postoperative pain, and inflammation. Dexmedetomidine (DEX) can inhibit sympathetic nerve activity, inflammation, and pain.

AIM

To observe whether DEX promotes bowel movements in patients after laparoscopic nephrectomy.

METHODS

One hundred and twenty patients undergoing laparoscopic nephrectomy were assigned to three groups: C (normal saline infusion), D1 (DEX 0.02 µg/kg/h), and D2 (DEX $0.04 \mu g/kg/h$). The primary outcomes were the recorded times to first flatus, defecation, and eating after surgery. The secondary outcomes were postoperative pain, assessed using the numerical rating scale (NRS), adverse effects, and the duration of the postoperative hospital stay.

RESULTS

The times to first flatus, defecation, and eating in groups D1 and D2 were significantly shorter than those in group C (P < 0.01). The NRS scores at 8 h and 24 h after surgery were significantly lower in groups D1 and D2 than in group C (*P* < chictr.org (ChiCTR-IPR-15007628)

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CONCLUSION

Postoperative infusion of DEX at $0.04~\mu g/kg/h$ facilitates bowel movements in patients undergoing laparoscopic nephrectomy.

Key Words: Dexmedetomidine; Bowel movement; Recovery; Flatus; Postoperative

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Core Tip: Postoperative ileus (POI) is a perplexing problem for clinical surgeons. In this study, laparoscopic nephrectomy was chosen to investigate postoperative gastrointestinal function recovery, avoiding damage to the gut itself. Based on the reported effects of DEX, the authors hypothesized that DEX could promote postoperative gastrointestinal function.

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INTRODUCTION

Postoperative ileus (POI) is a perplexing problem for clinical surgeons. It occurs not only after abdominal surgery but also after any surgery that requires general anesthesia[1,2]. POI is defined as the dysfunction of gastrointestinal motility after surgery, characterized by a decrease in, or stagnation of, intestinal peristalsis. Common clinical manifestations include abdominal pain, abdominal distention, nausea, vomiting, delayed flatus, delayed defecation, and inability to consume orally [3-5]. POI is an uncomfortable experience, enhances the possibility of postoperative complications, prolongs hospital stay[4], and increases the economic burden[6,7]. Postoperative gastrointestinal function recovery is of great concern. There is currently an urgent need to improve postoperative recovery of gastrointestinal function.

The mechanism of POI varies, including autonomic regulation, inflammatory response, gastrointestinal hormones, and postoperative use of opioid drugs. Surgical gut damage destroys the intestinal barrier, stimulates the sympathetic and parasympathetic nervous system, and enhances the release of inflammatory factors[1,5,8,9]. These factors precipitate the occurrence of POIs. The current use of laparoscopic techniques can reduce incision size and surgical trauma, enabling careful manipulation[10-12]. Thus, the influence of the surgical procedure itself has decreased. Some studies have shown that intraoperative use of short-acting opioids or postoperative use of opioid receptor antagonists can ensure postoperative analgesia and eliminate the impact of intraoperative use of opioids on POI. Adjuvant epidural analgesia, intraoperative restriction of fluid intake, reduction of intraoperative blood loss, and early oral administration of nutrients after surgery can promote POI recovery [13]. However, POI remains a medical problem during clinical surgery; therefore, a more effective and noninvasive method is required.

Dexmedetomidine (DEX), as a highly selective α -2 adrenergic receptor agonist, has the effects of synergetic analgesia, sedation, inhibition of sympathetic hyperactivity, and reduced release of inflammatory mediators with little respiratory inhibition[13, 14]. Previous studies on POI were all based on gastrointestinal tract surgery. Hence, in the present study, laparoscopic nephrectomy was chosen to investigate postoperative gastrointestinal function recovery, avoiding damage to the gut itself. Based on the reported effects of DEX, we hypothesized that DEX could promote postoperative gastrointestinal function.

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MATERIALS AND METHODS

Participants

This randomized, double-blinded, controlled trial was approved by the Institutional Medical Ethics Committee of Qilu Hospital of Shandong University. It was registered at chictr.org (ChiCTR-IPR-15007628) and is in accordance with the CONSORT guidelines. We chose patients who were treated by laparoscopic nephrectomy under general anesthesia at Qilu Hospital and did not have the following conditions: Body mass index greater than 32 kg/m² or less than 18 kg/m²; age older than 75 or younger than 18 years; presence of bradycardia [basal heart rate (HR) less than 60 bpm] or other cardiac arrhythmia; presence of clinically significant dysfunction, including cardiovascular, renal, or hepatic diseases; previous history of chronic pain or long-term use of analgesics (at least 3 mo); or allergy to the test drug. This trial was initiated in January 2016 and terminated in December 2017.

Randomization and masking

The patients who met the enrollment criteria provided informed consent for participating in the trial. Then, according to a computer-generated randomization table, participants were randomly assigned to one of the three groups: C (normal saline infusion), D1 (DEX $0.02 \mu g/kg/h$), and D2 (DEX $0.04 \mu g/kg/h$). On the day of surgery, the drugs and patient-controlled analgesia (PCA) were prepared by an anesthetist who was blinded to the group assignment. Furthermore, the associated doctors and nurses were blinded to group assignment.

Process of anesthesia

Patients were premedicated with atropine 0.5 mg by intramuscular injection in the ward. Before anesthesia induction, each patient was monitored for electrocardiography, noninvasive blood pressure measurements, pulse oximetry saturation (SpO₂), and end-tidal carbon dioxide (EtCO₂) using an automated system (Philips IntelliVue MP50; Philips Company, Beijing, China). HR, SpO₂, and mean blood pressure (MBP) were monitored every 5 min.

After obtaining a baseline measurement of HR and MBP, groups D1 and D2 received 0.5% DEX, and group C received 0.9% normal saline for 10 min. We used propofol, rocuronium, and sufentanil for sequential induction. The laryngeal mask airway (LMA) was intubated after positive pressure mask ventilation for 5 min. An arterial cannula was required to monitor invasive arterial blood pressure in the left radial artery. Anesthetic depth was monitored using a bispectral index (BIS) monitor, and sevoflurane was administered to maintain the depth of anesthesia (BIS scores in the range of 40 to 60). Controlled ventilation was performed with 100% oxygen, and EtCO₂ was maintained at 35-40 mmHg. We inserted a temperature probe through the nasal cavity and maintained the body temperature at 36-37 °C. We started to infuse the test drugs (groups D1 and D2 received the DEX infusion at rates of 0.2 µg/kg/h and 0.4 μg/kg/h, respectively, while group C received saline instead of DEX) after the establishment of pneumoperitoneum and suspended them for 30 min before the end of surgery. Rocuronium was administered intermittently to maintain satisfactory muscle relaxation.

If more than a 20% fluctuation in the MBP baseline level was detected, vasoactive drugs (noradrenaline 5-10 μg or nitroglycerin 50-100 μg) were used to maintain hemodynamic stability. If the HR decreased to less than 45 bpm, atropine 0.5 mg was administered. Conversely, if the HR was greater than 100 bpm, esmolol 0.5 mg/kg was administered to decrease the HR. When the laparoscope was withdrawn, palonosetron (0.25 mg) was intravenously administered to prevent postoperative nausea and vomiting (PONV). When spontaneous breathing appeared at the end of the surgery, neostigmine 0.04 mg/kg and atropine 0.02 mg/kg were administered to antagonize neuromuscular blockade before LMA extubation. If the SpO₂ was greater than 90% without oxygen for at least 5 min, patients could be sent back to the ward.

At the end of the surgery, a PCA pump was started (group C with sufentanil 0.02 μg/kg/h; group D1 with both sufentanil and DEX 0.02 μg/kg/h; group D2 with sufentanil 0.02 μg/kg/h and DEX 0.04 μg/kg/h). The PCA was programmed to deliver at a constant speed of 2 mL/h, and an additional dose (0.5 mL) was administered with a lockout time of 10 min.

Regarding postoperative bowel movements, patients were given abdominal massage, miso soup, or both if the time to flatus was more than 48 h. Intravenous nutrition was provided if the time to flatus was more than 72 h.

Outcomes

The primary outcome measures were the times to first flatus and defecation, and the duration of postoperative hospital stay. The secondary outcome measures were postoperative pain scores, both at rest and during movement, and adverse effects.

HR, MBP, and SpO₂ were collected at the following six time points: Entering the operating room (T0), 5 min after finishing the baseline test drug infusion (T1), 5 min after pneumoperitoneum establishment (T2), 1 h after pneumoperitoneum establishment (T3), 2 h after pneumoperitoneum establishment (T4), and 5 min after extubation (T5). In addition, EtCO₂ was recorded from T1 to T4. Pain scores were assessed using the numerical rating scale (NRS) (0 = no pain to 10 = worst pain) at 1, 8, 24, and 48 h postoperatively.

Statistical analysis

Statistical analyses were performed using SPSS software (version 21.0, SPSS Inc. Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess the distribution of the variables. Levene's test was used to compare the homogeneity of variance among the three groups. Normally distributed data are expressed as the mean and standard deviation, whereas data with a skewed distribution are expressed as the median and number (n). Percentages (%) are used to represent categorical data. Parameters such as age, operation time, anesthesia time, time to first flatus and defecation, MBP, and HR among these groups were compared using two-way analysis of variance. The Mann-Whitney test was used to evaluate the NRS scores among the three groups, and adverse reactions were analyzed using the χ^2 test. Multiple comparisons were performed using the LSD post-hoc test. Statistical significance was set at P < 0.05.

RESULTS

A total of 123 patients were randomly distributed into three groups. Among the patients, two were eliminated due to conversion to open nephrectomy (one from group D1 and one from group D2). In addition, one patient was excluded after surgery because of incomplete clinical data (from group C) (Figure 1). The baseline characteristics and demographics of the patients were comparable among the three groups (Table 1).

The times to first flatus and defecation after surgery in groups D1 (41.50 \pm 8.24 h and 73.33 ± 19.19 h, respectively) and D2 (38.66 ± 7.60 h and 71.33 ± 19.70 h, respectively) were significantly shorter than those in group C (51.31 \pm 11.78 h and 92.80 \pm 25.51 h, respectively, P < 0.05; Table 2). The time to eating after surgery in groups D1 (44.50 \pm 8.94 h) and D2 (42.29 \pm 7.75 h) was shorter than that in group C (54.78 \pm 11.58 h) (P < 0.05; Table 2).

MBP at T1 in groups D1 and D2 was significantly lower than that in group C. MBP was lower than the baseline at T2, T3, T4, and T5 in group C, and at T1 and T4 in groups D1 and D2 (P < 0.05, Table 3). HR at T1 and T2 in group D1 was significantly lower than that in group C. HR was lower than the baseline at T2, T3, and T4 in group C, and at T1, T2, T3, and T4 in groups D1 and D2 (P < 0.05; Table 3). The NRS scores at rest or with movement at 8 h and 24 h after surgery were significantly lower in groups D1 and D2 than in group C (P < 0.05; Figure 2).

Adverse effects were not significantly different among the three groups (P > 0.05;

DISCUSSION

The perioperative use of 0.04 μg/kg/h DEX enhanced the recovery of postoperative gastrointestinal function in our study.

Experts agree that patients with POI present with several related symptoms, such as abdominal pain and distension, nausea, vomiting, absence of normal bowel sounds, intolerance of oral intake, and difficulty in defecation [15]. We did not observe the time at which bowel sounds occurred in our study because such data is subjective.

POI occurs temporarily after surgery and is not caused by mechanical reasons[15]. The mechanism of POI is complicated and involves many factors, in particular, the regulation of sympathetic and parasympathetic nerves, the inflammatory response, and postoperative use of opioid drugs. In this study, we observed the influence of DEX on the postoperative outcomes of nephrectomy to avoid gut damage.

Table 1 Clinical characteristics of patients in groups C, D1, and D2				
	Group C (<i>n</i> = 40)	Group D1 (<i>n</i> = 40)	Group D2 (n = 40)	P value
Sex, F/M	11/29	12/28	10/30	0.8820
Age, yr	52.73 ± 10.68	52.33 ± 7.99	51.73 ± 8.58	0.886
BMI, kg/m^2	25.58 ± 2.70	26.15 ± 1.70	25.95 ± 2.04	0.505
Hypertension, Yes/No	11/29	12/28	15/25	0.606
DM, Yes/No	6/34	5/35	5/35	0.930
ASA, I/II	10/30	7/33	6/34	0.497
Duration of anaesthesia, min	148.95 ± 49.54	145.90 ± 47.24	144.60 ± 50.24	0.920
Duration of surgery, min	128.48 ± 46.83	130.90 ± 47.13	127.33 ± 50.18	0.944
Dosage of sufentanil during surgery, µg	32.58 ± 7.20	31.63 ± 3.28	32.75 ± 3.91	0.570
Dosage of sufentanil after surgery (8 h), mL	16.35 ± 0.51	16.15 ± 0.43	16.29 ± 0.53	0.180
Dosage of sufentanil after surgery (24 h), mL	48.41 ± 0.59	48.26 ± 0.76	48.30 ± 0.60	0.566

Variables are presented as the mean \pm SD or number of patients. None showed any statistical significance (P > 0.05). ASA: American Society of Anesthesiologists, BMI: Body mass index, DM: Diabetes mellitus.

 8.38 ± 1.35

 8.43 ± 1.68

0.803

 8.60 ± 1.72

Table 2 Bowel movement after surgery in groups C, D1, and D2				
	Group C (n = 40)	Group D1 (<i>n</i> = 40)	Group D2 (<i>n</i> = 40)	P valves
Time to first flatus, h	51.31 ± 11.78	41.50 ± 8.24	38.66 ± 7.60	0.001 ¹ /0.001 ² /0.179 ³
Time to defecation, h	92.80 ± 25.51	73.33 ± 19.19	71.33 ± 19.70	$0.001^{1}/0.001^{2}/0.680^{3}$
Time to eating, h	54.78 ± 11.58	44.50 ± 8.94	42.29 ± 7.75	$0.001^{1}/0.001^{2}/0.303^{3}$

¹Group D1 vs group C.

Postoperative stay in hospital, d

Gastrointestinal peristalsis mainly depends on parasympathetic stimulation and is inhibited by sympathetic stimulation. Sympathetic hyperactivity is considered one of the main causes of postoperative intestinal paralysis[3,5]. Surgery, pain, gut damage, CO₂ used to establish pneumoperitoneum, and other factors directly or indirectly activate the sympathetic nerves and inhibit postoperative gastrointestinal function recovery. Activated sympathetic nerves increase the release of catecholamines, which inhibit postoperative gastrointestinal function by restricting intestinal smooth muscle contraction[16,17]. DEX is a highly selective $\alpha 2$ -adrenoceptor agonist that acts on $\alpha 2$ adrenoceptors in the central nervous system to reduce the upregulation of sympathetic nerve activation and decrease catecholamine release[18]. Consequently, we firmly believe that treatment with DEX could inhibit sympatholytic excitation, reduce catecholamine activation, excite the parasympathetic nerves, and facilitate postoperative gastrointestinal function. Shorter times to flatus and defecation were observed in our study, which was in accordance with our hypothesis.

Surgical stress and gut damage activate the intestinal immune system, causing the release of inflammatory factors. Inflammatory factors released due to intestinal injury increase intestinal permeability and damage the intestinal lining. White blood cells can easily migrate to the muscle layer, and inflammatory substances can inhibit smooth muscle contraction and weaken gastrointestinal peristalsis[19]. DEX treatment enhances postoperative intestinal function, as it increases the efferent activity of the parasympathetic nerves, the release of acetylcholine, and the expression level of α7 nicotinic acetylcholine receptor (α7nAchR), and reduces the release of some inflammatory transmitters[20,21]. DEX was also found to play an anti-inflammatory role through α7nAchR, reducing postoperative intestinal inflammation and promoting the recovery of intestinal function[22]. Better gastrointestinal function was observed after

²Group D2 vs group C.

 $^{^3}$ Group D1 vs group D2. Variables are presented as the mean \pm SD.

Table 3 Vital signs in groups C, D1, and D2				
Time point	Group C (n = 40)	Group D1 (n = 40)	Group D2 (n = 40)	P value
MBP, mm Hg				
Т0	103.80 ± 11.34	99.73 ± 11.28	99.53 ± 9.91	0.144
T1	101.53 ± 9.45	$88.88 \pm 13.07^{a,c}$	87.65 ± 12.71 ^{a,c}	0.001
T2	98.90 ± 9.81^{a}	98.88 ± 11.65	97.85 ± 12.53	0.895
Т3	97.40 ± 10.11 ^a	96.38 ± 7.78	95.88 ± 8.72	0.739
T4	98.88 ± 8.33 ^a	$94.58 \pm 9.62^{a,c}$	$93.83 \pm 8.54^{a,c}$	0.025
T5	105.45 ± 13.24^{a}	102.50 ± 13.55	102.38 ± 12.14	0.490
HR, bpm				
T0	75.93 ± 11.18	71.43 ± 9.48	74.30 ± 8.70	0.122
T1	74.78 ± 10.22	$63.56 \pm 10.96^{a,c}$	$65.88 \pm 8.56^{a,c}$	0.001
T2	64.88 ± 7.74^{a}	$59.80 \pm 10.02^{a,c}$	63.48 ± 6.93^{a}	0.022
Т3	66.43 ± 11.53 ^a	62.45 ± 9.01^{a}	65.53 ± 7.97^{a}	0.158
T4	67.30 ± 10.47^{a}	66.05 ± 11.08^{a}	67.55 ± 9.85^{a}	0.791
T5	75.80 ± 9.32	73.05 ± 9.86	72.90 ± 6.20	0.242

 $^{^{}a}P < 0.05 vs$ baseline.

 $^{^{}c}P$ < 0.05 vs group C. Variables are presented as the mean \pm SD. MBP: Mean blood pressure; HR: Heart rate.

Table 4 Adverse reactions after surgery in groups C, D1, and D2, n (%)					
	Group C (<i>n</i> = 40)	Group D1 (n = 40)	Group D2 (n = 40)	P values	
Abdominal massage/simo soup	5 (12.5)	3 (7.5)	2 (5)	0.466	
Intravenous nutrition	0 (0)	0 (0)	0 (0)	1.000	
Nausea and vomiting	8 (20)	7 (17.5)	8 (20)	0.948	
Severe abdominal pain and distention	6 (15)	5 (12.5)	4 (10)	0.796	
Drowsiness	1 (2.5)	2 (5)	4 (10)	0.346	
Serious respiratory depression	0 (0)	0 (0)	0 (0)	1.000	
Delirium	0 (0)	0 (0)	0 (0)	1.000	

the use of DEX in our study, which verified our hypothesis.

Visualizing laparoscopic surgery and pneumoperitoneum induction can lead to sympathetic nerve activation[16,23]. In addition, CO₂ pneumoperitoneum can induce hypercarbia, which can directly or indirectly stimulate the sympathetic nervous system and cause elevated levels of catecholamines [16,24]. These factors lead to greater excitability of sympathetic nerves than parasympathetic nerves. Subsequently, gastrointestinal function is inhibited, and POI occurs. DEX, a highly selective α-2 adrenergic receptor agonist, acts on α2-adrenoceptors in the central nervous system to reduce sympathetic nerve activation and decrease catecholamine secretion[24,25]. DEX has been proven to attenuate sympathetic nerve activation induced by pneumoperitoneum and surgical stress[26], and to decrease the inflammatory response[20] to facilitate postoperative bowel movements. Groups D1 and D2 had significantly shorter times to flatus and defecation in our study than group C. Although group D2 had shorter times to flatus and defecation than group D1, and the difference was not significant for patients in the clinic, the observed 1-h difference is still important. This study provided evidence for the relief of postoperative gastrointestinal function in patients undergoing endoscopic surgery.

Although opioids are a priority for postoperative pain, they are unfavorable because they inhibit gastrointestinal motility and aggravate POI[27-29]. The perioperative use of DEX has been previously reported to relieve postoperative pain and reduce the total

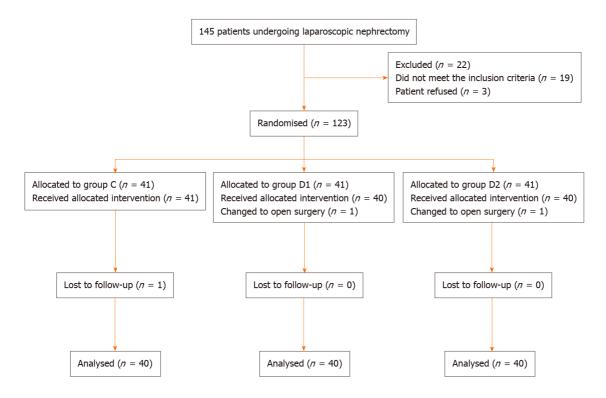


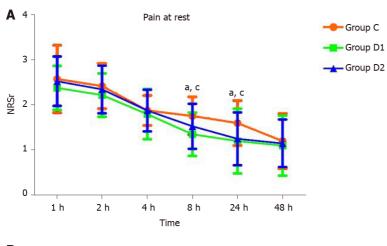
Figure 1 Patient enrolment flow diagram. This illustrates the flow of all patients screened, excluded, and randomized.

volume of opioids required[30,31]. The total volume of opioid drugs used in our study did not differ among the three groups, which may be due to a reduced level of postoperative pain experienced following laparoscopic surgery compared with that associated with open surgery. However, the use of DEX still significantly relieved postoperative pain with rest and movement at 8 h and 24 h after surgery in our study. Effective pain relief contributed to the alleviation of POI and allowed patients who received DEX to resume activity earlier postoperatively than those who did not. We hypothesized that DEX accelerated gastrointestinal function to relieve postoperative pain.

The blood vessels contracted when DEX was administered as a bolus, and hypertension was observed in the first 1-3 min. Hypertension has been observed but not measured in other studies, and when DEX was used as an infusion drug, its central sympatholytic effect was the main effect[32,33]. The incidence of bradycardia and hypotension (requiring treatment) was increased only when a loading and maintenance dose of DEX > 0.07 μ g/kg/h was given to critically ill patients[34]. The HR and MBP were significantly lower but without evidence of bradycardia and hypotension after treatment with the loading dose of DEX in our study. The infusion of DEX during anesthesia resulted in medium variations in MBP and HR among the three groups, but the difference was not significant. These findings are in accordance with those of previous reports[35,36]. There was no significant difference in HR and MBP among the three groups; therefore, the two doses of DEX used were both safe for the patients.

DEX produces sedation with minimal respiratory inhibition[37]. No respiratory inhibition was observed in the present study. There were no significant differences in easily arousable drowsiness, PONV, or postoperative delirium among the groups.

Our study had some limitations. First, DEX was administered at a rate of 0.5 mg/kg for 10 min before the induction of anesthesia and then at a rate of 0.2 to 0.4 µg/kg/h during the operation. However, we were unable to determine the effect of plasma DEX concentrations on intraoperative hemodynamics because we did not measure the serum concentrations of DEX at any time point. Finally, laparoscopic nephrectomy was performed using two different surgical methods: Transabdominal and retroperitoneal. Therefore, different surgical techniques might have had different effects on postoperative analgesia and recovery of gastrointestinal function.



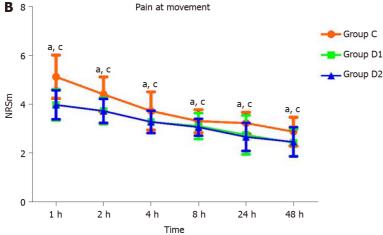


Figure 2 Pain scores during 48 h after surgery in groups C, D1, and D2. Variables are presented as the mean ± SD. The numerical rating scale scores at 8 h and 24 h were significantly lower in groups D1 and D2 than in group C at rest and at movement. *P < 0.05, group D1 vs group C; *P < 0.05, group D2 vs group C. NRS: Numerical rating scale.

CONCLUSION

Perioperative DEX infusion at 0.04 µg/kg/h resulted in better and faster recovery of gastrointestinal function and a more favorable analgesic effect without additional adverse effects in patients who underwent laparoscopic nephrectomy.

ARTICLE HIGHLIGHTS

Research background

Postoperative ileus (POI) is a perplexing problem for clinical surgeons. POI occurs not only after abdominal surgery, but also after any other surgery that requires general anesthesia.

Research motivation

Regarding enhanced recovery after surgery, postoperative gastrointestinal function recovery is of great concern. Currently, there is an urgent need to improve postoperative recovery of gastrointestinal function.

Research objectives

This study aimed to observe whether dexmedetomidine (DEX) promotes bowel movements in patients after laparoscopic nephrectomy

Research methods

A total of 120 patients who underwent laparoscopic nephrectomy were assigned into three groups: C (normal saline infusion), D1 (DEX 0.02 µg/kg/h), and D2 (DEX 0.04



 $\mu g/kg/h$).

Research results

Mean blood pressure (MBP) at T1 in groups D1 and D2 was significantly lower than that in group C. MBP was lower than the baseline at T2, T3, T4, and T5 in group C, and at T1 and T4 in groups D1 and D2.

Research conclusions

Perioperative DEX infusion at 0.04 µg/kg/h resulted in better and faster recovery of gastrointestinal function and a more favorable analgesic effect without additional adverse effects in patients who underwent laparoscopic nephrectomy.

Research perspectives

This study suggests a new method for postoperative intestinal function recovery.

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