Effects of Dexmedetomidine on Perioperative Serum Potassium and Postoperative Rehabilitation of Patients Undergoing Radical Resection of Gastrointestinal Malignancy

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Abstract

Background: To investigate the effects of dexmedetomidine on perioperative potassium and postoperative rehabilitation.

Methods: Totally 124 patients scheduled for elective radical resection of gastrointestinal malignant tumor under general anesthesia were included. and randomly assigned to four groups (n=31): groups D₁, D₂ and D₃ received dexmedetomidine loading dose 1, 1 and 0.5 µg/kg and maintenance dose 0.25, 0.5 and 0.5 µg/kg/h, respectively, group C received normal saline 50 ml/h for 10 min and maintenance dose 10 ml/h. Serum potassium and lactate changes were recorded at 5 min after arteriovenous puncture (T₁), 1 h after surgery beginning (T₆), surgery ending (T₇) and 1 h into the post-anesthesia care unit (PACU) (T₁₀). Serum potassium was examined at 48 h after surgery (T₁₁). Perioperative rehabilitation indicators were recorded.

Results: Compared with basal values, serum potassium concentration in groups C, D₁ and D₂ increased significantly at T₁₁ ($P=0.003$, 0.002 , and 0.001 , respectively) and at T₇ ($P=0.008$), T₁₀ ($P=0.015$) and T₁₁ ($P=0.001$) in group D₃. Serum potassium at T₁₁ in group D₂ was significantly lower than group C ($P=0.032$). Serum potassium at T₇ in group D₃ was significantly higher than group D₂ ($P=0.036$). There were no significant differences in perioperative rehabilitation indicators in all groups.

Conclusions: Dexmedetomidine did not decrease perioperative potassium significantly in patients undergoing radical resection of gastrointestinal malignancy, while its loading dose 0.5 µg/kg and maintenance dose 0.5 µg/kg/h can elevate potassium slightly with no adverse effect on perioperative rehabilitation.

Trial registration: This study was retrospectively registered on the clinicaltrials.gov website (registration number: NCT04771637).

1 Introduction

Dexmedetomidine is a highly selective α_2 -adrenergic receptor agonist, which is often used in clinical anesthesia and intensive care unit due to its sedative, analgesic and sympathetic suppressing effects[1]. For radical gastrointestinal malignancy surgery with long operation time and heavy trauma, dexmedetomidine is often used during general anesthesia to blunt strong stress response. Patients with gastrointestinal malignant tumors often harbor several risk factors such as advanced age, poor nutritional state owing to appetite loss and combined underlying diseases[2], which, with prolonged preoperative fasting, are prone to inducing electrolyte disorders. While prolonged use of dexmedetomidine is associated with a risk of prolonging QT interval and causing the incidence of tip torsion ventricular tachycardia[3]. Perioperative hypokalemia might occur during gastrointestinal surgery and affect myocardial repolarization to increase the risk of tip torsion ventricular tachycardia[4]. When severe, potassium disorders can lead to life-threatening cardiac conduction disturbances and neuromuscular dysfunction[5]. It is still not clear whether prolonged use of dexmedetomidine during gastrointestinal malignancy radical resection could induce or exacerbate hypokalemia or not.

The primary aim of this prospective, randomized, doubled-blind study is to observe the effects of prolonged use of dexmedetomidine on electrolytes concentration and postoperative rehabilitation. The second aim is to

explore the optimal dose of dexmedetomidine with the least effect on serum potassium concentration in patients undergoing radical resection of gastrointestinal tumors.

2 Materials And Methods

This study was approved by the Ethics Committee of the Affiliated Hospital of Yangzhou University (ethics number: 2017-YKL11-01) and registered on the clinicaltrials.gov website (registration number: NCT04771637). After obtaining informed written consent for participation in the study, patients aged 55-75 years of age, body mass index (BMI) 18.5-25 kg/m² and American Society of Anesthesiologists status I-III of both genders underwent general anesthesia for elective radical resection of gastrointestinal malignancy with an estimated operation time longer than 3 hours were enrolled in this study between January 2017 and October 2020. Patients were not admitted to the study if any of the following criteria were present: severe sinus bradycardia (heart rate < 50 beats/min), pacemaker implantation, atrioventricular block, severe circulatory disturbance during operation, malignant arrhythmia, impairment of liver or kidney, preoperative severe internal environmental disorders such as hypokalemia (serum potassium level < 3.0 mmol/L), hyperkalemia (serum potassium level > 5.5 mmol/L), hyperlactatemia (blood lactate concentration > 2.0 mmol/L), intraoperative blood transfusion and postoperative need to be transferred to intensive care unit for further treatment.

2.1 Randomization and blinding

Eligible patients were randomly assigned to one of four groups according to a computer generated table of random numbers: groups D₁, D₂ and D₃ received dexmedetomidine loading dose 1, 1 and 0.5 µg/kg, which was infused intravenously for 10 min, and maintenance dose 0.25, 0.5 and 0.5 µg/kg/h, respectively, group C received normal saline 50 ml/h for 10 min and maintenance dose 10 ml/h. Dexmedetomidine and normal saline maintenance doses in the four groups were continued until approximately 30 min before surgery completion. The sealed opaque envelope technique was used for group allocation. A researcher not involved in the study implementation opened the envelopes. Patients, surgeons, and the outcome assessor were blinded to the technique used.

2.2 Anesthesia

None of the patients received preoperative medication. Routine monitoring including electrocardiograph (ECG), pulse oxygen saturation (SpO₂) and noninvasive blood pressure (NBP) were performed after patients entering the operating room. Narcotrend monitoring (MT MonitorTechnik GmbH&Co.KG, Germany) was used to monitor the depth of anesthesia. Ultrasound-guided right internal jugular vein puncture was performed under local anesthesia, and a double-lumen catheter was inserted to a depth of 12-13 cm. After that, a combination of 0.9 % sodium chloride solution and 6% hydroxyethyl starch solution 130/0.4 at a ratio of 1:2 was infused at a rate of 6-7 mL/kg/h. Patients with a normal result on the modified Allen's test were catheterized with radial artery puncture under local anesthesia to monitor invasive arterial pressure (IAP). Vital signs [mean blood pressure (MAP) and heart rate (HR)] were recorded 5 min after arteriovenous puncture. Groups D₁, D₂, and D₃ were given an intravenous injection of dexmedetomidine (18092931, 19012631, 19081331, Yangzijiang Pharmaceutical Co., Ltd.) with the loading dose for 10 min before general anesthesia induction and the maintenance dose until approximately 30 min before the end of surgery. Group C was given intravenous normal saline at a rate of 50 mL/h for 10 min, followed by continuous infusion at a rate of 10 mL/h until about 30 min

before the end of surgery. Dexmedetomidine or normal saline was prepared by the study personnel who did not participate in data collection, and the syringe pumped through the fourth channel of a syringe pump (CP-2100, Beijing Silugao Medical Technology Co., Ltd., China) was covered with a piece of opaque sheet.

General anesthesia induction was carried out with midazolam 0.05 mg/kg, sufentanil 4 µg/kg and propofol 1.5 mg/kg in all groups. Endotracheal intubation and mechanical ventilation were performed after sufficient muscle relaxation with cisatracurium 0.2 mg/kg. Mechanical ventilation was maintained with inhaled oxygen concentration 60%, tidal volume 6-8 mL/kg, ventilation frequency 12-14 times/min, and inspiration/expiration ratio 1:1.5 to maintain $P_{ET}CO_2$ at 35-45 mmHg. Temperature was maintained at 36°C-37°C. General anesthesia maintenance was implemented with intravenous propofol and remifentanil and inhaled sevoflurane 1 MAC in all groups. Muscle relaxation was maintained with cisatracurium infusion at $0.15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The doses of propofol and remifentanil were adjusted according to the Narcotrend monitoring, the stage of which was maintained between D2 to E1 (sedation index 20-46) throughout surgery in all groups. Train of four (TOF) monitoring was used to monitor the muscle relaxation during the surgery. When the changes of IAP or HR were >20% of basic levels, prepared vasoactive drugs including norepinephrine, ephedrine or atropine was used. Sevoflurane and cisatracurium were stopped at about 30 minutes before surgery ending, and propofol and remifentanil were continued until the end of surgery. Residual neuromuscular blockade was antagonized at TOF ratio more than 0.75 with intravenous neostigmine 0.04-0.07 mg/kg and atropine 0.01-0.02 mg/kg. Patients were extubated when achieved extubation conditions and transferred to PACU thereafter.

2.3 Outcome variables

MAP and HR were recorded at 5 min after artery puncture (T_1), dexmedetomidine loading dose finish (T_2), surgery beginning (T_3), 5 min (T_4), 10 min (T_5) and 1 h (T_6) after surgery beginning, surgery ending (T_7), extubation (T_8), 5 min after extubation (T_9) and 1 hour after into PACU (T_{10}). Serum potassium and lactic acid were recorded at T_1 , T_6 , T_7 and T_{10} . Serum potassium was also examined at 24 h postoperatively (T_{11}). Liver and kidney function, intraperitoneal drainage volume at 24 h postoperatively, length of hospital stay and postoperative complications such as pulmonary infection were also recorded.

2.4 Statistical analysis

The necessary sample size was calculated using PASS 15.0 (NCSS LLC., USA). The sample size calculation was based on the primary endpoint of this study, serum potassium concentration. Based on our pilot study, serum potassium concentrations in patients treated with dexmedetomidine infusion were found to have an average increase of 0.24 mmol/L with a standard deviation of 0.36 mmol/L. Consequently, enrollment of 25 patients in each group would obtain a power of 80% ($\beta=0.2$) at a significant level of 0.05 ($\alpha=0.05$, two-tailed). Considering study withdrawals or protocol violation, recruitment of 30 in each group was determined.

Statistical analysis was done using SPSS 25.0 (SPSS Inc., USA). Parametric data were expressed in means $\pm$ standard deviation (SD), and Student's t test was used for analyses. Nominal variables were compared using chi-square test. Changes in mean blood pressure and heart rate among groups were analyzed by repeated measures ANOVA. $P<0.05$ was considered significant.

3 Results

A total of 140 patients were assessed for eligibility, and 124 subjects were enrolled in the study. The remaining 16 patients were excluded because either they did not meet the inclusion criteria ($n=10$) or they refused to participate ($n=6$). Thirty-one patients were allocated to each group. Due to protocol violation, 1 patient was excluded from group D₂. Therefore, 31 patients in group D₁, 30 patients in group D₂, 31 patients in group D₃, and 31 patients in group C were analyzed (Figure 1).

There were no significant differences of the demographics among the four groups (Table 1). Compared with group C, urine volume increased significantly in groups D₂ and D₃ ($P=0.004$ and 0.039 , respectively), while other intraoperative data were similar among the four groups (Table 2).

3.1 Potassium and lactate

Compared with the basic serum potassium values, the concentrations at T₁₁ increased significantly in groups D₁, D₂ and C ($P=0.003$, 0.002 , and 0.001 , respectively), while increased significantly at T₇ ($P=0.008$), T₁₀ ($P=0.015$) and T₁₁ ($P=0.001$) in group D₃. Compared with group C, the serum potassium concentration in group D₂ decreased significantly at T₁₁ ($P=0.032$). Compared with group D₂, the serum potassium concentration in group D₃ increased significantly at T₇ ($P=0.036$).

Compared with the basic serum lactate values, the concentrations decreased significantly at T₆ in groups D₂ and D₃ ($P=0.002$ and 0.003 , respectively). Compared with group D₂, the serum lactate concentrations in group D₃ decreased significantly at T₁₀ ($P=0.033$) (Table 3).

3.2 Hemodynamic results

Repeated-measures analysis of variance revealed significant variation in HR and MAP over time within each group (Table 4, 5).

Compared with T₁, HR decreased significantly at T₂ ($P=0.002$), T₃ ($P=0.001$), T₄ ($P=0.001$), T₅ ($P=0.001$), T₆ ($P=0.003$) and T₇ ($P=0.033$) in group D₁, at T₃ ($P=0.001$), T₄ ($P=0.001$), T₅ ($P=0.001$), T₆ ($P=0.001$), T₇ ($P=0.001$), T₈ ($P=0.030$), T₉ ($P=0.037$) and T₁₀ ($P=0.001$) in group D₂, at T₂ ($P=0.025$), T₃ ($P=0.001$), T₄ ($P=0.001$), T₅ ($P=0.001$), T₆ ($P=0.001$), T₇ ($P=0.001$), T₈ ($P=0.024$), T₉ ($P=0.022$) and T₁₀ ($P=0.001$) in group D₃, and at T₄ ($P=0.023$) in group C. Compared with group C, HR decreased significantly in group D₂ at T₅ ($P=0.010$), T₇ ($P=0.017$), T₈ ($P=0.005$), T₉ ($P=0.030$) and T₁₀ ($P=0.011$) and in group D₃ at T₅ ($P=0.042$), T₇ ($P=0.002$), T₈ ($P=0.007$), T₉ ($P=0.034$) and T₁₀ ($P=0.019$).

Compared with T₁, MAP at T₄ ($P=0.002$), T₅ ($P=0.007$), T₆ ($P=0.001$), T₇ ($P=0.001$), T₈ ($P=0.047$) and T₉ ($P=0.048$) decreased significantly in group D₁, at T₁₀ ($P=0.029$) in group D₂, and at T₆ ($P=0.006$) and T₁₀ ($P=0.002$) in group D₃, while decreased significantly at T₃ ($P=0.007$) and T₆ ($P=0.002$) and increased significantly at T₈ ($P=0.015$) in group C. Compared with group C, MAP increased significantly at T₂ ($P=0.040$) and decreased significantly at T₅ ($P=0.045$), T₇ ($P=0.018$), T₈ ($P=0.001$) and T₉ ($P=0.030$) in group D₁, decreased significantly at T₈ ($P=0.002$), T₉ ($P=0.049$) and T₁₀ ($P=0.037$) in group D₂, and at T₈ ($P=0.033$) and T₉ ($P=0.013$) in group D₃.

3.3 Perioperative drug use

Significantly, less dosage of propofol was required ($P=0.011$) in group D₂ as compared to Group C. Again, dose of remifentanyl was significantly lower in groups D₁, D₂ and D₃ ($P=0.039$, 0.004 and 0.042 , respectively) than group C. More patients in group C received ephedrine to treat intraoperative hypotension ($P=0.048$) than the other groups.

3.4 Postoperative recovery indicators

The activity of plasma alanine aminotransferase (ALT) was significantly higher at T₁₁ than T₁ in all groups ($P=0.030$, 0.001 , 0.005 and 0.011 in groups D₁, D₂, D₃ and C, respectively), and plasma aspartate aminotransferase (AST) activities increased significantly at T₁₁ than T₁ in groups D₂, D₃ and C ($P=0.037$, 0.034 and 0.031 , respectively). There was no significant difference in serum creatinine. Additionally, patients in group D₁ had significantly higher blood urea nitrogen at T₁₁ than T₁ ($P=0.014$) (Table 6). There were no significant differences in length of hospital stay, intraperitoneal drainage volume and pulmonary infection incidence at 24 h postoperatively among the four groups.

4 Discussion

The results of this prospective double-blind randomized study suggest that dexmedetomidine loading dose $0.5 \mu\text{g/kg}$ and maintenance dose $0.5 \mu\text{g/kg/h}$ could increase serum potassium concentration slightly during perioperative period.

The incidence of hypokalemia resulted from dexmedetomidine when administered for long-term sedation in the intensive care unit setting was reported to be more than 2% in adult[6] and more than 9% in newborns[7], the mechanism of which is still uncertain. Görges et al.[4] reported that potassium levels were depressed relative to baseline at 15 min and 30 min after intravenous injection of dexmedetomidine as a bolus administered over 60 seconds after general anesthesia induction. However, different from the results of the previous studies, dexmedetomidine did not produce a decreased effect on potassium levels in our study. We found an increase in serum potassium concentration at surgery ending, 5 min after extubation and 24 h postoperatively. when dexmedetomidine loading dose $0.5 \mu\text{g/kg}$ and maintenance dose $0.5 \mu\text{g/kg/h}$ was used. The mechanism by which dexmedetomidine causes a mild increase in serum potassium is still unclear.

Catecholamine-induced vasoconstriction results in peripheral tissue ischemia, which causes anaerobic metabolism and lactate production in peripheral tissue[8]. Dexmedetomidine can reduce the sympathetic nervous system activity and is useful in diminishing catecholamine release through its anti-sympatholytic properties[9]. Therefore, dexmedetomidine may alleviate excessive catecholamine-induced lactate overproduction[10, 11]. A previous study reported the impact of dexmedetomidine on tourniquet-induced systemic effects in total knee arthroplasty, in which lactic acid concentration was significantly lower in the dexmedetomidine group compared with the control group at 10 min after tourniquet release. The authors concluded that the reduced serum lactate level might be related to the reduction of tourniquet-induced pain and hemodynamic fluctuations, as well as the regulation of metabolism and coagulation induced from dexmedetomidine. Another study suggested that dexmedetomidine may ameliorate liver damage and decrease lactate level[12]. In the current study, serum lactate level was significantly lower in groups D₂ and D₃ at 1 h after

surgery beginning compared with the basic value, suggesting that dexmedetomidine loading dose 0.5 µg/kg or 1 µg/kg and maintenance dose 0.5 µg/kg/h might exert certain improvement effects on microcirculatory perfusion.

A transient increase in blood pressure in a short period of time after dexmedetomidine use may be associated with its direct activation on α_2 -adrenergic receptors on vascular smooth muscle cells and leading to vasoconstriction, after which blood pressure drops with dexmedetomidine acting on the locus ceruleus, inhibiting the sympathetic nervous system excitation and also increasing the vagal excitability[13, 14]. In the current study, it is noteworthy that MAP was significantly higher in group D₁ after dexmedetomidine loading dose finish compared to the control group, whereas there were no significant changes in MAP in group D₂ at this timepoint, which may be related to the higher basic MAP in the group D₁ than group D₂. Dexmedetomidine loading dose administration caused further vasoconstriction, resulting in an increase of MAP. MAP and HR in dexmedetomidine groups were significantly lower than those in the control group at several time points during operation, at extubation and at 1 hour after into PACU, which might be related to the inhibitory effect of dexmedetomidine on sympathetic nerve.

The antinociceptive effects of dexmedetomidine occurs at dorsal root neuron level, where it blocks the release of substance P in the nociceptive pathway and through action on inhibitory G protein[15, 16]. We found that remifentanyl dosage in each dexmedetomidine group was significantly lower than that in the control group, which might be related to its analgesic effect.

Dexmedetomidine inhibits arginine vasopressin release from the isolated hypothalamic paraventricular nucleus and paraventricular magnocellular neurons and thus producing a diuretic effect[17-19]. As reported in the current study, the urine volume in groups D₂ and D₃ was significantly higher than that in group C. While there were no significant changes in the urine volume in group D₁, which indicating that lower dose of dexmedetomidine might have no obvious diuretic effect. Though the blood urea nitrogen 24 h postoperatively in group D₁ was significantly higher than that before surgery, it was still in normal range, and the renal function in the other groups did not change significantly. Previous studies by Jiang et al.[20] have confirmed that dexmedetomidine has a protective effect on the liver. The activity of ALT and AST increased at 24 h postoperatively, which might be related to the decrease of the activity of digestive enzymes in combination with the decrease of nutrient digestibility due to the changes on the intestinal environment. While the ALT and AST levels were all in normal ranges. Additionally, there were no significant differences in length of hospital stay, intraperitoneal drainage volume and pulmonary infection incidence 24 h postoperatively among the four groups, which may be related to the modes of operation, the antibiotic treatment and standard procedure of the hospital.

There are still some shortcomings in this study. First, only patients undergoing radical resection of gastrointestinal malignant tumors were included in this study, whether the results are applicable to patients with other types of surgery still needs further study. Second, the three dosages of the dexmedetomidine were selected based on our previous studies reported in the literature. The optimal intra-operative dose of dexmedetomidine remain to be determined, and a further study is needed. Third, perioperative infusion of 0.9% sodium chloride solution may have a certain impact on electrolyte determination. Finally, randomized controlled trials of large samples and multicenter studies are needed to provide reliable evidence for the use of dexmedetomidine.

In summary, dexmedetomidine loading dose 0.5 µg/kg and maintenance dose 0.5 µg/kg/h can elevate serum potassium concentration slightly, reduce lactic acid and remifentanyl use significantly, relieve perioperative hemodynamic fluctuations, and have no adverse effect on postoperative rehabilitation in patients undergoing radical resection of gastrointestinal malignancy.

Abbreviations

Electrocardiograph (ECG), Pulse oxygen saturation (SpO₂), Noninvasive blood pressure (NBP), Mean blood pressure (MAP), Heart rate (HR), Invasive arterial pressure (IAP), Body mass index (BMI), Post-anesthesia care unit (PACU), Train of four (TOF), Alanine aminotransferase (ALT): Aspartate aminotransferase (AST), Standard deviation (SD).

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of the Affiliated Hospital of Yangzhou University (ethics number: 2017-YKL11-01) and registered on the clinicaltrials.gov website (registration number: NCT04771637)

Consent for publication: Not applicable.

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Competing interests: The authors certify that there was no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions: Zhang Zhuan designed the study, drafted and wrote the manuscript. Shunping Tian, Dongsheng Zhang, Ying Wang and Leyang Yu implemented the trial and contributed samples collection. Shinting Yan and Wei Zhou prepared drugs. Ning Li and Yanlong Yu collected the data and did statistical analysis. All authors reviewed the manuscript.

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Tables

Table 1 Patient demographic data

	Group D ₁	Group D ₂	Group D ₃	Group C	<i>P</i>
Age (years)	66.4±8.6	64.6±9.2	66.8±10.1	67.5±8.5	0.822
Gender (Male/Female)	14/17	14/16	16/15	12/19	0.566
Height (cm)	163.4±5.4	166.9±6.5	163.6±7.0	167.5±6.8	0.147
Weight (kg)	62.9±8.2	58.5±18.0	62.3±5.5	62.6±8.4	0.958
BMI (kg/m ²)	23.5±2.5	21.9±3.5	23.4±2.9	22.3±2.3	0.248
ASA grade (I/II/III)	5/18/8	9/18/3	7/17/7	7/20/4	0.611

Data are expressed as mean ± SD or number. BMI: body mass index. ASA: American Society of Anesthesiologists.

Table 2 Patient intraoperative data

	Group D ₁	Group D ₂	Group D ₃	Group C	<i>P</i>
Type of surgery (A/B)	13/18	12/18	10/21	11/20	0.661
Mode of operation (A'/B')	10/21	9/21	10/21	8/23	0.721
Operation time (min)	223.2±41.9	227.6±41.9	231.3±61.5	225.8±37.6	0.980
Anesthesia time (min)	282.8±79.9	291.8±73.0	291.6±39.7	286.9±36.9	0.952
Extubation time (min)	14.7±7.6	14.4±10.1	12.2±6.2	9.9±3.9	0.251
Total liquid volume (mL)	2300.0±313.8	2323.5±393.0	2362.5±453.7	2263.2±305.9	0.155
Urine volume (mL)	642.9±361.0	797.1±376.0	706.3±321.4	476.3±225.1	0.030
Bleeding volume (mL)	101.4±68.7	116.5±68.8	176.9±179.1	110.5±83.7	0.210

Data are expressed as mean ± SD or number. A: Radical resection for gastric tumor, B: Radical resection of colorectal tumor, A': Laparotomy, B': Laparoscopic surgery.

Table 3 Changes of potassium level and Lactate level in the four groups at different time points

		Group D ₁	Group D ₂	Group D ₃	Group C	P_a	P_b	P_c	P_d
Potassium level	T ₁	3.67±0.30	3.65±0.40	3.71±0.31	3.79±0.35	0.338	0.243	0.516	0.639
	T ₆	3.71±0.39	3.70±0.36	3.87±0.43	3.82±0.43	0.700	0.294	0.911	0.226
	T ₇	3.75±0.46	3.67±0.44	4.04±0.53	3.89±0.50	0.421	0.169	0.386	0.036
	T ₁₀	3.84±0.27	3.71±0.20	3.96±0.48	3.80±0.28	0.977	0.116	0.897	0.056
	T ₁₁	4.07±0.26	4.03±0.25	4.21±0.41	4.25±0.30	0.088	0.032	0.629	0.109
	P_{T1-6}	0.620	0.601	0.056	0.431				
	P_{T1-7}	0.470	0.902	0.008	0.180				
	P_{T1-10}	0.077	0.225	0.015	0.854				
	P_{T1-11}	0.003	0.002	0.001	0.001				
Lactate level	T ₁	0.84±0.30	1.06±0.31	0.86±0.26	0.82±0.44	0.497	0.246	0.600	0.052
	T ₆	0.74±0.29	0.76±0.36	0.71±0.28	0.78±0.35	0.860	0.901	0.785	0.693
	T ₇	0.78±0.42	1.01±0.45	0.83±0.32	0.80±0.29	0.949	0.055	0.724	0.136
	T ₁₀	1.02±0.61	1.13±0.53	0.81±0.27	0.94±0.37	0.639	0.493	0.176	0.033
	P_{T1-6}	0.248	0.002	0.003	0.133				
	P_{T1-7}	0.251	0.799	0.599	0.559				
	P_{T1-10}	0.739	0.579	0.338	0.153				

Data are expressed as mean ± SD. P_a , P_b and P_c for comparison between group C and groups D₁, D₂ and D₃, respectively. P_d for comparison between Groups D₂ and D₃.

Table 4 Perioperative changes of heart rate

	Group D ₁	Group D ₂	Group D ₃	Group C	<i>P_a</i>	<i>P_b</i>	<i>P_c</i>	<i>P_d</i>
T ₁	73.0±11.6	72.4±10.5	72.9±7.8	70.5±13.0	0.515	0.609	0.510	0.229
T ₂	65.5±8.8	69.2±16.3	67.3±8.8	71.1±14.3	0.217	0.652	0.377	0.679
T ₃	61.7±10.0	59.6±9.7	59.4±11.2	65.8±14.2	0.321	0.113	0.110	0.967
T ₄	61.9±9.9	58.8±9.8	61.0±7.3	63.8±12.8	0.599	0.149	0.419	0.477
T ₅	62.4±9.0	57.9±8.0	59.9±8.4	67.6±15.5	0.187	0.010	0.042	0.490
T ₆	61.3±7.5	59.8±5.3	58.9±7.8	64.0±20.5	0.540	0.314	0.231	0.702
T ₇	66.4±8.9	62.2±7.4	59.8±7.3	69.8±12.4	0.305	0.017	0.002	0.350
T ₈	70.1±8.6	66.4±9.4	66.6±10.4	76.1±11.1	0.094	0.005	0.007	0.965
T ₉	70.9±10.3	67.2±10.3	67.3±10.5	75.2±11.4	0.257	0.030	0.034	0.983
T ₁₀	71.4±8.5	62.6±8.9	63.2±9.9	71.6±12.6	0.904	0.011	0.019	0.856
<i>P_{T1-2}</i>	0.002	0.321	0.025	0.799				
<i>P_{T1-3}</i>	0.001	0.001	0.001	0.091				
<i>P_{T1-4}</i>	0.001	0.001	0.001	0.023				
<i>P_{T1-5}</i>	0.001	0.001	0.001	0.416				
<i>P_{T1-6}</i>	0.003	0.001	0.001	0.177				
<i>P_{T1-7}</i>	0.033	0.001	0.001	0.876				
<i>P_{T1-8}</i>	0.484	0.030	0.024	0.148				
<i>P_{T1-9}</i>	0.603	0.037	0.022	0.143				
<i>P_{T1-10}</i>	0.545	0.001	0.001	0.650				

Data are expressed as mean ± SD. *P_a*, *P_b* and *P_c* for comparison between group C and groups D₁, D₂ and D₃, respectively. *P_d* for comparison between Groups D₂ and D₃.

Table 5 Perioperative changes of mean arterial pressure

	Group D ₁	Group D ₂	Group D ₃	Group C	<i>P</i> _a	<i>P</i> _b	<i>P</i> _c	<i>P</i> _d
T ₁	104.7±14.8	98.4±12.1	100.3±10.4	100.5±14.1	0.465	0.625	0.961	0.633
T ₂	103.5±14.2	97.1±11.5	97.3±11.1	95.2±13.4	0.040	0.641	0.614	0.965
T ₃	97.9±15.2	96.5±17.0	92.8±11.7	90.8±15.0	0.162	0.253	0.697	0.472
T ₄	89.5±12.3	97.4±16.1	92.3±11.4	98.6±15.4	0.083	0.804	0.781	0.974
T ₅	91.9±11.8	99.3±11.3	97.8±15.0	102.1±13.8	0.045	0.530	0.343	0.750
T ₆	87.0±14.1	92.1±13.4	88.9±10.4	88.2±14.8	0.913	0.375	0.874	0.445
T ₇	86.1±17.3	92.4±14.8	92.4±13.8	99.8±16.7	0.018	0.157	0.169	0.987
T ₈	95.4±12.5	96.2±15.9	100.9±11.3	111.9±17.7	0.001	0.002	0.033	0.338
T ₉	94.7±11.7	96.1±16.5	100.6±13.1	106.8±20.3	0.030	0.049	0.258	0.386
T ₁₀	97.3±11.8	90.8±14.0	88.8±10.2	99.5±12.4	0.448	0.037	0.013	0.437
<i>P</i> _{T1-2}	0.678	0.553	0.136	0.236				
<i>P</i> _{T1-3}	0.051	0.664	0.054	0.007				
<i>P</i> _{T1-4}	0.002	0.817	0.351	0.585				
<i>P</i> _{T1-5}	0.007	0.799	0.558	0.706				
<i>P</i> _{T1-6}	0.001	0.125	0.006	0.002				
<i>P</i> _{T1-7}	0.001	0.139	0.145	0.880				
<i>P</i> _{T1-8}	0.047	0.550	0.867	0.015				
<i>P</i> _{T1-9}	0.048	0.543	0.951	0.215				
<i>P</i> _{T1-10}	0.132	0.029	0.002	0.750				

Data are expressed as mean ± SD. *P*_a, *P*_b and *P*_c for comparison between group C and groups D₁, D₂ and D₃, respectively. *P*_d for comparison between Groups D₂ and D₃.

Table 6 Changes of liver and kidney function in four groups

		Group D ₁	Group D ₂	Group D ₃	Group C
ALT (U/L)	T ₁	15.4±7.7	17.7±9.9	22.8±22.5	15.3±8.2
	T ₁₁	44.0±42.7	28.7±8.6	48.1±40.0	49.3±51.3
	<i>P</i>	0.030	0.001	0.005	0.011
AST (U/L)	T ₁	18.8±3.3	21.3±6.5	24.3±15.2	18.5±5.84
	T ₁₁	45.1±52.7	25.4±8.7	46.1±35.6	47.4±51.3
	<i>P</i>	0.081	0.037	0.034	0.031
Serum creatinine (μmol/L)	T ₁	64.0±11.3	64.1±10.6	67.5±15.3	70.5±15.1
	T ₁₁	58.4±10.8	65.3±9.4	64.6±13.7	69.7±13.1
	<i>P</i>	0.052	0.565	0.479	0.069
Blood urea nitrogen (mmol/L)	T ₁	5.9±1.6	5.1±1.5	5.5±3.4	4.9±2.3
	T ₁₁	4.8±1.6	4.7±1.8	4.9±1.3	4.8±2.2
	<i>P</i>	0.014	0.361	0.529	0.940

Data are expressed as mean ± SD. ALT: alanine aminotransferase. AST: aspartate aminotransferase.

Figures

Figure 1

Consort flow diagram for the study.