Anesthetic effects of dexmeditomidine-tiletamine/zolazepam combination in cats undergoing ovariohysterectomy

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Abstract

Common injectable anesthetics in cats are alpha-2 receptor agonists and tiletamine/zolazepam. Xylazine shows higher rate of side effects because its lower specificity to alpha-2 receptors than dexmeditomidine. However, the use of drug combinations in cats is not much known. Therefore, alternative anesthetic combination should be investigated. Here, we examined the use of tiletamine/zolazepam with two doses of dexmedetomidine in cats. A total of 24 female cats, weight 3.05 ± 0.10 kg (mean ± SEM). Cats were randomly blinded given intramuscularly injection (IM) with either of such drug combination, representing dosage of low dose dexmedetomidine 7.5 µg/kg with tiletamine/zolazepam 3 mg/kg; TD-Lo (n=8), high dose dexmedetomidine 15 µg/kg with tiletamine/zolazepam 3 mg/kg; TD-Hi (n=8), or xylazine 0.6 mg/kg with tiletamine/zolazepam 3 mg/kg; TX (n=8). After the IM injection, the sedative, analgesic, and cardiorespiratory effects and body temperature were assessed. All treatments showed clinically comparable induction effects resulting in spontaneous lateral/sternal recumbency and loss of paw withdrawal reflex within 7 minutes; TD-Lo (4.125 ± 0.74 min), TD-Hi (4.5 ± 0.32 min), and TX (4.12 ± 0.58 min). Notably, anesthesia time or the time from absent to regain of paw withdrawal reflex (Time LOPR to ROPR) was significantly higher in TD-Hi (52.75 ± 1.17 min) compared to TD-Lo (42.62 ± 2.51 min) and TX (41.12 ± 2.53 min); $p<0.01$. Likewise, a significant higher of time from IM to ROPR in TD-Hi (57.25 ± 1.29 min) were indicated vs in TD-Lo (46.75 ± 2.88 min; $p<0.05$), and vs in TX (45.25 ± 2.43 min; $p<0.01$). No vomiting or any adverse events were reported in all groups. TD-Lo, TD-Hi, and TX produced overall comparable cardiorespiratory effect with no significantly differences in all physiological values; heart rate (HR), respiratory rate (RR), body temperature (T), systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), and tissue oxygen saturation (SpO_2). TD supplied the effective anesthesia duration for ≥ 42 minutes, which can be fully reversed by atipamizole.

Introduction

Handling the cat has always been a critical challenging procedure for veterinary practices. Failure of the first attempt can lead to dramatic stress response or even shocking to death. Therefore, the intramuscular anesthetic injection becomes one of the most preferable approach when it comes to restraining the cats (Robertson *et al.*, 2018).

Common injectable anesthetics in cats are ketamine and xylazine. Ketamine, a dissociative, is controlled and has been shortage. Alpha-2 receptor agonists such as xylazine provide rapid onset of sedation, analgesia, anxiolysis, and muscle relaxation (Greene and Thurmon, 1988) and has been wildly used for anesthetizing the cats. Xylazine, an alpha-2 agonist, has low specificity to alpha-2 receptors leading to produce side effects. Alternative anesthetic combination should be investigated.

Tiletamine/zolazepam provide longer duration than ketamine. The addition of other anesthetic drugs is required as on top of xylazine premedication or as a mixture for reaching complete immobilization and general anesthesia. While one of the most popular mixtures is xylazine-tiletamine/zolazepam (James *et al.*, 1999), such mixture could prolonged recovery (Clarke *et al.*, 2014). When using as a sole anesthetic agent, tiletamine/zolazepam frequently cause ataxia, dysphoric recovery, or even sudden death (Maddison *et al.*, 2008). Moreover, xylazine usage has led to high mortality rate (Clarke and Hall, 1990). These usage precautions have raised concerns on veterinary anesthetic filed, especially in the cats whose unique temper highly depends on the injectable mixture. Therefore, finding the novel injectable anesthetic mixture which contain the appropriate amount of various anesthetic agents that enough to produce all general anesthesia requirements with the least adverse effects from each agent (balanced multimodal anesthesia and analgesia) (Brown *et al.*, 2018) would be ideal for cat anesthesia.

Dexmedetomidine, an alpha-2 agonist, has high specificity to alpha-2 receptors. However, the use of these combinations in cats is not much known. Dexmedetomidine is a highly selective alpha-2 agonist and has approximately 10 times greater alpha-2: alpha-1 affinity than xylazine (1620:1 for dexmedetomidine, vs. 160:1 for xylazine) (Sinclair, 2003). As a result from greater selectivity, dexmeditomidine not only have shown to produce fewer side effects but also can provide safely analgesia and sedation in cats (McSweeney *et al.*, 2012; Nicacio *et al.*, 2020; Norkus *et al.*, 2017; Oguntoye, 2020; Pypendop *et al.*, 2011; Volpato *et al.*, 2015). While a variety mixtures of anesthetic drugs have been proposed for use in veterinary medicine, alpha-2 agonist- either of xylazine or dexmeditomidine mixes with tiletamine/zolazepam would be more practically and easier accessible for most veterinary anesthesia. Because these anesthetic drugs are not categorized as restricted drugs like ketamine or opioid which required legal registration and routine drug usage report. To achieve the optimal dose of anesthetic drugs providing satisfied sedative and analgesic levels for general anesthesia and surgical procedures in cats, here we study the anesthetic effects of dexmeditomidine-tiletamine/zolazepam as a single injectable mixture in cats undergoing ovariohysterectomy. We tested the varied low doses of dexmeditomidine combination with low dose tiletamine/zolazepam as a single intramuscular (IM) injection. Here, we examined the use of tiletamine/zolazepam with two doses of dexmedetomidine in cats. We hypothesized whether a surgical anesthesia plane provided by tiletamine/zolazepam with high dose dexmedetomidine is more effective than that provided by tiletamine/zolazepam with low dose dexmedetomidine during ovariohysterectomy (OVH) in cats.

Materials and Methods

Animals: A total of 24 healthy female cats (n=24; weight 3.05 ± 0.10 kg), undergoing OVH. Experiments were approved by the animal ethics committee of the Soi Dog Foundation (Bangkok, Thailand). All cats were group housed and their food (not water) was removed 8-12 hours prior to anesthesia. Blood collection (CBC/chemistry) was performed on the day of anesthesia (cats with abnormal blood results were excluded from the study).

Study design: Cats were randomly assigned to 1 of 3 treatment groups: 1) tiletamine/zolazepam with xylazine [TX at 0.03 ml/kg IM; Zoletil®100, Virbac Corporation, USA; tiletamine 250 mg/zolazepam 250 mg; XYL-M2®, VMD Livestock pharma, Belgium; 20 mg/ml]; 2) tiletamine/zolazepam with low dose dexmedetomidine [TD-Lo at 0.03 ml/kg IM; 2.5 ml of dexmedetomidine (0.25 mg/ml, Dexdometor® Orion Pharma, Finland) + 2.5 ml 0.9% NaCl + tiletamine/zolazepam powder]; 3) tiletamine/ zolazepam with high dose dexmedetomidine [TD-Hi at 0.03 ml/kg IM; 5 ml of dexmedetomidine (0.5 mg/ml dexmedetomidine + tiletamine/zolazepam]. All IM injections were performed at a hindlimb using a 1 ml syringe (Nipro®, Nipro Corporation, Japan) with 23G x 1" needle (Nipro®, Nipro Corporation, Japan).

Anesthesia and surgery: After lateral or sternal recumbency, cats were placed in a prep area, an ophthalmic ointment was applied to both eyes, urinary bladders were manually expressed (if needed), and the cats intubated. An intravenous catheter was placed in a cephalic vein and balanced fluid was administered (10-20 ml/kg/h). The surgical area (ventral abdomen) was shaved, prepped with three alternating scrubs of betadine/alcohol, and draped for ovariohysterectomy (OVH). Cats were placed in an operating room on a water circulating heating pad and connected to anesthetic monitoring equipment. Cats were maintained with isoflurane (0.5-1.5% as needed, Aerrane®, Baxter Healthcare Corporation, USA; Isoflurane USP) in 100%O_2 (1-2 L/min) throughout the procedure. Once a surgical plane (absence paw withdrawal, palpebral reflexes, and/or jaw tone) was achieved, OVH was performed. At the end of procedure (30 min), atipamezole (0.1 mg/kg, IM,

Anitsedan®, Orion Pharma, Finland; atipamezole hydrochloride, 5 mg/ml) was administered.

Monitored parameters:
Duration parameters: After anesthetic administration (T0), all duration parameters below (Table 1) were monitored. The subjective pain analyses were performed by testing the paw withdrawal reflex. A loss of the paw withdrawal sign was defined as no paw withdrawal in response to pinching the hind paw using the evaluator's thumb and index fingers. A surgical anesthesia plane was defined as a loss of paw withdrawal reflex.

Table 1 Duration parameters.

Criteria	Description (min)
Onset of induction	T0 – spontaneous lateral/sternal recumbency
Onset of surgical anesthesia plane	T0 – loss of paw withdrawal reflex
Duration of surgical anesthesia plane	Loss of paw withdrawal reflex - return of paw withdrawal reflex
Onset of recovery	Isoflurane discontinuation - spontaneous sternal recumbency

Physiological parameters: During anesthesia, physiological parameters monitored were heart rate (HR, ECG/auscultation, (Monitor-mivet-M3T, TOOTOO, China), respiratory rate (RR, observation), tissue oxygen saturation (%SpO$_2$) body temperature (T, rectal thermometer), blood pressure [oscillometric method with 40% circumference cuff placed at radius/ulna area either left or right forelimb, systolic (SAP)/mean (MAP)/diastolic (DAP) pressure]. All physiological parameters were recorded every three minutes (before and during surgery) and five minutes (after surgery).

Statistical analysis: Data were analyzed using repeated measures ANOVA with Bonferroni correction for multiple comparison (The GraphPad Prism software, La Jolla, CA, USA). Data were expressed as mean ± SEM. A *P* values of less than 0.05 was considered significant.

Results

Duration parameters: TD-Hi significantly enhances time from IM to regain of paw withdrawal reflex, time from IM to extubation, and time from loss to return of paw withdrawal reflex compared to both TD-Lo and TX.

All cats were lateral recumbency, had loss of paw withdrawal reflex (LOPR), and were complete immobilization within 7 minutes of IM injection (Table 2). No differences of time from IM to lateral recumbency and time from IM to LOPR between three groups. All three treatments showed comparable rapid induction effect with Time IM to lateral recumbency (3.37 ± 0.49 min in TD-Lo, 3.37 ± 0.26 min in TD-Hi, and 4.12 ± 0.58 min in TX, respectively) (Figure 1A, blue dot). Likewise, time IM to LOPR of TD-Lo, TD-Hi, and TX was 4.12 ± 0.74, 4.5 ± 0.32, and 4.12 ± 0.58 min, respectively (Figure 1A, red square). No vomiting was indicated in all treatments. Endotracheal intubation was successfully performed in all cats.

Interestingly, time from IM to return of paw withdrawal reflex, ROPR was significantly differences between three groups (Figure 1B, blue dot). TD-Hi-treated cats had significantly higher time IM to ROPR (57.25 ± 1.29 min) than TD-Lo (46.75 ± 2.88 min; *p<0.05), and TX (45.25 ± 2.43 min; **p<0.01). Similarly, time IM to extubation was significantly higher in TD-Hi group (58.12 ± 0.85 min) compared to time IM to extubation on both TD-Lo group (47 ± 2.89 min) and TX group (45.25 ± 2.43 min) (**p<0.01) (Figure 1B, red square). While anaesthesia time was considered as the time interval from complete immobilization (LOPR) to the first attempt made by the animal to lift its head a few centimetres above the ground (ROPR and need to extubate). Therefore, the anesthesia time or the time from LOPR to ROPR (Time LOPR to ROPR) for TD-Hi was 52.75 ± 1.17 min, which was significantly higher than TD-Lo 42.62 ± 2.51 min and TX 41.12 ± 2.53 min; **p<0.01) (Figure 1C, red dot).

Physiological parameters:
Physiological values showed no significantly differences between all treatment groups: Whereas similar trend of physiological response was indicated in all treatment groups. No significantly differences in physiological values between all treatments was identified (Table 3 and 4).

Table 2 Effects of low dose dexmedetomidine-tiletamine/zolazepam (TD-Lo), high dose dexmedetomidine-tiletamine/zolazepam (TD-Hi), and xylazine-tiletamine/zolazepam (TX) on duration parameters.

Anesthetic combinations	Time IM to lateral recumbency (min)	Time IM to loss of paw withdrawal reflex (min)	Time IM to return of paw withdrawal reflex (min)	Time from loss to return of paw withdrawal reflex (min)	Time IM to extubation (min)
TD-Lo	3.37 ± 0.49	4.12 ± 0.74	46.75 ± 2.88 *	42.62 ± 2.51 **	47 ± 2.89 **
TD-Hi	3.37 ± 0.26	4.5 ± 0.32	57.25 ± 1.29	52.75 ± 1.17	58.12 ± 0.85
TX	4.12 ± 0.58	4.12 ± 0.58	45.25 ± 2.43 **	41.12 ± 2.53 **	45.25 ± 2.43 **

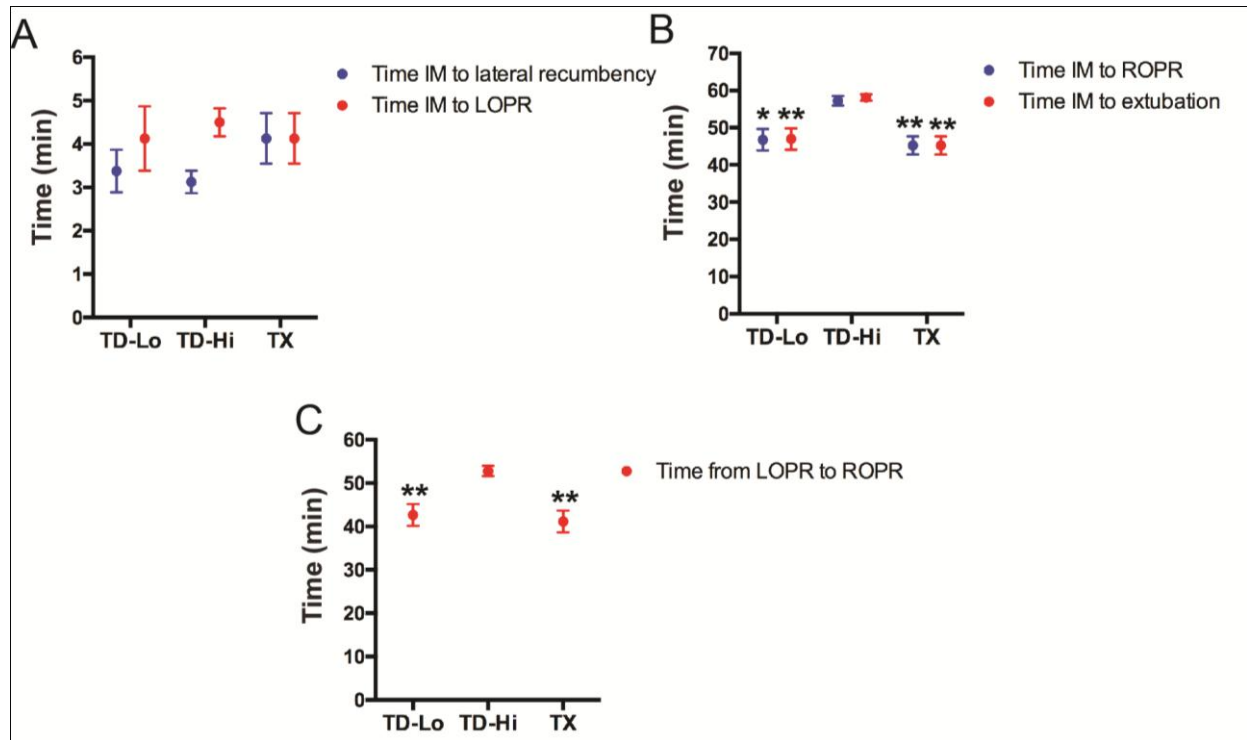(*p<0.05 vs TD-Hi), (**p<0.01 vs TD-Hi).

Figure 1 High dose dexmeditomidine with tiletamine/zolazepam significantly increases time from loss of paw withdrawal reflex (LOPR) to return of paw withdrawal reflex(ROPR).

No differences of time from IM to lateral recumbency and time from IM to LOPR between three groups (A). Time IM to lateral recumbency of TD-Lo, TD-Hi, and TX was 3.37 ± 0.49, 3.37 ± 0.26, and 4.12 ± 0.58 minutes, respectively. TD-Hi significantly enhances time from IM to ROPR, time from IM to extubation (B), and and time from LOPR to ROPR compared to both TD-Lo and TX (C). (*p<0.05 vs TD-Hi), (**p<0.01 vs TD-Hi). Error bars = SD. [low dose dexmedetomidine-tiletamine/zolazepam (TD-Lo), high dose dexmedetomidine-tiletamine/zolazepam (TD-Hi), and xylazine-tiletamine/zolazepam (TX)].

Table 3 Effects of low dose dexmedetomidine-tiletamine/zolazepam (TD-Lo), high dose dexmedetomidine-tiletamine/zolazepam (TD-Hi), and xylazine-tiletamine/zolazepam (TX) on heart rate, respiratory rate, temperature, and SpO_2.

Anesthetic combinations	Physiological parameters	TD-Lo	TD-Hi	TX
Before surgery	Heart rate (beats /min)	109.97 ± 5.01	116.77 ± 4.32	110.08 ± 6.20
	Respiratory rate (breaths/min)	21.97 ± 5.89	34.31 ± 7.80	19.5 ± 2.81
	SpO_2 (%)	97.53 ± 0.55	97.66 ± 0.78	96.65 ± 0.85
	Temperature (^{0}C)	38.43 ± 0.12	38.99 ± 0.17	39.15 ±0.22
During surgery	Heart rate (beats /min)	123.46 ± 5.22	119.29 ± 15.70	117.91 ± 6.76
	Respiratory rate (breaths/min)	32.95 ± 5.66	41.13 ± 7.76	24.52 ± 2.86
	SpO_2 (%)	98 ± 0.68	97.83 ± 0.61	96.78 ± 0.57
	Temperature (^{0}C)	37.97 ± 0.16	38.72 ±0.24	38.63 ± 0.27
After surgery	Heart rate (beats /min)	115.92 ± 6.22	103.17 ± 4.24	100.013 ± 5.20
	Respiratory rate (breaths/min)	39.76 ± 5.44	45.22 ± 7.15	30.87 ± 4.68
	SpO_2 (%)	98.06 ± 0.75	97.95 ± 0.66	96.96 ± 0.57
	Temperature (^{0}C)	37.25 ±0.22	37.74 ±0.23	37.92 ± 0.31

Table 4 Effects of low dose dexmedetomidine-tiletamine/zolazepam (TD-Lo), high dose dexmedetomidine-tiletamine/zolazepam (TD-Hi), and xylazine-tiletamine/zolazepam (TX) on systolic arterial pressure (SAP), mean arterial pressure (MAP), and diastolic arterial pressure (DAP).

Anesthetic combinations	Physiological parameters	TD-Lo	TD-Hi	TX
Before surgery	SAP (mmHg)	159.12 ± 5.64	165.87 ± 8.03	158.45 ± 5.31
	MAP (mmHg)	133.85 ± 4.95	135.27 ± 6.78	134.29 ± 5.46
	DAP (mmHg)	119.78 ± 5.81	124.75 ± 5.61	122.12 ± 5.38
During surgery	SAP (mmHg)	161.75 ± 5.67	169.84 ± 3.88	157.60 ± 4.56
	MAP (mmHg)	134 ± 2.11	140.07 ± 3.38	130.10 ± 2.76
	DAP (mmHg)	118.14 ± 3.67	127.53 ± 2.04	118.66 ± 3.25
After surgery	SAP (mmHg)	134.5 ± 3.94	138.90 ± 3.60	142.5 ± 3.38
	MAP (mmHg)	105.07 ± 5.30	112.96 ± 3.43	118.56 ± 2.28
	DAP (mmHg)	89.15 ± 6.63	99.63 ± 3.24	107.37 ± 1.94

Heart rate in all groups increased from before surgery to during surgery and then decreased after surgery; TD-Lo (before surgery 109.97 ± 5.01 beats/min, during surgery 123.46 ± 5.22 beats/min, and after surgery 115.92 ± 6.22 beats/min), TD-Hi (before surgery 116.77 ± 4.32 beats/min, during surgery 119.29 ± 5.55 beats/min, and after surgery 103.17 ± 4.24 beats/min), and TX (before surgery 110.08 ± 6.20 beats/min, during surgery 117.91 ± 6.76 beats/min, and after surgery 100.013 ± 5.20 beats/min) (Figure 2A).

Increased respiratory rate over time from before surgery to during surgery and after surgery in all treated cats; TD-Lo (before surgery 21.97 ± 5.89 breaths/min, during surgery 32.95 ± 5.66 breaths/min, and after surgery 39.76 ± 5.44 breaths/min), TD-Hi (before surgery 34.31 ± 7.80 breaths/min, during surgery 41.13 ± 7.76 breaths/min, and after surgery 45.22 ± 7.15 breaths/min), and TX (before surgery 19.5 ± 2.81 breaths/min, during surgery 24.52 ± 2.86 breaths/min, and after surgery 30.87 ± 4.68 breaths/min) (Figure 2B) were indicated.

Similar to the respiratory rate, SpO_2 in TD-Lo group (before surgery 97.53 ± 0.55 %, during surgery 98 ± 0.68 %, and after surgery 98.06 ± 0.75 %), in TD-Hi group (before surgery 97.66 ± 0.78 %, during surgery 97.83 ± 0.61 %, and after surgery 97.95 ± 0.66 %), and in TX group (before surgery 96.65 ± 0.85 %, during surgery 96.78 ± 0.57 %, and after surgery 96.96 ± 0.57 %) (Figure 2D) increased over time from beginning of the surgery to during surgery and then to after surgery.

Whereas respiratory rate and SpO_2 increased overtime, body temperature decreased from before surgery to during surgery and after surgery in all treatment groups; TD-Lo (before surgery 38.43 ± 0.12 ^{0}C, during surgery 37.97 ± 0.16 ^{0}C, and after surgery 37.25 ±0.22 ^{0}C), TD-Hi (before surgery 38.99 ± 0.17 ^{0}C, during surgery 38.72 ±0.24 ^{0}C, and after surgery 37.74 ±0.23 ^{0}C), and TX (before surgery 39.15 ±0.22 ^{0}C, during surgery 38.63 ± 0.27 ^{0}C, and after surgery 37.92 ± 0.31 ^{0}C) (Figure 2C).

Average values of systolic, mean, diastolic arterial pressure were higher at before surgery (Figure 3A) and during surgery (Figure 3B), and then decreased after surgery (Figure 3C) in all treatment groups. (Table 4).

Additional of inhalation Isoflurane was administered briefly during surgery in 3 cats; (2 cats in TD-Lo for 2 min and 3 min, and 1 cat in TX for 3 min).
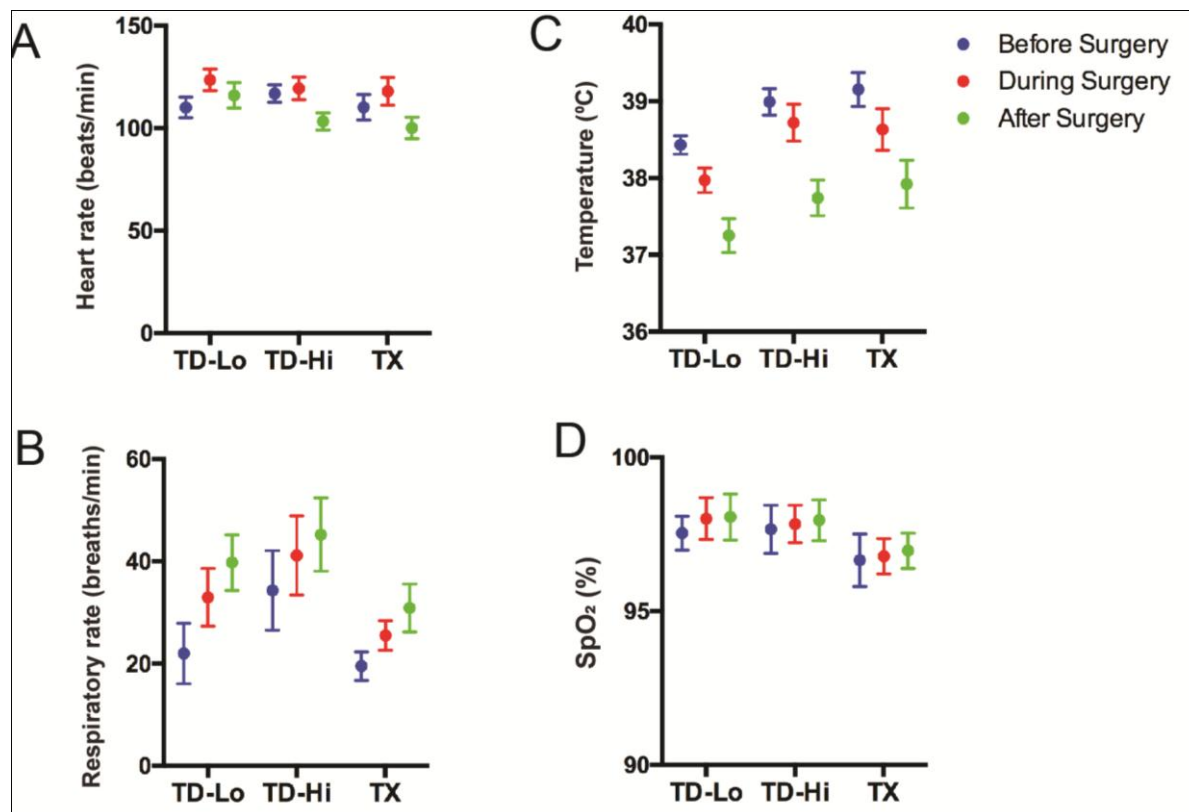
Figure 2   No significantly differences in cardiorespiratory responses and body temperature among three treated groups of low dose dexmeditomidine-tiletamine/zolazepam; TD-Lo, high dose dexmeditomidine-tiletamine/zolazepam; TD-Hi, and xylazine-tiletamine/zolazepam; TX. Representative graph of physiological values in all treatment groups; (blue) before surgery, (red) during surgery, and (green) after surgery. While the changed physiological values between before, during, and after surgery showed similar trend of shifting up/down in all treatment groups. No significance difference in (A) heart rate, (B) respiratory rate, (C) body temperature, and (D) SpO2 between TD-Lo, TD-Hi, and TX ($p<0.05$) was indicated. Error bars = SD. [low dose dexmedetomidine-tiletamine/zolazepam (TD-Lo), high dose dexmedetomidine-tiletamine/zolazepam (TD-Hi), and xylazine-tiletamine/zolazepam (TX)].
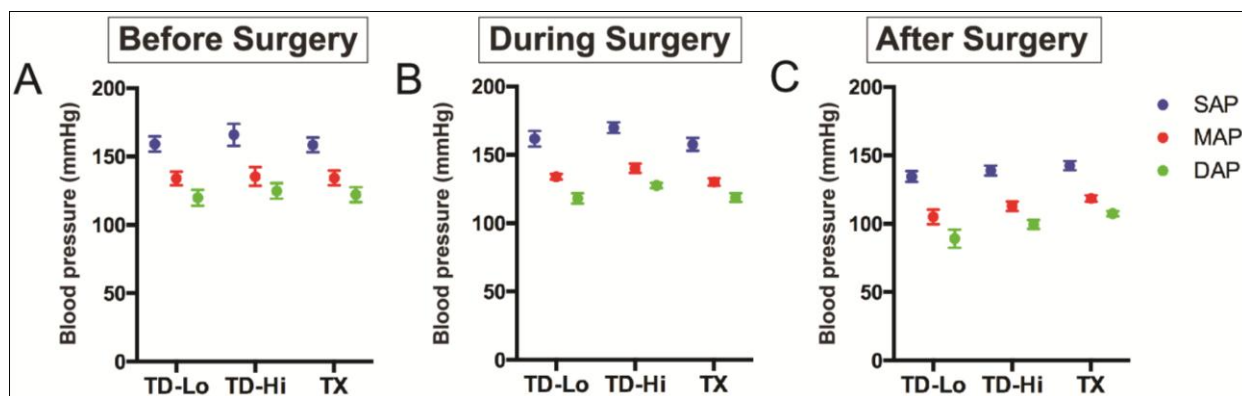

Figure 3   Blood pressure before during and after surgery. No significantly differences between blood pressure of before surgery (A), during surgery (B), and after surgery (C). Error bars = SD. systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP). [low dose dexmedetomidine-tiletamine/zolazepam (TD-Lo), high dose dexmedetomidine-tiletamine/zolazepam (TD-Hi), and xylazine-tiletamine/zolazepam (TX)].

Discussion

Here we demonstrated that low dosage mixture of dexmedetomidine-tiletamine/zolazepam provided the effective multimodal anesthesia for cats during ovariohysterectomy procedures. Rapid onset of sedation was similar in all groups. While all cats 16/16 (100%) which received dexmeditomidine in both TD-Lo and TD-Hi groups were successfully and smoothly intubated, some xylazine-treated cats had closed epiglottis and made them difficult to intubate. It has

been suggested that types and dosage of anesthetic drugs may affect the intubation success rate (McSweeney *et al.*, 2012). The previous studies reported that the combinations of dexmedetomidine-ketamine with either of butorphanol, hydromorphone, or buprenorphine had 13/30 (43%) cats successful intubation rate (Ko *et al.*, 2011). Whereas various dosage of dexmedetomidine (McSweeney *et al.*, 2012) from 7 - 20 µg /kg (Hassen *et al.*, 2019; Martin-Flores *et al.*, 2016; Thawley and Drobatz, 2015) have been used for inducing emesis in cats, our study suggested that

dexmeditomidine 7.5 or 15 µg /kg using in combination with tiletamine/zolazepam had not cause emesis in all treated cats. However, further studies for underlying pathway with more number of cats would be needed to come for conclusion.

The typical adverse effects of alpha 2-agonists are bradycardia, hypoxia, and hypertension +/- hypotension (Sinclair, 2003) (Carollo *et al.,* 2008). In addition, anticholinergic has been previously reported to counter act the bradycardia effect of alpha-2 agonist, but may cause following hypertension and increase myocardial oxygen consumption (Monteiro *et al.,* 2009). Therefore, using reversing drug such as atipamizole would be have higher benefit when facing with such adverse effects.

While cats treated with ketamine-propofol-dexmeditomidine (2 mg/kg - 2 mg/kg - 3 µg mg/kg IV) had significantly lower mean heart rate than without dexmeditomidine (Ravasio *et al.,* 2012), mean heart rate in all groups of our study increased from before surgery to during surgery and then decreased after surgery.

All treated cats had respiratory rate and SpO_2 increased over time from before surgery to during surgery and after surgery. Supplemental isoflurane was needed in some cats that received dexmeditomidine-ketamine-opioid mixtures (Ko *et al.,* 2011). Similarly, TD-Lo-treated 2/8 (25%) cats and TX-treated 1/8 (12.5%) cats in our study were needed supplemental isoflurane for briefly 2 - 3 min during the strong stimulus as pulling uterus was applied. One study reported that butorphanol-dexmedetomidine mixture had superior analgesia level than buprenorphine-dexmedetomidine mixture (Bhalla, Trimble *et al.,* 2018). We previously demonstrated that morphine and tramadol had a comparable antinociceptive effect by increasing the thermal threshold response in cat. It should be noted that these antinociceptive effect was inter-individual variation, meaning some cat had higher thermal threshold when treated with morphine and some with tramadol (Jiwlawat and Durongphongtorn, 2011). To reach the successful feline pain management, a closely monitoring the clinical signs of pain in the cat is critical and must be applied in every clinical practices. Therefore, the further study should be performed to answer whether by adding different types of opioid or partial-opioid on TD treatment could increase the analgesia level or not. All in all, our study demonstrated that TD mixture had efficacy in decreasing the need for other maintained anesthetic drugs.

TD produced rapid recovery with or without atipamizole (Bruniges *et al.,* 2016). After extubation, all cats in TD-Lo and TD-Hi groups were instantly sternal recumbency. Conversely, all cats in TX group were still lay down in lateral recumbency for over an hour.

Comparing average values of systolic, mean, diastolic arterial pressure, and heart rate between TD-Lo and TD-Hi, no trends of decreasing values which would be expected when the higher anesthetic dosage were used (Figure 3A, 3B, 3C, and 2A). Therefore, our result suggested that the effects of dexmeditomidine on cardiovascular systems showed no dose-dependence which in agreeable with the previous study (Monteiro *et al.,* 2009). In addition, SpO_2 of TD-Lo and TD-Hi were in similar range and respiratory rate of TD-Hi was higher than TD-Lo. Our data suggested that the effect of dexmedetomidine on respiratory system seemed not be dose-related.

While the manufacturer dose of dexmedetomidine in cat is 0.040 mg/kg (40 µg /kg) IM, our dose is only 0.0075 or 0.015 mg/kg (7.5 – 15 µg/kg) which is 5.3 - 2.6 times lower. In similar, the manufacturer dose of zoletil is 0.1 - 0.15 ml/kg or 10 -15 mg/kg IM vs our zoletil dose is only 3 mg/kg (5 times lower). While cats which received the drug combination of dexmedetomidine 10 µg/kg, tiletamine/zolazepam 5 mg/kg, and ketamine 10 mg/kg with or without tramadol showed the effective anesthesia duration for 75 -175 minutes (Liang *et al.,* 2021), our result which using a lower dosage of both dexmedetomidine (7.5 µg/kg) and tiletamine/zolazepam (3 mg/kg) without ketamine could provide adequate analgesia in cats for ≥ 42 minutes. Therefore, such data would support the possibility of adding other anesthetic and analgesic drugs such as ketamine and tramadol to our present drug combination.

Previous studies have been shown that a single IM injection of anesthetic mixtures was not enough to induce sedation and anesthesia in some animals; therefore, the second IM injection of the half dose was effective and required in the remaining animals (Pasolini *et al.,* 2013). From our additional experiences outside the research settings, when using either of these 3 drug combinations (TD-Lo vs TD-Hi vs TX), there are some cats that the successful general anesthesia, complete sedative and immobilization can be reached by injecting the second half dose IM. In these circumstances, longer recovery time is expected.

In conclusion, TD provided an effective multimodal anesthesia for cats undergoing ovariohysterectomy. TD as a single IM injection had the anesthesia duration for ≥ 42 minutes, and can be fully reversed by atipamizole. Due to the variation of the respiratory rate, supplementary of oxygen was recommended in all alpha-2 agonist-treated cats. Therefore, TD would have higher benefit over TX because TD-treated cats were easier intubated than TX. Moreover, TD showed strikingly more rapid and calm recovery over TX both with or without atipamizole.

Acknowledgements

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