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Effects of esketamine-based opioid-sparing anesthesia protocol in Bama miniature pigs undergoing robot-assisted nephrectomy

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The safety and efficacy of the esketamine-based opioid-sparing anesthesia protocol, though validated, are understudied in robotic surgeries. This study used robot-assisted nephrectomy in Bama miniature pigs to explore its application. Six healthy Bama miniature pigs were randomly assigned to esketamine group (K) and control group (C). In Group K, based on the anesthetics of Group C, 0.5 mg/kg esketamine was used for anesthesia induction, and anesthesia was maintained with 0.5 mg/kg·h esketamine. Results showed Group K exhibited more stable hemodynamics intraoperatively, particularly at 5 min after the start of surgery and at the time of extubation ($p < 0.05$). Dosages of propofol (250 ± 8.7 mg vs. 347 ± 6.1 mg), sufentanil (12.3 ± 0.6 μg vs. 25 ± 1.0 μg) and remifentanil (498.3 ± 27.5 μg vs. 828.3 ± 20.2 μg) in group K were significantly reduced($p < 0.001$). Recovery times for eyelid reflex (22.0 ± 2.0 min vs. 28.0 ± 2.6 min), extubation (24.7 ± 2.5 min vs. 32.3 ± 2.5 min), and righting reflex (37.7 ± 2.5 min vs. 48.7 ± 5.5 min) were significantly shorter in group K ($p < 0.05$). In conclusion, the esketamine-based opioid-sparing anesthesia protocol can be safely and effectively used in Bama miniature pigs undergoing robot-assisted nephrectomy.

Keywords Esketamine, Bama mini-pig, Nephrectomy, Micro hand S surgical robot

With advancements in science and technology, minimally invasive surgery has garnered significant attention as the primary surgical approach[1]. Robot-assisted laparoscopic surgery results in minimal trauma and shorter postoperative recovery period compared to the traditional laparoscopic surgery, therefore it is the most preferred surgical procedure[2,3]. Currently, numerous effective robotic surgical systems have been developed, including the prominent Da Vinci Surgical System[4,5]. Another system is the Chinese surgical robot Micro Hand S system (model: WG-NST600T) developed in 2021 by Shandong Weigao Group in China and approved by the National Medical Products Administration (NMPA)[6–9]. Previous studies have shown that compared to the Da Vinci surgical robot, the Micro Hand S exhibits no significant adverse effects except for its longer installation time[10,11].

In recent years, the utilization rate of esketamine-based opioid-sparing anesthesia protocols in clinical practice has significantly increased[12]. Esketamine, a dextrorotatory isomer of ketamine, exhibits analgesic and hypnotic effects that are approximately twice as potent as those of ketamine, requiring only half the dosage to achieve equivalent therapeutic outcomes. Additionally, esketamine exhibits a faster elimination, resulting in quicker recovery from anesthesia, mild adverse reactions on the nervous system, and minimal respiratory tract secretions[13]. Furthermore, the use of esketamine has significantly reduced postoperative adverse reactions and improved the quality of recovery[14]. However, esketamine remain infrequently used in general anesthesia for animal trails.

Urology is among the fields to adopt the use of robots in surgeries, especially during the early phases of the technology[15]. Subsequently, the application of robotic surgeries is in a relatively mature stage in urology[16]. Therefore, this study aims to investigate the safety and efficacy of the esketamine-based opioid-sparing anesthesia protocols in Bama mini-pigs undergoing Chinese Micro Hand S surgical robot-assisted nephrectomy.

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Methods

Study design and animals

This was a prospective, blinded, randomized clinical animal trial conducted between December 2023 and June 2024. Six male Bama mini-pigs were obtained from the animals' laboratory of Weihai Desheng Technology Testing Co., Ltd. (ShangDong, China). The study was approved by the Animal Ethics Committee of Weihai Desheng Technology Testing Co., Ltd. (Approval No. 2023-002). All experimental procedures were performed in strict accordance with the ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments), the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the Chinese Regulations on the Management of Laboratory Animals[17]. Post-operatively, miniature pigs were euthanized via intravenous administration of sodium pentobarbital (100 mg/kg) in accordance with the AVMA Guidelines for the Euthanasia of Animals. All remains were handled following institutional biosafety protocols.

The study subjects were Chinese Bama mini-pigs of an average age of 4–6 months and a body weight of 20–25 kg. Before the test, the experimental animal center confirmed that the mini-pigs were free of parasitic infections and exhibited normal health status and reflexes. The animals underwent a one-week acclimatization period under the same environmental and husbandry conditions. Before the experiments, the whole bodies of the mini-pigs were cleaned and then they were fasted for 12 h and subsequently deprived of water for 4 h. Preoperative preparation included skin preparation at surgical site. All miniature pigs underwent nephrectomy under general anesthesia assisted by the Micro Hand S surgical robot.

The random number table method was used to assign the mini pigs into two groups: the esketamine (Group K, $n = 3$) and control (Group C, $n = 3$). The group K was anesthetized using esketamine combined with conventional agents for both induction and maintenance, whereas the group C was anesthetized solely using conventional agents for both phases. Individuals who conducted data collection and result assessments were independent of the anesthesiologists who administered the drugs during the operation; that is, the data collectors and assessors were blinded of the drug regimens assigned to the two groups.

The main instruments used in this experiment included the Micro Hand S surgical robot (model: WG-NST600T, Shandong Weigao Group, China), the Intelli Vue MP30 monitor (Philips, Germany), and conventional surgical instruments. The drugs used were esketamine (2 ml: 50 mg, Jiangsu Hengrui Pharmaceutical Co., Ltd.), propofol (20 ml: 200 mg, Yangtze River Jiangsu Pharmaceutical Co., Ltd.), sufentanil (1 ml: 50 μg, Yichang Renfu Pharmaceutical Co., Ltd.), remifentanil (2 mg, Yichang Renfu Pharmaceutical Co., Ltd.), cisatracurium (5 ml: 10 mg, Jiangsu Hengrui Pharmaceutical Co., Ltd.), and midazolam (2 ml: 10 mg, Jiangsu Enhua Pharmaceutical Co., Ltd.).

Anesthesia and surgery

Before anesthesia, the electronic sphygmomanometer cuff was positioned on the internal femoral artery of the hind leg of the miniature pig, ensuring that it was at the same level as the heart. The blood pressure and heart rate of the mini-pigs were measured twice and the average value recorded. The mini-pigs in both groups received intramuscular injection of atropine 0.05 mg/kg and midazolam 0.1 mg/kg 30 min before intravenous anesthesia administration, and then the pigs were positioned on the operating table. The body temperatures of mini-pigs were monitored during the surgery, with a warming blanket used to maintain their temperatures to avoid hypothermia. After exposing the posterior auricular vein of the mini-pigs, they were ready to receive anesthesia induction. In group K, anesthesia induction was performed using propofol 2 mg/kg, esketamine 0.5 mg/kg, sufentanil 0.5 μg/kg, and cisatracurium besylate 0.2 mg/kg, whereas in group C, propofol 2 mg/kg, sufentanil 1 μg/kg, and cisatracurium besylate 0.2 mg/kg were used[18]. A 5.0 endotracheal tube was used for tracheal intubation to establish an artificial airway, with the endotracheal tube connected to a ventilator to provided assisted ventilation. The ventilation mode was volume-controlled: tidal volume 8–10 mL/kg, respiratory rate 15–20 breaths/min, positive end-expiratory pressure 0 mmHg, and fraction of inspired oxygen 40%. After anesthesia induction, the surgical site was disinfected. Urologists incised the right groin of the mini-pig, opened the right femoral vein and artery, and performed invasive arterial blood pressure monitoring of the femoral artery. In group K, anesthesia maintenance was conducted using esketamine 0.5 mg/kg·h, remifentanil 0.1–1.0 μg/kg·min, propofol 4–10 mg/kg·h, and intermittent intravenous infusion of the cisatracurium[18]. In group C, anesthesia maintenance was performed using remifentanil 0.1–1.0 μg/kg·min, propofol 4–10 mg/kg·h, and intermittent intravenous infusion of cisatracurium. The dosage of anesthetic drugs was adjusted depending on the intraoperative hemodynamics.

During the procedure, the pneumoperitoneum pressure was maintained at 12 mmHg in both groups. Under the laparoscopic vision, the left lateral fascia of the kidney was separated and the kidney was fully exposed. Subsequently, the renal hilum was exposed and the renal artery and vein separated. The ureter was identified on the caudal side of the kidney, the upper part of the ureter was dissected. Subsequently, the ureter, renal artery, and renal vein were ligated and transected. The kidney was then fully dissociated, excised, and loaded into a specimen retrieval bag. It was then extracted through a 3 cm incision created at the cannula site. The titanium clip used for abdominal fixation was secured and the hemostatic clip was gradually loosened to determine adequate kidney suturing and to ensure effective hemostatis.

Postoperative management

At the conclusion of the procedure, the mini-pig was transferred to a quiet recovery environment and monitored until it regained consciousness. The endotracheal tube was removed only after the pig exhibited full recovery and the ability to move freely. After 2 and 12 h of restoration of normal activity, the pigs were provided with drinking water and a liquid diet, respectively. After the procedure, both groups of animals received intravenous injections of 50 mg flurbiprofen axetil to relieve pain. In the first three days post-operation, cefazolin sodium (50 mg/kg) was injected intramuscularly to prevent infection. Subsequently, miniature pigs were euthanized via

intravenous administration of sodium pentobarbital (100 mg/kg) in accordance with the AVMA Guidelines for the Euthanasia of Animals. All remains were handled following institutional biosafety protocols.

Outcome measurements

The primary observation indices were the changes in hemodynamics in two groups. The blood pressure and heart rate were recorded at the following time points: before anesthesia induction (T0); upon establishment of femoral artery blood pressure (T1); 5 min after the start of surgery (T2); 30 min after the start of surgery (T3); 60 min after the start of surgery (T4); 90 min after the start of surgery (T5); at the end of the surgery (T6); at the time of extubation (T7). The secondary outcome indices were the consumption of opioids and propofol, level of consciousness after anesthesia, and existence of postoperative adverse reactions.

Statistical analysis

Statistical analyses were conducted using the SPSS 26.0 software package Statistical analysis was performed on the perioperative data, as well as the primary and secondary outcomes data, for each group. For continuous variables, the Shapiro-Wilk test was used to assess the distribution. Normally distributed variables were expressed as mean ± standard deviation (SD), and homogeneity of variance was evaluated using Levene's test. Independent samples *t*-test or Welch's *t*-test was selected based on the homogeneity of variances. Non-normally distributed variables were expressed as median (25th -75th percentiles), with comparisons between groups performed using the Mann-Whitney *U* test. For categorical variables, the data were analyzed using the χ_2 test and the results expressed as frequency or percentage (%).Repeated measures analysis of variance (ANOVA) was used to compare continuous variables at different time points. A statistical significance level of $p < 0.05$ was considered significant. The GraphPad Prism version 10.1 for Windows was used to generate the graphs.

Results

Between December 2023 and June 2024, we performed nephrectomy assisted by the Micro Hand S surgical robot on six Bama miniature pigs, among which 3 were assigned to group K and 3 to group C (Fig. 1). There were no differences in baseline data, anesthesia time, operation time, blood loss, and intraoperative crystalloid fluid supplementation volume between the two groups of mini-pigs (Table 1).

We recorded the hemodynamic data at each time point during the operation, with the result indicating that the intraoperative hemodynamics in group K were significantly stable compared to group C. Among these measures, 5 min after the start of the operation, the blood pressure, and heart rate in group K were significantly higher compared to those in group C ($p < 0.05$). Then at the end of the operation, the heart rate, and blood pressure in group K were higher and substantially stable compared to those in group C, but there was no statistical difference between the two groups. At the time of extubation, the fluctuations in blood pressure and heart rate in group K were smaller compared to those in group C and this difference was statistically significant ($p < 0.05$) (Fig. 2).

Furthermore, our study recorded and compared the medication usage of the two groups. The usage of propofol (250 ± 8.7 mg vs. 347 ± 6.1 mg, $p < 0.001$), sufentanil (12.3 ± 0.6 μg vs. 25 ± 1.0 μg, $p < 0.001$), and remifentanil (498.3 ± 27.5 μg vs. 828.3 ± 20.2 μg, $p < 0.001$) in group K were significantly reduced compared to group C (Fig. 3). There were no statistical differences in the respiratory recovery time and the restoration to normal activity time between the two groups after the surgery. However, compared with group C, the recovery time of eyelid reflex (22.0 ± 2.0 min vs. 28.0 ± 2.6 min, $p = 0.035$), extubation time (24.7 ± 2.5 min vs. 32.3 ± 2.5 min, $p = 0.020$), and the recovery time of righting reflex (37.7 ± 2.5 min vs. 48.7 ± 5.5 min, $p = 0.035$) in group K were significantly lower. Additionally, there were no significant differences in postoperative adverse reactions between the two groups (Table 2).

Discussion

This study demonstrated that esketamine is safe and effective for robot-assisted nephrectomy in Bama mini-pigs. Esketamine maintains stable hemodynamics during operation, reduce the dosages of sedative and opioid drugs, accelerate the recovery of consciousness of mini-pigs; additionally, it exhibits minimal adverse reactions. The study also validated the safety and feasibility of the Micro Hand S surgical robot.

Bama mini-pigs are an inbred population with stable genetics formed through over 30 years of controlled breeding within a closed population of Bama fragrant pigs. Bama mini-pigs exhibit similar anatomical structures and physiological characteristics to humans, in addition to features such as small size, ease of breeding, consistent genetic background, high genetic purity, and strong inbreeding tolerance[19–21]. In recent years, Bama mini-pigs have been extensively used in various biomedical research fields. Consequently, we identified Bama mini-pigs as the subjects of our study.

We observed that both anesthesia protocols in the two groups ensure a relatively stable hemodynamic level during surgery. However, at T2 and T7, the fluctuations of blood pressure and heart rate in group K were significantly better compared to those in group C. The most significant effect of propofol on the circulatory system is the dose-dependent reduction of arterial blood pressure during the anesthesia induction period[22,23]. Additionally, opioid drugs cause circulatory system inhibition through mechanisms including blocking of the sympathetic nervous system, exciting the vagus nerve system, acting on cardiac pacemaker cells, the releasing of histamine in the body, and dilating peripheral blood vessels[24,25]. Due to the effects of propofol and opioid drugs, post-induction hypotension (PIH) is a common phenomenon in clinical practice[26,27]. Research reveal that PIH is closely associated with adverse outcomes such as postoperative acute kidney injury, prolonged hospital stay, and mortality, significantly affecting the prognosis of patients[26,28,29]. Previous studies have confirmed that esketamine exhibits sympathomimetic effects, including the ability to excite the sympathetic nerve, increase blood pressure,

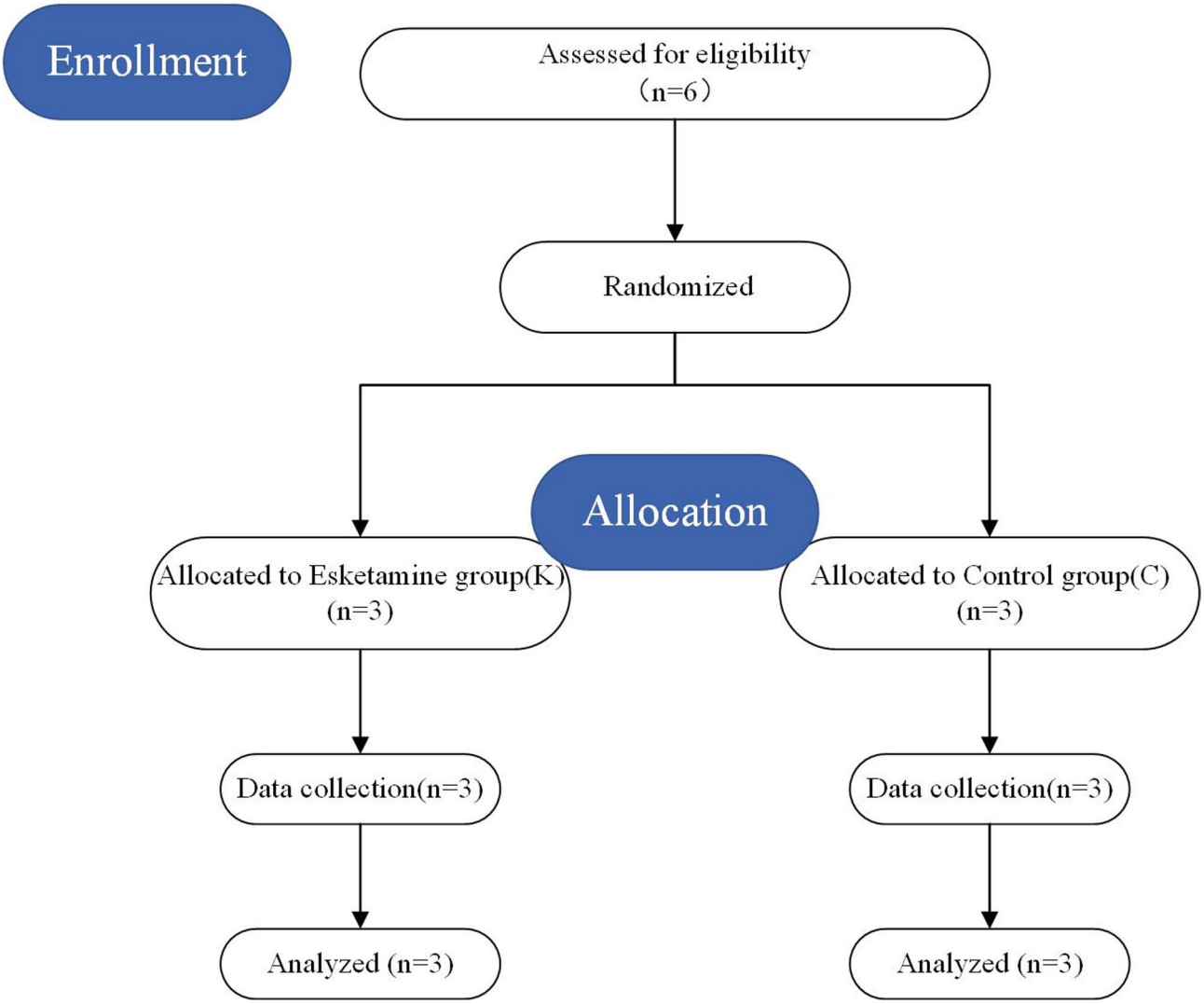

Fig. 1. Flow diagram of the study.

	Group K ($n=3$)	Group C ($n=3$)	*P* Value
Weight (kg)	24.0 ± 1.3	24.6 ± 1.3	0.578
Anesthesia time (min)	138.3 ± 3.2	134.3 ± 4.9	0.305
Operation time (min)	125.0 ± 5.0	121.7 ± 5.8	0.492
Blood loss (ml)	66.7 ± 20.8	76.7 ± 25.2	0.624
Intraoperative fluid infusion (ml)	1200 ± 100	1266 ± 76.4	0.411
Cisatracurium consumption (mg)	8.3 ± 1.5	9.7 ± 2.1	0.422
Esketamine (mg)	37.7 ± 1.2	0	NS

Table 1. Baseline characteristics and perioperative data for all mini-pigs categorized by group. Data are presented as mean ± standard deviation.

and elevate heart rate; which can effectively prevent PIH and maintain hemodynamic stability[30,31]. We observed that the hemodynamics of group K were significantly better compared to those of group C at T1. Additionally, the hemodynamics level of group K was more stable compared to that in group C, although this was not statistically significant. At the time of extubation, the blood pressure, and heart rate of group C were significantly higher compared to those of group K. We hypothesize that the relatively long drug half-life of esketamine exhibits an analgesic effect and reduces the hemodynamic fluctuations during extubation.

The results of this study indicate that the esketamine-based opioid-sparing anesthesia protocol significantly reduce the dosage of perioperative opioid drugs and intraoperative propofol. This is observation is consistent

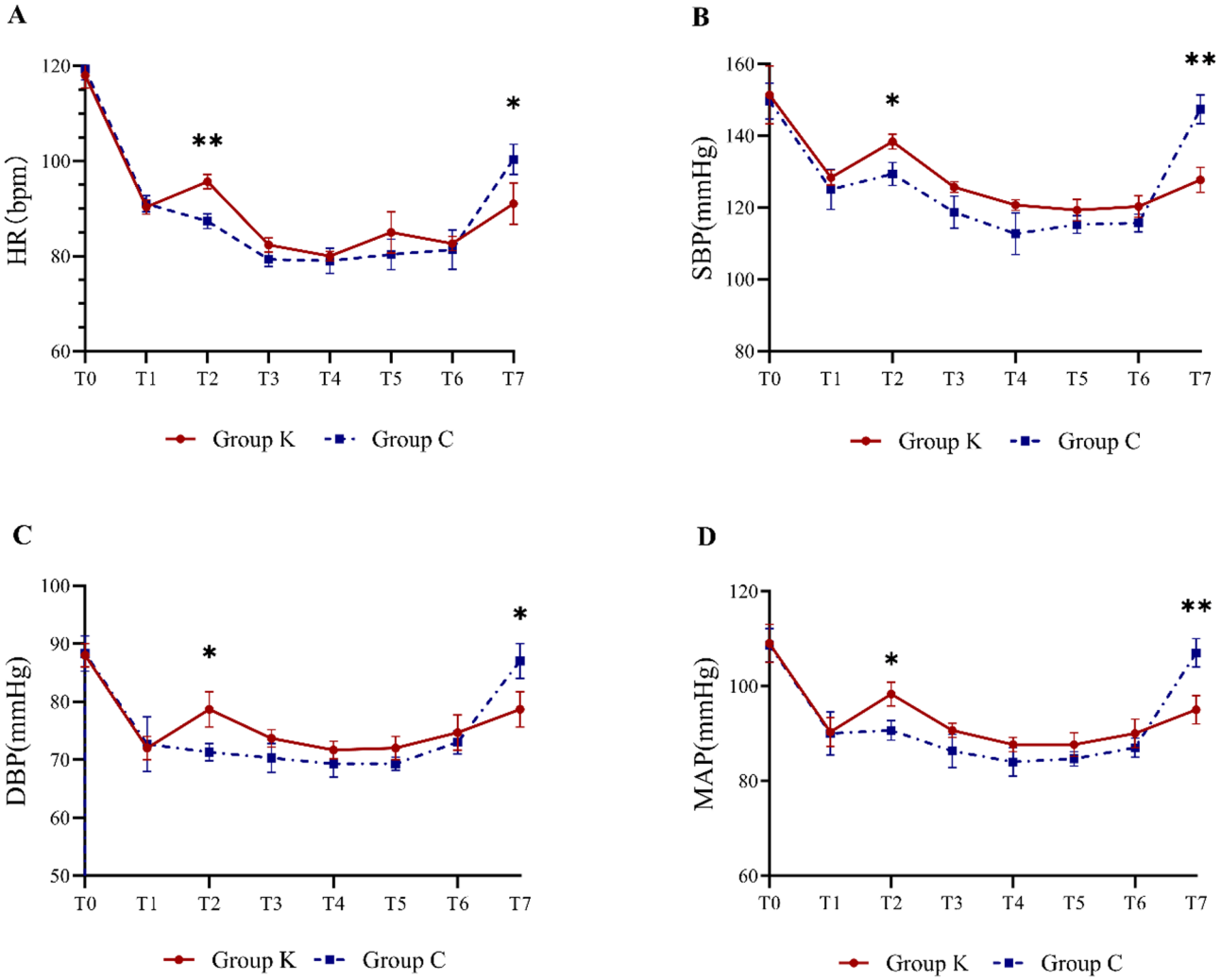

Fig. 2. Trends and mean values of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) measured before anesthesia (T0), establishment of femoral artery blood pressure (T1), 5 min after the start of surgery (T2), 30 min after the start of surgery (T3), 60 min after the start of surgery (T4), 90 min after surgery (T5), at the end of the surgery (T6), and at the time of extubation (T7) indicated by solid line for the group K and a dashed line for the group C. *p<0.05, **p<0.05.

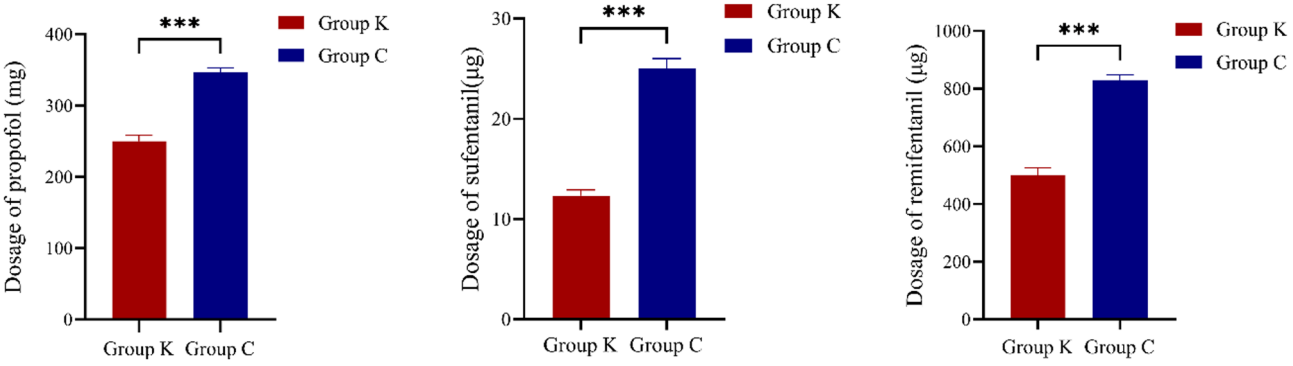

Fig. 3. The dosages of propofol, sufentanil, and remifentanil during the operation in group K and C. ***P<0.001.

	Group K($n=3$)	Group C($n=3$)	*P* Value
Respiratory recovery time (min)	20.0 ± 2.6	20.3 ± 3.5	0.902
Eyelid reflex recovery time (min)	22.0 ± 2.0	28.0 ± 2.6	0.035*
Extubation time (min)	24.7 ± 2.5	32.3 ± 2.5	0.020*
Righting reflex recovery time (min)	37.7 ± 2.5	48.7 ± 5.5	0.035*
Standing and walking time (min)	62.3 ± 2.5	70.7 ± 5.1	0.065
PONV	0	3 (100%)	0.100
Agitation	1 (33.3%)	1 (33.3%)	1.000
Groaning and drooling	2 (66.7%)	1 (33.3%)	1.000
Postoperative chills	0	1 (33.3%)	1.000

Table 2. The postoperative awakening quality and adverse reactions of the two groups of mini-pigs. Data are presented as mean ± standard deviation or percentage (%). PONV, postoperative nausea and vomiting. *Compared with the Group C, $p < 0.05$.

with those of previous studies[32] that indicate that esketamine exhibits both sedative and analgesic effects. Notably, during the anesthesia recovery period, group K exhibited better recovery time of eyelid reflex, extubation time, and righting reflex recovery time compared to group C. Currently, esketamine can accelerate the rate of awakening after isoflurane general anesthesia by activating paraventricular thalamic glutamatergic neurons in mice[33]. This study results showed that esketamine promote awakening level after total intravenous general anesthesia. However, the dosage of propofol in group K was significantly lower compared to that in group C, which may be attributed to the faster anesthesia recovery in group K. Therefore, additional studies are needed to explore the effect of esketamine on anesthesia recovery.

There was no statistical difference in the postoperative adverse reactions, between the two groups. However, group C mini-pigs exhibited postoperative nausea and vomiting which was not observed in group K. A recent study indicates that opioid drugs are one of the significant risk factors causing postoperative nausea and vomiting. Subsequently, reducing the use of perioperative opioid drugs can effectively lower the incidence of postoperative nausea and vomiting[34].

Despite these insightful findings, this has several limitations. Firstly, the research subjects of this study were Bama mini pigs and the sample size was relatively small, which may limit the generalizability and persuasiveness of the conclusions. In the future, large-sample clinical studies on humans are required. Secondly, the degree of sedation and the level of analgesia were not monitored during the operation in this study to enhance the persuasiveness of the research findings. Finally, the opioid-sparing protocol in this study was based on a single non-opioid analgesic drug, esketamine, further limiting the generalizability of the study. Consequently, future studies should consider a combination of multiple non-opioid drugs and regional block techniques to explore the safety and feasibility of the opioid-sparing anesthesia protocol.

Conclusion

The esketamine-based opioid-sparing anesthesia protocol can be safely and effectively used in robot-assisted nephrectomy in Bama mini-pigs, achieving a more stable hemodynamics during the operation, effective reduction of the dosages of opioid drugs and propofol, and better postoperative recovery quality. Additionally, the study validated that the Micro Hand S surgical robot can be safely used in clinical surgeries.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to contractual agreements with collaborating institutions that prohibit public sharing at this time but are available from the corresponding author on reasonable request.

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Declarations

Competing interests
The authors declare no competing interests.

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