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Dog's Laparotomy trail for Cardiorespiratory Efficacy of Low-Dose Ketamine Constant Rate Infusion Combined with Propofol or Sevoflurane

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Abstract | Ketamine is known for its analgesic and sedative properties. However, the effectiveness of low-dose ketamine in minimizing the cardiorespiratory depression caused by propofol and sevoflurane in spontaneously breathing dogs during laparotomy remains uncertain. This study aimed to investigate the effects of low-dose continuous ketamine infusion to mitigate the hemodynamic fluctuations associated with propofol, sevoflurane, and surgery. Therefore, sixteen healthy male dogs were randomly divided into four groups. G1 and G3 were induced by intravenous propofol (1 mg/kg/min), G2 and G4 received a ketamine bolus (2 mg/kg IV) followed by propofol (1 mg/kg/min). Maintenance anesthetics varied: G1 had sevoflurane (initial end-tidal concentration 2%) given in 1 L/min of 100% oxygen; G2 had ketamine CRI (0.6 mg/kg/h) and sevoflurane as in G1; G3 had a continuous propofol infusion (at a starting rate of 0.125 mg/kg/min); and G4 had ketamine CRI (0.6 mg/kg/h) and propofol CRI as in G3. Cardiorespiratory variables, including heart rate, respiratory rate, blood pressure, were recorded 30 minutes after premedication (baseline), 15 until 90 minutes post-induction, along with end-tidal sevoflurane, tidal volume, end-tidal carbon dioxide, oxygen saturation. The results revealed that G2 and G4 demonstrated superior hemodynamic stability, with more consistent in HR and MAP, reflected by the lowest coefficient of variation (18.7, 20.5% for HR; 15.8, 20.5% for MAP) throughout anesthesia and during the surgical procedure (2, 6% for HR; 5, 6% for MAP). In conclusion, combining a low dose of ketamine 0.6 mg/kg/h with propofol or sevoflurane can enhance hemodynamic stability in spontaneously breathing dogs undergoing laparotomy.

Keywords: General anesthesia, Propofol, Sevoflurane, Ketamine CRI, Inhalation anesthesia

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INTRODUCTION

In veterinary practice, sevoflurane and propofol are widely used for anesthetic management (Tsai *et al.*, 2007; Steffey *et al.*, 2015; Cattai *et al.*, 2018; Raffe, 2020). People like sevoflurane because it goes into and out of anesthesia quickly and doesn't slow down breathing as much as some other inhalant anesthetics (Haitjema and Cullen, 2001; Steffey

et al., 2015). However, sevoflurane is a dose-dependent cardiorespiratory depressant; increasing its concentration can cause rapid hemodynamic changes (hypotension), hypoventilation, and decreased cardiac contractility (Mutoh *et al.*, 1997; Steffey *et al.*, 2015).Previous studies have reported that a mean minimum alveolar concentration (MAC) of sevoflurane required to inhibit movement in 50% of patients to a noxious stimulus, with values ranging from 2.1% to 2.4% (Wilson *et al.*, 2008; Thengchaisri and Mahidol, 2019; Yamashita *et al.*, 2008; Marzok *et al.*, 2023).

Propofol is a sedative-hypnotic agent that stimulates gamma aminobutyric acid (GABAa) within the central nervous system (CNS). Propofol is good for total intravenous anesthesia (TIVA) because it has good pharmacokinetic properties, such as quickly putting you to sleep, quickly breaking down, and a smooth recovery (Nolan and Reid, 1993; Duke, 2013; Sahinovic *et al.*, 2018). However, higher propofol infusions are required to increase the anesthetic depth for surgery, which is accompanied by profound respiratory depression when it is involved alone in TIVA (Aguiar *et al.*, 2001; Suarez *et al.*, 2012; Bustamante *et al.*, 2022). The mean propofol rate used for maintaining general anesthesia in premedicated dogs (0.18±0.06 mg/kg/ min) was associated with fewer hemodynamic changes (Cuniberti *et al.*, 2023).

Thus, balanced anesthesia involves using a combination of anesthetic drugs rather than single anesthetic agent to provide sedation and analgesia throughout the preoperative phase, surgery, and recovery (Quandt, 2013). This multimodal approach can provide synergism between analgesics, sedatives, and inhalant anesthetics to reduce the requirement of each component in the anesthetic protocol and decrease adverse effects (Muir *et al.*, 2003; Wilson *et al.*, 2008; Duke, 2013; Cubeddu *et al.*, 2023). The nalbuphine-xylazine combination (0.5mg/kg each) is effective for premedication, providing greater sedation than xylazine alone and improving both handling, comfort and analgesia for the animal (Lester *et al.*, 2003). Furthermore, preemptive multimodal analgesia involves using various analgesics acting on different sites of the pain pathway to enhance the analgesic effect before the surgery (Beverly *et al.*, 2017; Cubeddu *et al.*, 2023).

When used in small amounts, ketamine is a strong painkiller that works by blocking N-methyl D-aspartate (NMDA) in both humans and animals (Schmid *et al.*, 1999; Gorlin *et al.*, 2016; Kalmoe *et al.*, 2020). In humans, administration of ketamine preemptively and intraoperatively can ameliorate the intraoperative cardiovascular response, maintain outlasted analgesia, and reduce the need for rescue analgesia (Saxena *et al.*, 2017). Ketamine was used as an adjunct to isoflurane at a low dose (0.6 mg/kg/h) to inhibit recovery side effects, including ataxia, vocalization, delirium and salivation correlated with increased dosages (Muir *et al.*, 2003). Ketamine (2 mg/kg IV followed by 0.6 mg/kg/h) combined with alfaxalone for total intravenous anesthesia, maintained stable cardiovascular conditions in dogs undergoing dental procedures (Bustamante *et al.*, 2020).

Preoperative ketamine administration can alleviate the hemodynamic response to the surgical stimulus and decrease the requirement for additional analgesia intraoperatively in dogs (Slingsby *et al.*, 2000; Sarturi *et al.*, 2021).

Although multimodal anesthesia is widely used in veterinary practice, there is limited data on the cardiorespiratory effects of low-dose ketamine combined alone with propofol or sevoflurane anesthesia in dogs, particularly concerning its influence on hemodynamic stability in response to surgery and recovery outcomes. We hypothesized that low-dose ketamine when combined with propofol or sevoflurane would help mitigate hemodynamic fluctuations during the anesthetic procedure and surgery in healthy premedicated dogs. Therefore, the present study aimed to evaluate the efficacy and safety of a low-dose ketamine constant-rate infusion combined with propofol or sevoflurane anesthesia on cardiorespiratory function in dogs undergoing laparotomy.

MATERIALS AND METHODS

The study was approved by the Zagazig University Committee of Animal Welfare and Research Ethics (ZU-IACUC/2/F/332/2023) and performed at the Department of Surgery, Anesthesiology, and Radiology, Faculty of Veterinary Medicine, Zagazig University, Egypt. The study was carried out on 16 male mongrel dogs (9 months–1 year old) with an average weight of 20–25 kg. A post-hoc power analysis using G*Power indicated that our sample size was sufficient to achieve a power of approximately 75% which is acceptable.

The American Society of Anesthesiologists, class 1 (ASA I), classified dogs as healthy without underlying diseases. All animals arrived 1 week before the procedure to acclimatize the environment, were housed in separate kennels with free access to food and water. Animals were fasted for 12 hours before the procedure and had free access to water until premedication.

Anesthetic protocol

All dogs were premedicated intramuscularly with xylazine (0.7 mg/kg, Adwia Co., Egypt) and nalbuphine (0.5 mg/kg, Nalufin®, Amoun Pharmaceuticals Co., Egypt) mixed in the same syringe and meloxicam (0.2 mg/kg, Mobitil® Medical Union Pharma, Egypt). After 20 minutes, a 20-gauge intravenous catheter was inserted into each cephalic vein

for the administration of the anesthetic drugs and Ringer's lactate. After 30 minutes (baseline time, T0), physiological parameters include heart rate (HR), respiratory rate (RR), non-invasive arterial blood pressure and rectal temperature (RT). Prior to induction, all dogs were preoxygenated by face mask at 3 L/min for 5 min.

Dogs were randomly allocated into four groups, with four dogs per group (n=4): Group 1 (G1) (control group) was administered slow propofol at a rate of 1 mg/kg/min using Propofol® 1% Fresenius; Fresenius Kabi Co LTD., Germany for anesthesia induction. They also received sevoflurane with an initial end-tidal concentration of 2% for maintenance, adjusted according to the anesthetic depth (Sevoflurane®, Cairo Pharmaceuticals and Chemical Industries Co (CPCI), Egypt, and AbbVie Icn., England). Group 2 (G2) got an IV bolus of ketamine (2 mg/kg, Ketam®; Egyptian International Pharmaceutical Industries Co., EPICO., Egypt), which was given by hand over 15 seconds. This was followed by slow propofol administration at a rate of 1 mg/kg/min for induction and sevoflurane with an initial end-tidal concentration of 2%, in addition to ketamine CRI (0.6 mg/kg/min) for maintenance. Group 3 (G3) (control group) received IV propofol (1 mg/kg/min) for anesthesia induction and was maintained with a propofol constant rate infusion at an initial rate of 0.125 mg/kg/min, adjusted according to the anesthetic depth. Group 4 (G4) received an IV ketamine bolus at a dose of 2 mg/kg, followed by propofol (1mg/kg/min) for induction, propofol CRI (0.125 mg/kg/min) and ketamine CRI (0.6 mg/kg/h) for maintenance. We prepared a ketamine constant rate infusion by calculating the volume of ketamine, adding it to 500 ml of Ringer's lactate after removing the same amount of solution, and delivering it at a rate of 10 ml/kg/h throughout the procedure. The rate of propofol in all groups was programmed into a syringe pump (injectomate Agilia®; Fresenius Kabi Co., Germany) and set in ml/h for the induction of anesthesia. The propofol infusion continued until the right conditions for endotracheal intubation were met, which included the eyeball being ventromedial, there being no palpebral reflex, jaw tone, swallow reflex, or tongue resistance to laryngoscope blade placement. All animals were intubated with a KRUUSE PVC Endotracheal Tubus (China) that was the right size and had a cuff that was chosen by feeling the outer diameter of the animal's trachea in the mid-neck area. The endotracheal tube's (ETT) cuff was inflated with air until no leak was heard, and the adjustable pressure-limiting valve was closed at a pressure of 20 mm H2O. EETs were connected to a rebreathing circle system (COSY., Fabius plus XL., Drägerwerk AG and Co. Lübeck, Germany), and dogs were dependent on spontaneous breathing, receiving 100% oxygen at 1L/min. For assessment of cardiorespiratory function, heart rate (HR) and rhythm were continuously monitored by a Lead II electrocardiogram. A cuff (NIBP Cuff Neonate, Dräger®, Drägerwerk AG and Co. Lübeck, Germany) was placed above the hock joint and its width was approximately about 40% of the limb's circumference. This was done to measure systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP). The peripheral capillary oxygen saturation (SpO2) was measured by placing a pulse oximeter probe on the tongue. For assessment of respiratory function, a sampling line was connected to the luer lock on the Y-piece of the breathing circuit and an infrared gas analyzer (Scio 4, Dräger®, Drägerwerk AG and Co. Lübeck, Germany) to measure end-tidal concentration of sevoflurane (ETSEVO), end-tidal carbon dioxide (ETCO2), and respiratory rate (RR), all the time. All these variables were measured using a multiparametric monitor (Vista 120, Dräger®, Drägerwerk AG and Co., Lübeck, Germany). Tidal volume (VT) was measured by flow sensor settled at expiratory port of breathing circuit and displayed on the monitor of anesthesia machine. Rectal temperature (RT) was measured by a digital thermometer. Using a heating blanket, the temperature was maintained.

Surgical procedures

All dogs were placed in a dorsal recumbency and underwent a ventral midline exploratory laparotomy under aseptic conditions. All animals were subjected to two consecutive abdominal surgical manipulations by hand, each lasting 1 minute with a 10-minute interval. The expected time of surgery (from the skin incision until the last suture performed on the skin) was 45–50 minutes. All surgeries were performed by the same surgeon. All dogs received ceftriaxone, a broad-spectrum antibiotic (Wintriaxone® 1000 mg, SANOFI, Zeitoun, Egypt) (25 mg/kg IV) 30 min before surgery and continued for 3 successive days after the operation. Data was collected during the maintenance of anesthesia at specific time-points: prior to skin incision (T1), immediately post-skin incision (T2), at the opening of the peritoneum (T3), during abdominal surgical manipulation (55 to 65 min post-induction at 10-minute intervals), during muscle suturing (70 to 75 min post-induction), during subcutaneous suturing (80 min post-induction), and during skin suturing (85 to 90 min post-induction). After the completion of the surgery, we stopped all infusions and inhaled anesthesia, marking the conclusion of the anesthesia phase. When dogs regained their swallowing reflex, they were extubated and allowed to recover undisturbed in a calm room. We recorded the time of extubation (elapsed from the termination of propofol or sevoflurane to extubation), the time to the first head lift, and the time to sternal recumbency for each dog. Animals received meloxicam IM (0.2 mg/kg) for two successive days after the procedure.

Intraoperative interventions

If bradycardia (defined as HR below 60 beats per minute) occurred in a normotensive patient, it was left untreated.

Hypotension was defined as a MAP below 60 mmHg, and it was treated if it continued for more than 5 minutes by decreasing the sevoflurane concentration by 20%. When hypotension was accompanied by bradycardia, an intravenous dopamine infusion was initiated at 10µg kg-1 min-1 to effect (Dopasunny, Sunny Pharmaceutical Co., Egypt). We used mechanical ventilation with VT (10 ml/kg), RR (10 breaths/min), and an inspiration to expiration ratio (I: E) of 1:2. If MAP or HR increased 20% above pre-incision values, it was identified as a painful response to surgical stimulation. In such cases, sevoflurane concentrations increased by 20%.

Statistical analysis

The data were tested for normal distribution using the Shapiro-Wilk test and Levene's test for assessing homogeneity of variance. The coefficient of variation (CV) is reported to monitor the changes between groups over the period of operation. A repeated measure ANOVA with Duncan's multiple comparison post hoc test was used to investigate differences over time points broken down by four treatment groups. As the data collected over consecutive time points so, El-Bayomi *et al.* (2019) recommended using repeated measures ANOVA over traditional ANOVA. The analyses were performed using the R language (R Core Team, 2023) and SPSS version 25. The significance level is defined as $p < 0.05$.

RESULTS AND DISCUSSION

Assessing cardiovascular function

Heart rate (HR)

The analysis revealed a significant interaction between time and groups for heart rate ($F(71,213)=5.02$, $P < 0.0001$, $\eta^2=0.26$). This indicates that the observed changes in heart rate over time are influenced by group membership, and this is clear by the $\eta^2=0.26$ which indicates that the interaction between time and groups explains a substantial portion of the variance in heart rate. HR increased at induction in G1, G2, and G4 compared to baseline. G1 and G3 showed an overall consecutive change (mostly an increase) in HR level until 90 minutes post-induction. Generally, G2 exhibited the most stable HR performance with the lowest percentage of variation (18.7%), followed by G4 as shown in Table 1 and Supplementary Figure S1.

Systolic arterial pressure (SAP)

G2 maintained stable SAP level throughout the anesthetic procedure, with no significant change over-time ($F(71:213) = 4.48$, $p > 0.05$, partial eta square(η^2) = 0.8), despite the lack of statistical significance, the $\eta^2 = 0.8$ suggests that time explains a substantial amount of variance in SAP levels. This indicates that while there might have been some variability in SAP levels over time, the overall trend was not consistent enough to be statistically significant. In contrast, the SAP levels in G1, G3, and G4 showed significant changes over time compared to the baseline time. G3 and G4 had the highest SAP levels during skin suture (182.5[a] and 168.8[a] mmHg, respectively) (Figure 1A, Supplementary Table 1S).

s: Showing heart rate (beats/min) of the 4 groups from baseline values to 90 min post-induction and coefficient of variation.

Time	1	2	3	4
30 m	43.2[d]	53.4[d]	56.3[d]	46[d]
At induction	60[bc]	96.2[bc]	49.8[d]	90.3[bc]
Post.15m	68.8[bc]	77[bc]	59.5[c]	60.5[c]
Post.20m	79.2[bc]	94.8[bc]	62.5[c]	74.5[bc]
Post.25m	80.5[bc]	85.2[bc]	69.5[bc]	74.5[bc]
Post.30m	87.8[bc]	80.8[bc]	80[bc]	75.2[bc]
Post.35m	96[bc]	91[bc]	78.5[bc]	81.5[bc]
Post.40m	100.8[bc]	96.5[bc]	83.8[bc]	84.2[bc]
Post.45m	95.2[bc]	82[bc]	90.2[bc]	81.5[bc]
Post.50m	89.2[bc]	99[bc]	85[bc]	73.2[bc]
Post.55m	99.8[bc]	94.8[bc]	94[bc]	75[bc]
Post.60m	95.8[bc]	101[bc]	94.8[bc]	78.8[bc]
Post.65m	93.2[bc]	101[bc]	100[bc]	83.5[bc]
Post.70m	108[bc]	103.5[bc]	110.8[b]	88.2[bc]
Post.75m	105[bc]	101[bc]	120[a]	92.5[bc]
Post.80m	109[bc]	98.5[bc]	125.5[a]	101.5[bc]
Post.85m	109[bc]	101.3[bc]	126.8[a]	110.8[b]
Post.90m	109.2[bc]	106.7[bc]	124.2[a]	113.5[b]
C.V%	23%	18.7%	20.3%	20.5%

ab Means with different superscript within same column are statistically different $p < 0.05$. AB Means with different superscript within same row are statistically different $p < 0.05$.

Diastolic and mean arterial pressure (DAP and MAP)

Significant interactions between time and groups were observed for both DAP ($F(71,213) = 5.04$, $P < 0.0001$, $\eta^2=0.96$) and MAP ($F(71,213) = 5.02$, $P = 0.007$, $\eta^2=0.70$), respectively. G2 and G4 showed stable DAP and MAP levels, while G1 and G3 exhibited significant fluctuations throughout anesthesia. In G3, MAP sharply increased during muscle, subcutaneous and skin suture at 75, 80 and 90 min post-induction, respectively. No hypotension (MAP< 60mm Hg) was observed in any group during anesthesia maintenance. Overall, G2 showed a semi-steady pace of DAP and MAP, as indicated by the lowest percentage of variation (CV) of 22.4% and 15.8%, respectively (Figure 1B, C; Supplementary Table 1S).

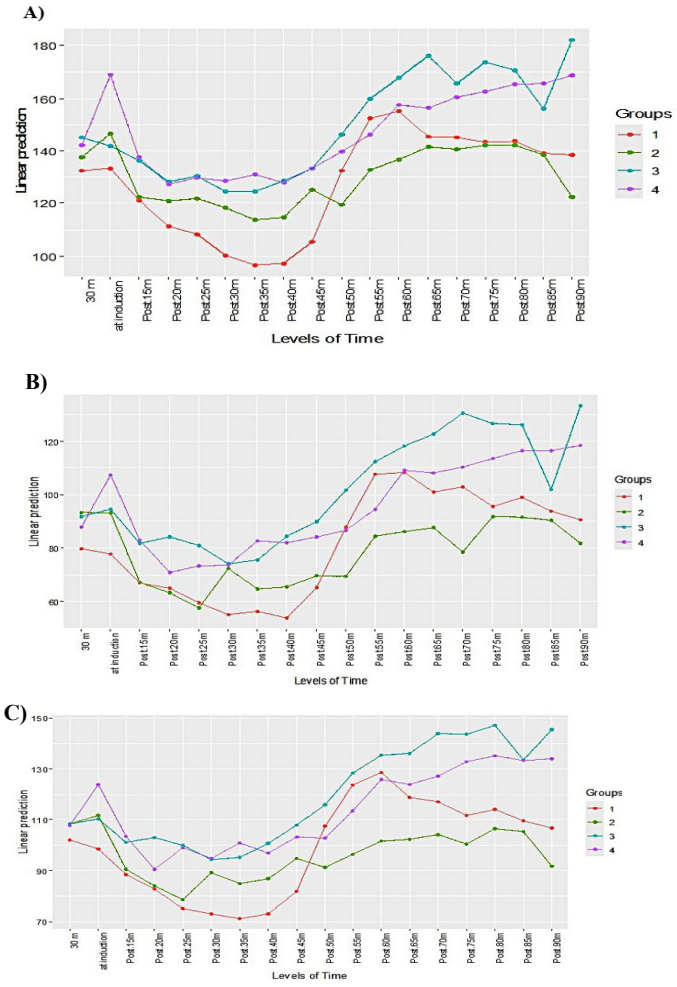

Figure 1: A, Systolic arterial pressure (SAP) level mmHg; B, Diastolic arterial pressure (DAP) level (mmHg); C, Mean arterial pressure (MAP) level in mmHg in 17th consecutive time points in the 4 groups.

Peripheral oxygen saturation (SpO_2)

The results of SpO_2 showed a non-significant interaction between time and treatments (groups 1, 2, 3, and 4) ($F(16, 238) = 1.89$, $P > 0.05$, $\eta^2 = 0.12$). There was no difference among groups and the effect size is small, as shown in (Table 2).

Assessing respiratory function
End-tidal sevoflurane (ET SEVO)

In G1 and G2, there was a statistically significant interaction between the time of anesthesia and the type of treatment ($F(16, 109) = 4.68$, $p < 0.05$), and the value of $\eta^2 = 0.50$ indicates that 50% of the variance in the ET SEVO measure can be attributed to the interaction between time and treatment type. G1 showed higher levels of ET SEVO that started 60 minutes post-induction during surgical procedure. This increase revealed a significant difference compared to G2 (Figure 2A, Supplementary Table S2).

Respiratory rate (RR)

Analysis of respiratory rate (RR) revealed fluctuations across all groups throughout the anesthetic period. G1 exhibited the greatest average change in RR, followed by G3.G3 exhibited significant decrease during suture (75 to 90 min post-induction) compared to the baseline. In contrast, G2 and G4 demonstrated the most stable RR patterns, as shown in (Figure 2B, Supplementary Table 3S).

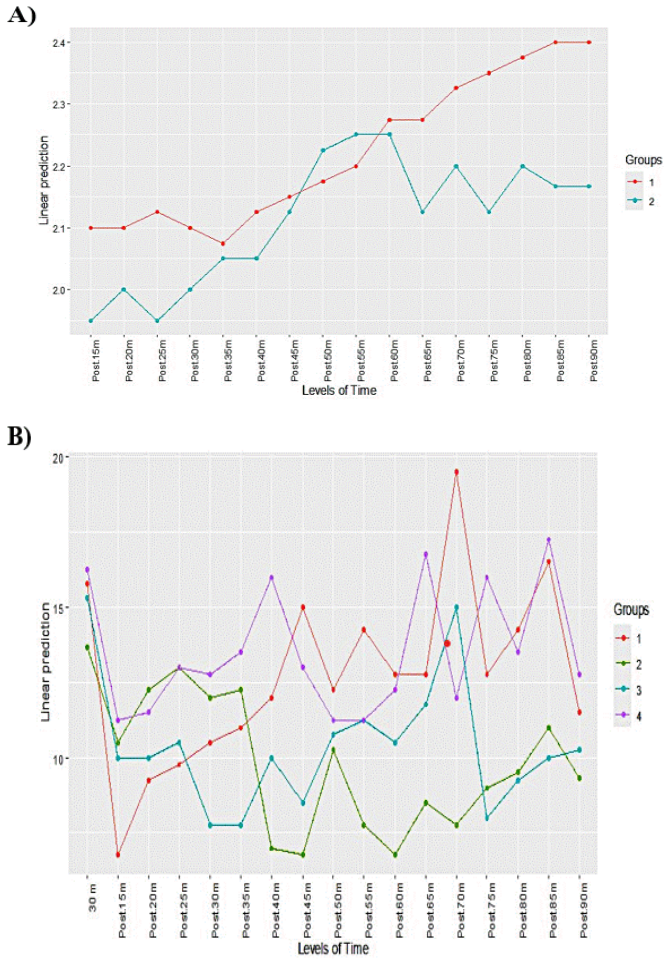

Figure 2: A, The estimated marginal means for ETSEVO level in G1and G2 during the anesthetic procedure at consecutive time points (post 15 min to post 90). B, The estimated marginal means for respiratory rate (RR) breaths/minute in 4 groups during the anesthetic procedure at consecutive time points (post 15 min to post 90).

Tidal volume (VT)

The results showed that the interaction between the time of anesthetic procedure and the type of treatment is statistically significant ($F(16, 236) = 1.34$, $p < 0.05$, $\eta^2 = 0.10$). G3 showed unstable and highly variable values of tidal volume (VT), as CV value was 23% compared to other groups. At 35 minutes post-induction, G3 recorded the lowest VT (166) among the groups. On the other hand, the level of VT in G2 was more steady, with less variability (CV = 15.91%) compared to other groups (Figure 3A, Supplementary Table 3S).

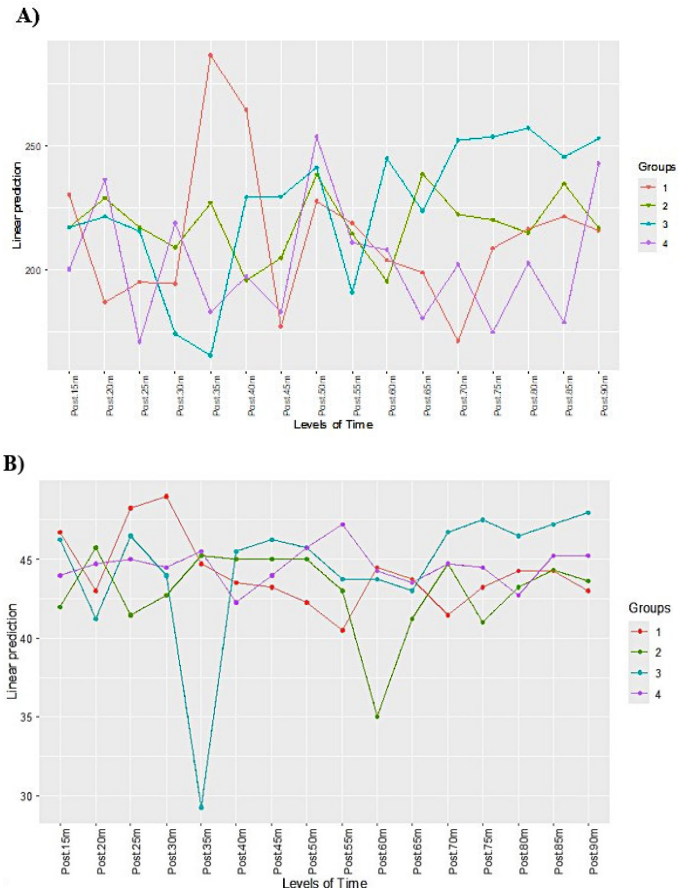

Figure 3: A, the estimated marginal means for VT level (ml) by applying four different treatments during the anesthetic procedure at consecutive time points (post 15 min to post 90). B, the estimated marginal means for end-tidal carbon dioxide (ET CO_2) mm Hg by applying four different treatments during the anesthetic procedure at consecutive time points (post 15 min to post 90).

End-tidal carbon dioxide ($ETCO_2$)

The results for $ETCO_2$ did not show a significant interaction between time and treatments (groups 1, 2, 3, and 4). However, the simple effect analysis for testing changes in $ETCO_2$ over the duration of the experiment revealed a significant change in G3, with the lowest mean (29.2) at 35 minutes post-induction (Figure 3B, Supplementary Table 4S).

Assessment of rectal temperature (RT)

RT gradually decreased throughout the procedure, with no significant differences between groups. However, G2 had a lower RT (36.9°) than G3 (38.2) at 30 minutes after the induction, and G1 had a lower RT (36.8°) than G3 (38°) at 60 minutes after the induction.

During a surgical procedure

The results for heart rate showed a statistically significant interaction between the time of the experiment and the type of anesthetic protocol (G1 to G4), with $p < 0.05$. Compared to baseline (T0), all groups showed a significant increase from the prior skin incision (T1) until the opening of the peritoneum (T3) (Table 3).

Table 2: Estimated marginal means for simple effects of the SPO2% level change between groups at each time point and over times for each of the 4 groups.

Time	1	2	3	4	Significance among groups
Post.15m	98%	98.5%	97.8%	98%	$P > 0.05^{ns}$
Post.20m	98%	98.5%	97.8%	97.5%	$P > 0.05^{ns}$
Post.25m	98.3%	98.3%	97.5%	97.5%	$P > 0.05^{ns}$
Post.30m	98.3%	98.5%	97.3%	98.3%	$P > 0.05^{ns}$
Post.35m	98%	98.5%	97.5%	98.8%	$P > 0.05^{ns}$
Post.40m	98%	97.8%	97%	98%	$P > 0.05^{ns}$
Post.45m	97.5%	97.3%	97%	97.5%	$P > 0.05^{ns}$
Post.50m	96%	97.5%	97%	97.3%	$P > 0.05^{ns}$
Post.55m	96%	97%	96.5%	96.8%	$P > 0.05^{ns}$
Post.60m	96.3%	97%	96%	96%	$P > 0.05^{ns}$
Post.65m	96.3%	97.3%	97%	96.3%	$P > 0.05^{ns}$
Post.70m	96.5%	97.3%	96.5%	96.3%	$P > 0.05^{ns}$
Post.75m	96.5%	97.5%	96.8%	96.3%	$P > 0.05^{ns}$
Post.80m	96.8%	97%	96.8%	96%	$P > 0.05^{ns}$
Post.85m	96.5%	96.5%	97%	96%	$P > 0.05^{ns}$
Post.90m	96.3%	97.3%	97%	96.3%	$P > 0.05^{ns}$
Significance of simple effect over time	$P > 0.05^{ns}$	$P > 0.05^{ns}$	$P > 0.05^{ns}$	$P > 0.05^{ns}$	

ns: non-significant difference $P > 0.05$; * significantly different $P < 0.05$.

The respiratory rate over time was significantly influenced by the type of treatment ($p < 0.05$). G2 showed the most stable RR value after skin incision (T2) and at the opening of peritoneum (T3) with the lowest variability 9% for both (Table 3).

SAP level remained relatively stable, G3 and G4 recorded higher SAP levels T2 and T3, G3 had higher DAP and MAP levels at T2 and T3, while G2 and G4 showed more stable response to surgical stimulus (Table 3).

The average change rate of propofol in G4 was not significantly different from G3 (0.18 ± 0.01) and (0.2 ± 0.02) mg/kg/min throughout anesthetic procedure, respectively ($p > 0.05$).

Recovery

Extubation time was not significantly different among groups ($P > 0.05$). However, there was a significant difference in the first head lift time between groups. G1 and G2 showed the shortest times to the first head lift

(6.5±0.65^{c}, 7.25±0.48^{c} minutes, respectively) (P< 0.05), while G3 and G4 recorded the longest times (15.0±1.6^{a}, 11.25±1.3^{b} minutes, respectively). There was a highly significant difference in the time to sternal recumbency and standing and walking among groups (P< 0.001). G1 had the shortest sternal recumbency time (8.75±0.85 minutes). Additionally, G1 and G2 recorded the shortest times (10.5±0.65 ^{c} and 12.5±0.65 c minutes, respectively) for standing and walking compared to G3, G4, and G5. Overall, the longest times were found in G3.

Table 3: Mean ± SEM of heart rate HR (beats/min), systolic arterial pressure SAP (mmHg), diastolic arterial pressure DAP (mmHg), mean arterial pressure MAP (mmHg), respiratory rate RR (breaths/min). T0, baseline time (30 minutes after premedication); T1, prior skin incision; T2, after skin incision; T3, at the opening of peritoneum, and CV coefficient of variation.

Parameter		1	2	3	4
HR	T0	43.2^{d}	53.4^{d}	56.3^{d}	46^{d}
	T1	94.2^{a}	93.2^{a}	85.5^{bc}	78.5^{bc}
	T2	91.5^{ab}	97.2^{a}	89.2^{ab}	81.5^{bc}
	T3	97.8^{a}	97^{a}	88.8^{abc}	77^{c}
	C.V	28 %	22.8%	17.7 %	21.6 %
	C.V$^{\#}$	5 %	2 %	7 %	6 %
RR	T0	15.8^{ab}	13.8^{bc}	14.5^{bc}	17.7^{a}
	T1	11^{bc}	12.8^{c}	10.2^{c}	13.5^{b}
	T2	16^{ab}	11.5^{c}	11.2^{bc}	16.8^{a}
	T3	14.2^{bc}	13.5^{bc}	9.5^{c}	13^{bc}
	C.V	19 %	9 %	20 %	17 %
	C.V$^{\#}$	19 %	9 %	12.6 %	15 %
SAP	T0	132^{ab}	138^{ab}	145^{ab}	142^{ab}
	T1	115^{c}	119^{b}	137^{ab}	146^{a}
	T2	123^{b}	120^{bc}	151^{a}	149^{a}
	T3	124^{b}	122^{b}	151^{a}	149^{a}
	C.V	8 %	6 %	6 %	5 %
	C.V$^{\#}$	8 %	2 %	7 %	5 %
DAP	T0	79.8^{ab}	93.2^{ab}	91.8^{ab}	88^{ab}
	T1	76.5^{ab}	57.5^{c}	92.2^{ab}	92.5^{ab}
	T2	79.5^{ab}	60.5^{c}	108.5^{a}	105.5^{ab}
	T3	81^{ab}	59.5^{c}	108.2^{a}	100.5^{ab}
	C.V	13.35%	23 %	13 %	11 %
	C.V$^{\#}$	12.8 %	6 %	13 %	11 %
MAP	T0	102^{ab}	108.5^{ab}	108.5^{ab}	107.8^{ab}
	T1	88.5^{ab}	91.5^{c}	111.8^{ab}	111.8^{ab}
	T2	96^{bc}	94^{bc}	126.2^{a}	119^{ab}
	T3	97^{bc}	86.8^{c}	126.2^{a}	119^{ab}
	CV	12 %	9 %	8 %	6 %
	CV$^{\#}$	11%	5 %	7 %	6 %

^{abc} Means with different superscript are statistically different p < 0.05 for each parameter independently. CV: Coefficient of variation. # Coefficient of variation from prior to skin incision till the opening of the peritoneum.

Hemodynamic changes, such as tachycardia and increased blood pressure, along with alterations in breathing patterns, can be evaluated to assess intraoperative pain (Katoh *et al*., 1999; Hernández-Avalos *et al*., 2020; Interlandi *et al*., 2022; Cardozo *et al*., 2024). In humans and animals, the addition of ketamine to the anesthetic plan can improve hemodynamic stability throughout the entire anesthetic and surgical procedure (Smischney *et al*., 2012; Jalili *et al*., 2016; Lee *et al*., 2017). Our findings are consistent with this, showing stable vital parameters (HR, SAP, DAP, and MAP) in both G2 and G4.

In this study, a reduced hemodynamic response to the surgical stimulus was observed in G2, and G4 compared to G1, and G3, likely due to the low dose of ketamine CRI combined with the anesthetic protocols. The stable HR and MAP levels in G2 due to the reduced sevoflurane concentration combined with ketamine's sympathetic stimulatory effect throughout surgery. These finding fit with what Love *et al*. (2011) found: Giving dogs low doses of ketamine (0.75 mg/kg/min) along with sevoflurane reduced blood pressure fluctuations from a noxious electrical stimulus (50 V, 50 Hz, 10 ms) and lowered their need for sevoflurane (2.62±0.02) to keep their blood pressure stable. This effect has also been emphasized in humans undergoing laparoscopic cholecystectomy received low -dose ketamine (loading dose 0.5 mg/kg, followed by 0.6 mg/kg/h), exhibited stable hemodynamics in response to pneumoperitoneum (Chen *et al*., 2021).

In addition, Seliskar *et al*. (2007) reported that using ketamine (loading dose 1 mg/kg; CRI 2mg/kg/h) with propofol CRI (0.075mg/kg/min) in premedicated dogs, Kennedy and Smith (2015) observed that (0.3mg/kg/min) a propofol-ketamine CRI in unpremedicated dogs, Reed *et al*. (2015) found that ketamine (loading dose 2mg/kg; CRI 1.2mg/kg/h) with a propofol CRI(0.60±0.1 mg/kg/min) in unpremedicated dogs , were more effective in maintaining MAP than propofol alone in the absence of an actual surgical stimulus. These studies used higher doses of ketamine compared to our study. Among groups, G3 exhibited the highest values of HR and MAP during suturing and necessitating an increase in the infusion rate. This finding is consistent with Jia *et al*. (2015), where a propofol rate was (0.4-0.6 mg/kg/min) to maintain adequate anesthesia depth in dogs undergoing splenectomy. However, the mean propofol infusion rate in the current was lower (0.2 ± 0.02), to maintain surgical anesthesia compared to the previous study.

According to Murrell *et al*. (2005) and Suarez *et al*. (2012), the effective average propofol rate in G3 was different and lowers than the mean propofol rates (0.33 ± 0.03 mg/kg/min) and (0.37 ± 0.09 mg/kg/min) in dogs that were given premedicaion before abdominal surgeries.

The effective average propofol rate in G4 was lower than the rate reported by Bustamante *et al.* (2022), which was 0.23 ± 0.08 mg/kg/min using a ketamine CRI of 1.5 mg/kg/h, twice the ketamine CRI (0.18 ± 0.01 mg/kg/min) used in the present study.

Propofol reduces the heart rate in a dose-dependent manner by depressing sinoatrial node activity and myocardial contraction (Nagashima *et al.*, 1999). However, the animals in G3 did not show a significant drop in HR after starting low-propofol CRI. The increased HR in G1 and G3 prior to the surgical procedure counteracted the vasodilatory effects of sevoflurane and propofol. This finding aligns with Wang *et al.* (2004), Kato *et al.* (2024) and Fabus *et al.* (2024). Furthermore, Su *et al.* (2022) said that the body's baroreceptor-induced rise in HR can be stronger than propofol's calming effects on them. Another cause, as declared by Wang *et al.* (2004) and Fabus *et al.* (2024), is that propofol shifts sympathetic/parasympathetic autonomic balance, leading to reduced parasympathetic effects with slow propofol infusion. In our study, sevoflurane was linked to less respiratory depression than propofol alone. This was shown by the fact that G3 patients needed more help breathing. This finding may be due to the respiratory motor system being less sensitive to volatile anesthetics compared to injectable ones (Yang *et al.*, 2020). This result aligned with Quickfall *et al.* (2024), which examined the effects of these drugs on humans without assisted ventilation. Moreover, sevoflurane tends to reduce tidal volume in animals (Steffey *et al.*, 2015). According to Saraswat (2015), this reduction may be accompanied by an increased respiratory rate while maintaining the minute volume. Increased VT in G2 compensated for the significant decrease in RR, providing adequate ventilation, as evidenced by the values of ETCO2 and SpO2. The current study found that SpO2 and end-tidal CO2 levels were all within clinically acceptable ranges across all groups. This meant that the four different anesthetic protocols used were able to keep peripheral tissue perfusion high.

In the current study, hypopneic hypoventilation was observed, defined as low ETCO2 of 30 mmHg or less, as reported by Langhan *et al.* (2015). This resulted from decreased tidal volume and increased air in anatomical dead space instead of alveoli, leading to less CO_2 being exhaled. In G3, a low $ETCO_2$ level was observed with a mean value of 29.5, corresponding to a decrease in VT. This finding is similar to that of Aşkın *et al.* (2023), who reported hypopnea in patients receiving propofol with a mean value of 29.6 mmHg. Redondo *et al.* (2012) defined hypothermia as a temperature decrease below 36.5°, a temperature that was not observed in the present study.

There was a greater fluctuation in the respiratory rate among groups. Respiratory depression is a common complication in anesthesia maintenance with propofol in dogs, as reported by Ambros *et al.* (2008) and Reed *et al.* (2015). In G3, which received propofol CRI alone, three dogs showed respiratory depression in the first half-hour of maintenance and required manual and mechanical ventilation. This is because propofol is a dose-dependent respiratory depressant. Propofol stops the breathing response to low oxygen and high carbon dioxide levels by lowering breathing centers in the brain stem. This lowers the drive to breathe. This can be influenced by the depth of sedation, resulting in decreased tidal volume, minute volume, and respiratory rate (Glowaski and Wetmore, 1999; Liu *et al.*, 2017; Jansen *et al.*, 2024).

Ketamine has a sympathomimetic effect on the central nervous system (CNS) and can increase the respiratory rate. However, high doses of ketamine or its combination with other CNS depressant drugs can cause respiratory depression by blunting the sympathomimetic effect (Lerche *et al.*, 2000). A small amount of ketamine (2 mg/kg loading dose, 0.6 mg/kg/min CRI) was given to dogs that had already been given xylazine, nalbuphine, sevoflurane, or propofol. This combination may have a synergistic effect on respiratory depression in the first half-hour of maintenance. Additionally, the adjunctive use of ketamine in G4 provided beneficial effects for reducing respiratory depression and decreased the need for supportive mechanical ventilation compared to propofol alone in G3. This finding is in line with Aşkın *et al.* (2023), who reported that ketamine-propofol causes less respiratory depression compared to propofol alone in humans.

In the current study, multimodal analgesia involving NSAIDs, opioids, and NMDA receptor antagonists was used to improve analgesia efficacy and reduce anesthetic doses. It is reported that synergy can be obtained by combining NSAIDS and NMDA receptor antagonists. They effectively inhibit peripheral and central sensitization by inhibiting prostaglandin production after surgical trauma (Mathews *et al.*, 2001; Kelly *et al.*, 2001; Pozzi *et al.*, 2006; Yamashita *et al.*, 2008).

Prolonged recovery times were observed in G3 and G4. This is associated with a prolonged infusion of propofol for approximately 90 minutes, which agrees with the findings of Jia *et al.* (2015). However, our recovery times were shorter than those in the previous study, likely due to the use of a lower infusion rate, despite the longer infusion duration in the present study.

Instead of giving more painkillers, increasing the end-tidal concentration of sevoflurane or the propofol rate controlled the rise in blood pressure in response to surgery. This is to alleviate the bias in the study, aligning with Cardozo *et al.* (2024), who emphasized that additional analgesia could

interfere with other anesthetics.

The current study has several limitations. First, blood pressure was measured using non-invasive technique instead of invasive blood pressure (IBP) monitoring, which is the gold standard for accuracy. The study conducted on only male dogs, which may limit the extrapolation of findings to female dogs. Finally, sample size was limited as ethical considerations are strictly applied. It would be better if sample size increased for better generalizability of results.

CONCLUSIONS AND RECOMMENDATIONS

Mixing a low-ketamine CRI with either sevoflurane or propofol made the blood pressure stable enough with only a little breathing depression and a lower need for sevoflurane. However, it had a less profound effect on the percentage change of propofol CRI in dogs undergoing laparotomy. We recommend incorporating low-dose ketamine infusion with sevoflurane or propofol for a procedure lasting longer than one hour to stabilize hemodynamic parameters and decrease the need for additional anesthetic interventions. Further research should evaluate the effectiveness of low-dose ketamine combined to sevoflurane or propofol in orthopedic surgeries, as these procedures may present different challenges related to intensity and the duration of the procedure.

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NOVELTY STATEMENT

A low dose of ketamine (2mg/kg IV, followed by a continuous rate infusion at 0.6 mg/kg/h) effectively attenuates the cardiorespiratory depression of propofol or sevoflurane in spontaneously breathing dogs undergoing laparotomy.

AUTHOR'S CONTRIBUTION

All authors contributed equally to the manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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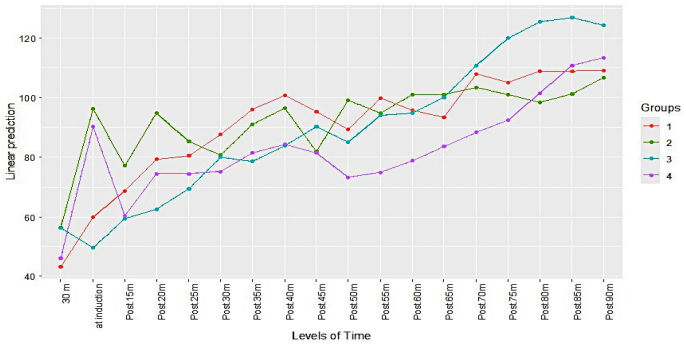
Supplementary Table 1S: Showing systolic arterial pressure (SAP) level (mmHg), diastolic arterial pressure (DAP) level in mmHg, and mean arterial pressure (MAP) level mmHg in 17th consecutive time points in the 4 groups.

	SAP (mmHg)					DAP (mmHg)				MAP (mmHg)			
	1	2	3	4		1	2	3	4	1	2	3	4
30 m	132.5^{abcd}	137.5^{a}	145 ^{bcd}	142.2 ^{abc}	ns	79.8 ^{bc}	93.2 ^{bc}	91.8 ^{bc}	88 ^{bc}	102 ^{ab}	108.5^{ab}	108.5 ^{ab}	107.8 ^{ab}
at.ind.	133.33 ^{abcd}	146.5 ^{a}	141.75 ^{bcd}	169^{a}	ns	77.7 ^{bc}	93 ^{bc}	94.5 ^{bc}	107.3 ^{b}	98.7 ^{ab}	111.8^{ab}	110.2 ^{ab}	124 ^{ab}
post.15m	121.2^{bcde}	122.5 ^{a}	136.2 ^{bcd}	137.8 ^{a}	ns	67 ^{bc}	67.2 ^{bc}	81.8 ^{bc}	83 ^{bc}	88.5 ^{ab}	90.5^{ab}	101.2 ^{ab}	103.5 ^{ab}
post.20m	111.2^{cde}	121 ^{a}	128.2 ^{cd}	127.2 ^{c}	ns	65 ^{bc}	63.2 ^{bc}	84.2 ^{bc}	70.8 ^{bc}	82.8 ^{ab}	84^{ab}	103 ^{ab}	90.5 ^{ab}
post.25m	108.5b^{de}	122 ^{a}	130.2 ^{cd}	129.8 ^{bc}	ns	59.5 ^{bc}	57.5^{bc}	81 ^{bc}	73.2 ^{bc}	75^{b}	78.5 ^{ab}	100 ^{ab}	99 ^{ab}
post.30m	100.2^{e}	118.2 ^{a}	124.5 ^{d}	128.5 ^{c}	ns	55^{c}	72.2 ^{bc}	74 ^{bc}	73.5 ^{bc}	73^{b}	89.2^{ab}	94.2 ^{ab}	94.8 ^{ab}
post.35m	96.5^{e}	113.8 ^{a}	124.5 ^{d}	131 $^{bc\#}$	*	56.2^{c}	64.8 ^{bc}	75.5 ^{bc}	82.8 ^{bc}	71^{b}	85^{ab}	95.2 ^{ab}	101 ^{ab}
post.40m	97.2^{e}	114.8 ^{a}	128.5 ^{cd}	128 $^{c\#}$	*	53.8^{c}	65.5 ^{bc}	84.5 ^{bc}	82 ^{bc}	73^{b}	86.8^{ab}	100.8 ^{ab}	97 ^{ab}
post.45m	105.2^{de}	125.2 ^{a}	133.5 ^{bcd}	133.5 ^{a}	ns	65.2 ^{bc}	69.8 ^{bc}	89.8 ^{bc}	84.2 ^{bc}	82 ^{ab}	94.8^{ab}	108 ^{ab}	103.2 ^{ab}
post.50m	132.5^{abcd}	119.5 ^{a}	146.2 ^{bcd}	139.8 ^{abc}	ns	88 ^{bc}	69.5 ^{bc}	101.8 ^{b}	86.8 ^{bc}	107.5 ^{ab}	91.2^{ab}	116 ^{ab}	102.8 ^{ab}
post.55m	152.2^{a}	132.8 ^{a}	160 ^{abc}	146.2 ^{abc}	ns	107.5 ^{b}	84.5 ^{bc}	112.2 ^{b}	94.5 ^{bc}	123.8 ^{ab}	96.5^{ab}	128.5 ^{ab}	113.8 ^{ab}
post.60m	155^{a}	136.8 ^{a}	167.8 ^{abc}	157.5 ^{abc}	ns	108.2 ^{b}	86.2 ^{bc}	118.2 ^{b}	109 ^{b}	128.8^{ab}	101.8^{ab}	135.5 ^{ab}	125.8 ^{ab}
post.65m	145.5^{ab}	141.5 ^{a}	176.2^{ab}	156.2 ^{abc}	ns	101 ^{b}	87.8 ^{bc}	122.8 ^{b}	108 ^{b}	118.8 ^{ab}	102.2^{ab}	136.2 ^{ab}	124 ^{ab}
post.70m	145.2^{ab}	140.5 ^{a}	165.8^{abcd}	160.5 ^{abc}	ns	103 ^{b}	78.5 ^{bc}	130.5^{ab}	110.2 ^{b}	117.2 ^{ab}	104.2^{ab}	144^{a}	127.2 ^{ab}
post.75m	143.2^{a}	142.2 ^{a}	173.8 ^{ab}	162.5 ^{abc}	*	95.5 ^{b}	91.8 ^{bc}	126.5 ^{ab}	113.5 ^{b}	111.8 ^{ab}	100.5^{ab}	143.8^{a}	133 ^{ab}
post.80m	143.5^{a}	142 ^{a}	170.8 ^{abc}	165.2 ^{ab}	ns	99 ^{b}	91.5 ^{bc}	126 ^{ab}	116.5 ^{b}	114 ^{ab}	106.5^{ab}	147.2^{a}	135.2 ^{ab}
post.85m	139.2^{abc}	138.5 ^{a}	156 ^{abcd}	165.8 ^{ab}	ns	93.8 ^{bc}	90.2 ^{bc}	102 ^{b}	116.5 ^{b}	109.8 ^{ab}	105.5^{ab}	133.6 ^{ab}	133.5 ^{ab}
post.90m	138.5^{abc}	122.6 ^{a}	182.5^{a}	168.8 ^{a}	***	90.5 ^{bc}	81.7 ^{bc}	133.2^{a}	118.5 ^{b}	106.8 ^{ab}	91.8^{ab}	145.7^{a}	134 ^{ab}
C.V						28%	22.4%	26%	25.4%	23%	15.8%	20.3%	20.5%

^{abcd} means with difference superscript within same column are statistically difference $p < 0.05$



Supplementary Figure 1S: Showing the heart rate of the 4 groups from the baselisne values to 90 min post-induction.

Supplementary Table 2S: The estimated marginal means and coefficient of variation of the ET SEVO level change over the time of anesthetic procedure for G1 and G2.

Time	1	2
Post.15m	2.1^{b}	1.95^{c}
Post.20m	2.1^{b}	2^{b}
Post.25m	2.12^{b}	1.95^{c}
Post.30m	2.1^{b}	2^{b}
Post.35m	2.08^{b}	2.05 ^{b}
Post.40m	2.12 ^{b}	2.05 ^{b}
Post.45m	2.15 ^{b}	2.12 ^{b}
Post.50m	2.17 ^{b}	2.23 ^{b}
Post.55m	2.2 ^{b}	2.25^{b}
Post.60m	2.27 ^{ab}	2.25 ^{b}
Post.65m	2.27 ^{ab}	2.12 ^{b}
Post.70m	2.33 ^{a}	2.2 ^{b}
Post.75m	2.35 ^{a}	2.12 ^{b}
Post.80m	2.38 ^{a}	2.2^{b}
Post.85m	2.4 ^{a}	2.17^{b}
Post.90m	2.4 ^{a}	2.17 ^{b}
C.V	7%	7%

^{abc} means with different superscript are statistically different $p < 0.05$

Supplementary Table 3S: Showing the estimated marginal means for respiratory rate (RR) breath/minute, tidal volume (VT) in the 4 groups during the anesthetic procedure at consecutive time points (post 15 min to post 90).

	RR (breaths/min)				VT (ml)			
	1	2	3	4	1	2	3	4
30 m	15.75 ^{b}	13.67 ^{bc}	15.25 ^{b}	16.25 ^{ab}				
Post.15m	6.75 ^{e}	10.5 ^{cd}	10 ^{cd}	11.25^{bc}	230^{ab}	217 ^{ab}	217 ^{ab}	200 ^{ab}
Post.20m	9.25^{d}	12.25 ^{bc}	10 ^{cd}	11.5 ^{bc}	187 ^{ab}	229 ^{ab}	222 ^{ab}	236 ^{ab}
Post.25m	9.75 ^{d}	13 ^{bc}	10.5 ^{cd}	13 ^{bc}	195 ^{ab}	217 ^{ab}	216 ^{ab}	171 ^{c}
Post.30m	10.5 ^{cd}	12 ^{bc}	7.75 ^{e}	12.75 ^{bc}	194 ^{ab}	209 ^{ab}	174 ^{c}	219 ^{ab}
Post.35m	11 ^{bc}	12.25 ^{bc}	7.75 ^{e}	13.5 ^{bc}	286^{a}	227 ^{ab}	166 ^{c}	183 ^{ab}
Post.40m	12 ^{bc}	7^{e}	10 ^{bc}	16 ^{ab}	264 ^{ab}	196 ^{ab}	229 ^{ab}	197 ^{ab}
Post.45m	15^{b}	6.75 ^{e}	8.5 ^{d}	13 ^{bc}	177 ^{ab}	205 ^{ab}	230 ^{ab}	183 ^{ab}
Post.50m	12.25 ^{b}	10.25 ^{cd}	10.75 ^{b}	11.25 ^{bc}	228 ^{ab}	238 ^{ab}	241 ^{ab}	254 ^{ab}
Post.55m	14.25 ^{b}	7.75 ^{e}	11.25 ^{b}	11.25 ^{bc}	219 ^{ab}	214 ^{ab}	191 ^{ab}	211 ^{ab}
Post.60m	12.75 ^{b}	6.75 ^{e}	10.5 ^{b}	12.25 ^{bc}	204 ^{ab}	196 ^{ab}	245 ^{ab}	208 ^{ab}
Post.65m	12.75 ^{b}	8.5^{d}	11.75 ^{bc}	16.75 ^{ab}	199 ^{ab}	239 ^{ab}	224 ^{ab}	180 ^{ab}
Post.70m	19.5^{a}	7.75 ^{e}	15 ^{b}	12 ^{bc}	171^{c}	222 ^{ab}	252 ^{ab}	202 ^{ab}
Post.75m	12.75 ^{b}	9 ^{c}	8^{d}	16 ^{ab}	209 ^{ab}	220 ^{ab}	254 ^{ab}	175 ^{ab}
Post.80m	14.25 ^{b}	9.5 ^{c}	9.25^{c}	13.5 ^{bc}	216 ^{ab}	215 ^{ab}	257 ^{ab}	203 ^{ab}
Post.85m	16.5 ^{ab}	11 ^{b}	10 ^{cd}	17.25^{a}	221 ^{ab}	235 ^{ab}	246 ^{ab}	179 ^{ab}
Post.90m	11.5^{b}	9.33 ^{c}	10.25 ^{cd}	12.75 ^{bc}	216 ^{ab}	217 ^{ab}	253 ^{ab}	243 ^{ab}
C.V	35%	27%	32%	26%	19.75%	15 %	23%	19%

^{abc} means with different superscript are statistically different for each measured parameter, $p < 0.05$.

Supplementary Table 4S: Estimated marginal means of the ETCO2 level change over the time of the anesthetic procedure for the 4 groups.

Time	1	2	3	4	Significance of simple effect between groups at each time point
Post.15m	46.8	42	46.2 ^{ab}	44	P > 0.05^{ns}
Post.20m	43	45.8	41.2 ^{ab}	44.8	P > 0.05^{ns}
Post.25m	48.2	41.5	46.5 ^{ab}	45	P > 0.05^{ns}
Post.30m	49^{A}	42.8^{B}	44 ^{abB}	44.5^{B}	< 0.05*
Post.35m	44.8 ^{A}	45.2 ^{A}	29.2 $^{b\ B}$	45.5 ^{A}	P < 0.05*
Post.40m	43.5	45	45.5 ^{ab}	42.2	P > 0.05^{ns}
Post.45m	43.2	45	46.2 ^{ab}	44	P > 0.05^{ns}
Post.50m	42.2	45	45.8 ^{ab}	45.8	P > 0.05^{ns}
Post.55m	40.5	43	43.8 ^{ab}	47.2	P > 0.05^{ns}
Post.60m	44.5 ^{A}	35 ^{B}	43.8 $^{ab\ A}$	44.2 ^{A}	P < 0.05*
Post.65m	43.8	41.2	43 ^{ab}	43.5	P > 0.05^{ns}
Post.70m	41.5	44.8	46.8 ^{ab}	44.8	P > 0.05^{ns}
Post.75m	43.2	41	47.5^{a}	44.5	P > 0.05^{ns}
Post.80m	44.2	43.2	46.5^{ab}	42.8	P > 0.05^{ns}
Post.85m	44.2	44.3	47.2^{a}	45.2	P > 0.05^{ns}
Post.90m	43	43.7	48^{a}	45.2	
Significance of simple effect over time	P > 0.05^{ns}	P >0.05^{ns}	P<0.05*	P >0.05^{ns}	

^{ab} means with different superscript within same column are statistically different $p < 0.05$. ^{AB} means with different superscript within same row are statistically different $p < 0.05$. ns: non-significant difference $P > 0.05$; * significantly different $P < 0.05$.