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Research Article

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Effect of Low-Dose Dexmedetomidine on Intestinal Barrier and Functional Recovery in Elderly Patients Undergoing Orthopedic Surgery for Lower Limbs

Yin Xuejun*, Du Fuyang, Wang Mingzhu, Cheng Qinyun

Department of Anesthesiology, Eighth People's Hospital of Hefei (238000, Hefei, Anhui Province).

***Corresponding Author**
Yin Xuejun, Department of Anesthesiology, Eighth People's Hospital of Hefei (238000, Hefei, Anhui Province). E-mail:1814016899@qq.com

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Abstract

Objective: *This study used the minimum recommended clinical dose of dexmedetomidine to investigate whether it can protect the intestinal barrier and the effects on intestinal function recovery in elderly patients undergoing lower limb orthopedic surgery.*

Methods: *56 patients, who underwent elective lower limb orthopedic surgery in our hospital from November 1, 2019 to November 1, 2021, were divided into control group (saline group) and DEX group (dexmedetomidine group) by random numbers method. The DEX group received dexmedetomidine at 0.5 μg/kg, pumped within 15 min and then maintained at 0.1 μg/kg/h until 30 min before the skin suture. The control group performed the same procedure with normal saline instead. The primary outcomes included the time of first hepatic gate exhaust, serum diamine oxidase, and D-lactate levels. Secondary outcomes include total amount of sufentanil, mean arterial pressure, heart rate, duration of anesthesia, duration of surgery, tumor necrosis factor- α, C-reactive protein, lipopolysaccharide levels.*

Results: *The time of first anal exhaust in the DEX group was significantly shorter compared with the control group (13.23 ± 4.98 hours vs19.67±5.16 hours; p<0.001), and the total amount of sufentanyl in the DEX group was significantly lower than that in the control group (35.32±10.23ug vs 42.33±12.19ug; p=0.002). At 24 hours after surgery, serum diamine oxidase, tumor necrosis factor-α, and C-reactive protein levels increased in both groups, but no difference was statistically significant (p>0.05), and there was no significant difference in LPS levels in the two groups before and 24 hours after surgery (p>0.05). D-lactate was increased in both groups at 24 hours after surgery, but the D-lactate increased more in control patients than in the DEX group (36.17±14.69 mg/L vs 29.10±12.19 mg/L;p=0.017). Correlation analysis showed that diamine oxidase, D lactate, age, APACHE II score, total amount, and time to first anal discharge in the DEX group (p<0.05).*

Conclusion: *The intraoperative administration of dexmedetomidine can accelerate the recovery of gastrointestinal function, which may be related to the protective effect of DEx on the gastrointestinal barrier.*

Keywords: Low Dose Dexmedetomidine, Orthopedic Surgery for Lower Limbs, Elderly Patients, Gastrointestinal Barrier

Introduction

Intestinal epithelial tissue acts as a barrier to resist the invasion of pathogens, produces and secrete antimicrobial peptides, which plays an important role in maintaining physiological homeostasis. Many stress factors will destroy the intestinal barrier, disrupt the homeostasis of intestinal flora, destroy the immune function, and bacterial metabolites enter the blood and cause intestinal sepsis [1]. Multiple protein components that constitute the tight junctions of intestinal epithelial cells such as junctional adhesion molecule-1 are functionally altered and ultimately disrupt the integrity of the tight junctions [2,3]. Currently, serum levels of D-lactate acid (D-LAC) and diamine oxidase (DAO) are usually used as important reference indicators for the evaluation of intestinal barrier function [4].

Relative to younger patients, older patients often require lower doses of sedation to achieve the same level of sedation [5] as younger patients. Dexmedetomidine (DEX) is a α 2 adrenergic receptor agonist that acts on both the central and peripheral nervous systems, regulates autonomic activity, and produces dose-dependent sedative, hypnotic, and anxiolytic [6-8], with minimal [9] effects on hemodynamic and strong sedative effects. Therefore, the present study used the minimum recommended clinical dose of dexmedetomidine to investigate whether it could protect the intestinal barrier and the effect on intestinal function recovery in elderly patients undergoing lower limb orthopedic surgery.

Data and Methods

General Information

Fifty-six patients undergoing elective lower limb orthopedic surgery in our hospital from November 1,2019 to November 1,2021 were selected to collect their baseline conditions, including age, gender, BMI, APACHE II score, and surgical site, etc. Inclusion criteria: 1) patient age>60 years; 2) recent need only for lower limb orthopedic surgery; 3) patients with informed consent. Exclusion criteria: 1) patients with severe heart and lung insufficiency, liver and kidney insufficiency; 2) dementia and poor mental status; 3) preoperative use of opioids; 4) intestinal diseases (such as ulcerative colitis, Crohn's disease, etc.). Patients were divided into control group (saline group) and DEX group) with 28 patients.

Methods

A standardized anesthesia management protocol was administered between the respective groups. All patients were fasted for 12 hours before surgery. After entering the operating room, the patients were given oxygen by conventional nasal catheter, vital signs detection, and venous access was established. Specific anesthesia operation: lumbar anesthesia and epidural anesthesia, L3~L4 lumbar space puncture, 0.5% bupivacaine injection 1.5 ml, and 2% epidural cavity injection, and the anesthesia level was controlled below T10. The DEX group received preoperative dexmedetomidine at 0.5 μg/kg for 15 min and then maintained at 0.1μg/kg/h until 30 min before the skin suture. The control group performed the same procedure with normal saline instead. In both groups, 0.125% ropivacaine hydrochloride combined with 0.5 ug/ml sufentanil provided epidural analgesia, a background dose of 2 ml/h, a single dose of 2 ml/30 min, and the total amount of sufentanil at the first anal discharge was recorded.

Observed Indicators

The main observations included time to first anal exhaust, serum diamine oxidase, and D-lactate levels. Secondary observation measures included total amount of sufentanil, mean arterial pressure, heart rate, duration of anesthesia, duration of surgery, tumor necrosis factor-α, C-reactive protein, lipopolysaccharide levels. Treatment of blood: blood samples (3ml each) were taken from the peripheral veins before induction and 24 h after surgery. All blood samples that were not anticoagulated were centrifuged for 15 min at 3000 rpm, serum collected and frozen at 80°C. Serum diamine oxidase, D-lactate, c-reactive protein, tumor necrosis factor-A and lipopolysaccharide were detected by enzyme-linked immunosorbent method (Shanghai Hengyuan Biotechnology Co., Ltd.). All samples were analyzed at diluted concentrations within the range of the standard curve.

Statistical Methods

Statistical analysis was performed using the SPSS20.0 statistical software. Measurement data are expressed as mean ± standard deviation, compared using t-test and Man-Whitney test by U; count data are expressed as rate (%) and $\chi 2$ test. Correlations between variables were assessed using Pearson's correlation test or Spearman's correlation coefficient. $P<0.05$ indicates that the differences were statistically significant.

2 Results

Bascomparison Between the Two Groups

The mean age of patients in the control group was 67.25±9.23 years, with 16 males and 12 females; the mean age of patients in the DEX group was 68.11±8.76 years, with 17 males and 11 females. There was no statistical significance in age, gender, BMI, APACHE II score, mean arterial pressure (MAP), heart rate (HR), constipation (%), and surgical site ($p>0.05$), as detailed in Table 1.

	Control group (n=28)	Control group (n=28)	P value
Age (year)	67.25±9.23	68.11±8.76	0.911
Gender (male/female)	16/12	17/11	0.734
BMI (kg/m^2)	21.33±3.90	20.98±44.01	0.153
APACHE II score	10.86±2.97	10.02±3.14	0.316
MAP (mmHg)	98.56±9.32	99.21±10.27	0.913
HR (bpm)	73.12±7.69	75.18±8.74	0.551
Constipation (%)	2 (7.14%)	3 (10.71%)	0.286
Operative site	-	-	0.523
Transcervical fracture	15 (53.57%)	11(39.29%)	-
Intertrochanter fracture of femur	9 (32.14%)	14(50.00%)	-
Other	4 (14.29%)	3(10.71%)	-

Note: BMI: Body Mass Index; APACHE II score: Acute Physiology and Chronic Health Status score II; MAP: Mean Arterial Pressure; HR: Heart Rate.

Table 1: Comparison of the baseline condition between the DEX group and the control group.

Comparison of the Two Groups of Clinical Indicators

The time to first anal veneration was significantly shorter in the DEX group (13.23±4.98 h vs 19.67± 5.16 hours; p<0.001); and the total sufentanil use was significantly lower in the DEX group (35.32±10.23ug vs 42.33±12.1 9ug; p=0.002); also, the incidence of slow center movement (center rate was less than 50 beats/min) was higher than in the DEX group, but none was significant (21.43% vs 14.29%, p=0.059). The duration of anesthesia and duration of surgery were not significantly between the groups (p> 0.05) (Table 2).

	Control group (n=28)	DEX group (n=28)	Pvalue
Duration of anesthesia (min)	88.29±58.83	89.73±50.36	0.245
The duration of the operation (min)	69.25±47.31	64.37±49.16	0.376
During the operation HR < 50 (bpm)	4 (14.29%)	6 (21.43%)	0.059
Total amount of sufentanil used (ug)	42.33±12.19	35.32±10.23	0.002
Time of the first anal exhaust (h)	19.67±5.16	13.23±4.98	< 0.001

Note: MAP: Mean Arterial Pressure; HR: Heart Rate.

Table 2: Comparison of intraoperative or postoperative clinical indicators between DEX and control groups.

Comparison of Serum D-LAC and DAO Levels in the Two Groups

Before surgery, there was no statistically significant difference in serum D-lactate, diamine oxidase levels between both groups (p>0.05). At 24 hours after surgery, D-lactate increased in both groups, but D-lactate increased more in the control group than in the DEX group (36.17±14.69 mg/L vs 29.10±12.19 mg/L; p=0.017) (Table 3).

	Control group (n=28)	DEX group (n=28)	P value
D-LAC(mg/L)	-	-	-
Preoperative	11.92±6.94	12.13±7.32	0.870
Postoperative 24 h	36.17±14.69	29.10±12.19	0.017
DAO(U/L)	-	-	-
Preoperative	6.42±5.36	6.33±4.70	0.391
Postoperative 24 h	19.06±14.35	15.81±12.52	0.058

Note: D-LAC: D-Lactacid; DAO: Diamine Oxidase.

Table 3: Serum D-LAC and DAO levels between the two groups before and 24 hours after surgery.

Before surgery, there was no statistically significant difference in TNF- α and C-reactive protein levels in both groups (p>0.05); at 24 hours after surgery, TNF-α and C-reactive protein levels increased in both groups, but no difference was statistically significant (p>0.05) (Table 4). There was no significant difference in LPS levels either before or after 24 hours (p> 0.05) (Table 4).

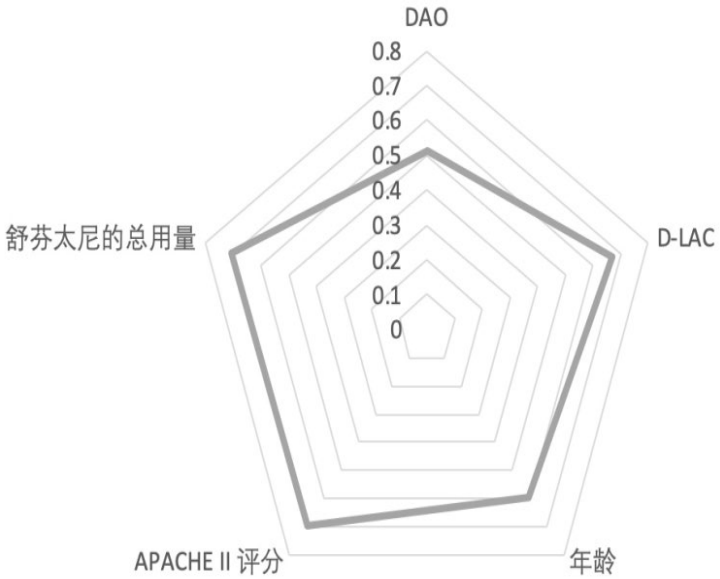
	Control group (n=28)	DEX group (n=28)	P value
TNF-a(ng/L)	-	-	-
Preoperative	13.96±9.37	16.98±12.17	0.914
postoperative24h	60.01±37.80	57.73±39.56	0.762
CRP(ng/L)	-	-	-
Preoperative	476±323	492±387	0.803
Postoperative 24h	13301±1890	12549±1973	0.457
LPS(EU/mL)	-	-	-
Preoperative	103.46±51.70	95.37±55.63	0.693
postoperative24h	94.25±53.86	88.67±48.15	0.135

Note: TNF-a: Tumor Necrosis Factor- α; CRP: C-Reactive Protein; LPS: Lipopolysaccharide.

Table 4: Comparison of laboratory indicators between the two groups before and 24 hours after surgery.

Index Related to the Intestinal Function Recovery of Patients in the DEX Group

The correlation between serum diamine oxidase, D lactate, tumor necrosis factor- α, C-reactive protein, lipopolysaccharide levels, age, gender, BMI, heart rate, surgical site, APACHE II score, total amount of sufentanil and time to first anal exhaust in the group of DEX showed that diamine oxidase, D lactate, age, APACHE II score, and total sufentanl were significantly positively associated with time to first anal exhaust gas ($p<0.05$; Figure 1).



Note: D-LAC: D-Lactic Acid; DAO: Diamine Oxidase.

Figure 1: Correlation between clinical and laboratory indicators and time of first anal exhaust in DEX group.

Discussion

Currently, the effect of dexmedetomidine on postoperative intestinal function is controversial, showing different effects on gastrointestinal function at different doses [10,11]. The mechanism of dexmedetomidine on gastrointestinal function is complex. On the one hand, it acts on the central A2 adrenaline receptors to promote peristaltic [10]; on the other hand, it can activate inhibitory 1 adrenoceptors located after the synapses of smooth muscle, or activate inhibitory 2 adrenoceptors on the excitatory cholinergic pathway to inhibit peristaltic [12]. Therefore this study used lower doses of dexmedetomidine to reduce side effects, ensure safety in elderly patients and still achieve facilitated gastrointestinal functional recovery. Our results showed that low-dose dexmedetomidine shortened the first anal exhaust time and accelerated the recovery of intestinal function. The analgesic and opioid sparing effects of dexmedetomidine are thought to be mediated with the CNS and spinal cord α2 adrenoceptors. [13], therefore, our results also show a significant positive correlation between the total amount of sufentanil used and the time to first anal discharge, suggesting that the opioid retention of dexmedetomidine may partially reduce opioid-induced intestinal motor inhibition and shorten the time to first anal discharge.

The gastrointestinal mucosa is vulnerable to injury, and although lower limb orthopedic surgery does not directly involve the gastrointestinal tract, there can be transient gastrointestinal dysfunction, including delayed defecation, abdominal distension, and even intestinal obstruction [14]. The myometrial of the gastrointestinal tract is filled with macrophages, and, when stimulated, many macrophages are released, further promoting the release of cytokines, prostaglandins, and other factors. Therefore, when mucosal injury occurs, these factors can cause local and systemic inflammatory responses, and even sepsis, leading to postoperative gastrointestinal dysfunction [15]. In recent years, more and more scholars have proposed that the intestine plays a vital role in the development of sepsis, and about 30% of sepsis patients who die from multiple organ dysfunction syndrome (MODS) can find bacterial [16-18] like intestinal bacteria in their blood cultures. The mechanism of injury may be abundant gastrointestinal mucosa and villous blood flow, sensitive to ischemia and hypoxia, and susceptible to hypoperfusion injury. When systemic circulating blood volume decreases by 10%, gastrointestinal blood perfusion decreases by about half. Long-term insufficient perfusion can cause oedema, villous degeneration and necrosis of intestinal mucosal cells, damaged or even loss of tight junctions between cells, and increased intestinal permeability. D-LAC is a metabolite of bacteria, present in the intestine, and may enter the blood when the intestinal mucosa is damaged and intestinal permeability increases, so serum D-LAC levels can reflect the degree of damage to the intestinal mucosal barrier and changes in intestinal permeability [19]. DAO, a highly active catalyst for the oxidation of diamines in the upper villi of the intestinal mucosa, is relatively stable under normal conditions and the serum DAO level increases when the intestinal permeability

is increased. Therefore, the serum DAO level can indirectly reflect the degree of intestinal mucosa damage [20]. Our study showed that serum D-LAC levels increased in both groups 24 hours after surgery, indicating that non-abdominal surgery also caused increased intestinal permeability, but D-LAC levels in the control group increased more significantly than in the DEX group, indicating that small doses of dexmedetomidine could significantly reduce intestinal permeability in elderly patients undergoing lower limb orthopedic surgery. In addition, although the change in serum DAO was not significantly different between the two groups, in the DEX group, diamine oxidase and D lactic acid and the first anal exhaust time showed a significant positive correlation, further indicating that the recovery of intestinal function in elderly patients undergoing low-dose dexmedetomidine was related to the intestinal barrier protection.

In conclusion, as a sedative, it has a protective effect on the intestinal barrier in elderly patients undergoing lower limb orthopedic surgery, and the intraoperative administration of small doses of dexmedetomidine can accelerate the recovery of intestinal function.

Infrastructure Project

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References

1. Sartelli M (2020) Evaluation and management of abdominal sepsis. CurrOpinCrit Care 26:205e211.
2. Yoseph BP, Klingensmith NJ, Liang Z, Breed ER, Burd EM, et al. (2016) Mechanisms ofintestinal barrier dysfunction in sepsis. Shock 46:52e59.
3. Bruewer M, Luegering A, Kucharzik T, Parkos CA, Madara JL, et al. (2003) Proinflammatory cytokines disrupt epithelial barrier function by apoptosisindependent mechanisms. J Immunol 171:6164e6172.
4. Qi YP, Ma WJ, Cao YY, Chen Q, Xu QC, et al. (2022) Effect of Dexmedetomidine on Intestinal Barrier in Patients Undergoing Gastrointestinal Surgery-A Single-Center Randomized Clinical Trial. J Surg Res 277:181-188.
5. Iirola T, Ihmsen H, Laitio R, Kentala E, Aantaa R, et al. (2012) Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients. Br J Anaesth 108:460-468.
6. Li CJ, Wang BJ, Mu DL, Hu J, Guo C, et al. (2020) Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. Br J Surg 107:e123ee132.
7. Nestor JE (2012) Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or Propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. Am J Respir Crit Care Med 186:1190.
8. Hu J, Zhu M, Gao Z, Zhao S, Feng X, et al. (2020) Dexmedetomidine for prevention of postoperative delirium in older adults undergoing oesophagectomy with total intravenous anaesthesia: a double-blind, randomised clinical trial. Eur J Anaesthesiol 38:S9eS17.
9. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, et al. (2019) Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 380:2506e2517.
10. Cho JS, Kim HI, Lee KY, An JY, Bai SJ, et al. (2015) Effect of intraoperative dexmedetomidine infusion on postoperative bowel movements in patients undergoing laparoscopic gastrectomy: a prospective, randomized, placebo-controlled study. Medicine 94 (24): e959.
11. Iirola T, Vilo S, Aantaa R,Wendelin-Saarenhovi M, Neuvonen PJ, et al. (2011) Dexmedetomidine inhibits gastric emptying and oro-caecal transit in healthy volunteers. Br J Anaesth 106(4): 522-527.
12. De Ponti F, Giaroni C, Cosentino M, Lecchini S, Frigo G (1996) Adrenergic mechanisms in the control of gastrointestinal motility: from basic science to clinical applications. Pharmacol Ther 69 (1):59-78.
13. Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR, et al. (2017) Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine.Clin Pharmacokinet 56(8): 893-913.
14. Li M, Wang T, Xiao W, Zhao L, Yao D (2019) Low-Dose Dexmedetomidine Accelerates Gastrointestinal Function Recovery in Patients Undergoing Lumbar Spinal Fusion. Front Pharmacol 10:1509.
15. Otani S, Coopersmith CM (2019) Gut integrity in critical illness. J Intensive Care 7:17.
16. Ross JT, Matthay MA, Harris HW (2018) Secondary peritonitis: principles of diagnosis and intervention. BMJ 361:k1407.
17. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, et al. (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:801e810.
18. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, et al. (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304e377.
19. Murray MJ, Barbose JJ, Cobb CF (1993) Serum D(-)-lactate levels as a predictor of acute intestinal ischemia in a rat model. J Surg Res 54:507e509.
20. Camilleri M (2019) Leaky gut: mechanisms, measurement andclinical implications in humans. Gut 68:1516e1526.