

Comparison of the anesthesia effects of ketamine, dexmedetomidine and tiletamine-zolazepam with or without tramadol in cats*

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Summary

This study investigated the analgesia effects of intramuscular injection of ketamine, dexmedetomidine and tiletamine-zolazepam combined with tramadol (KDZT) and compared the efficacy of this combination with that of ketamine, dexmedetomidine and tiletamine-zolazepam (KDZ) in Chinese local mongrel cats. Ten cats were tested twice as a comparison between the two groups, and the interval between the two groups was more than a week. The animals received ketamine (10 mg/kg), dexmedetomidine (10 µg/kg) and zoletil (5 mg/kg) combined with or without tramadol (2 mg/kg) for anesthesia in separate tests. Heart rate, respiration rate, non-invasive systolic pressure, hemoglobin oxygen saturation, rectal temperature, subjective pain scores and venous blood-gas analysis were measured simultaneously. The induction time, recovery time of the righting reflex, standing and walking, the time during the anesthesia period were recorded. Cardiopulmonary variables changed after injection, some of which were significantly different from baselines before anesthesia induction. Values regarding blood gas changed after intramuscular administration, and significant differences were found between two groups at one of the timepoints. Both KDZT and KDZ provided adequate analgesia in cats. The induction period of two anesthetic mixtures was within 1-3 min and could effectively maintain anesthesia for 75-175 min. The change of physiological parameters remained within a biologically acceptable range and was not significantly different between the two groups. The use of KDZT resulted in better anesthesia, with shorter anesthesia induction period and longer anesthesia period compared with KDZ. No side effects were observed, no rescue analgesic was required.

Keywords: tramadol, anesthesia, cats, physiological parameters

Felines tend to be wild and difficult to be tamed. If necessary, appropriate general anesthesia is required to perform a physical examination of cats. However, extra devices are necessary for inhalation anesthesia. The cat's trachea is narrow, prone to throat paralysis, and obstruction of the airway. Moreover, the dorsal tracheal ligament is weak in cats. When the tracheal intubation cuff's air pressure is too large, the soft tis-

sue of the trachea may be torn, causing respiratory complications, or gas may enter the loose tissue and spread to the head and neck or even the whole body. Therefore, intramuscular anesthesia for cats is safer than inhalation anesthesia and has been appreciated and studied by more and more veterinarians.

Dexmedetomidine is a novel, highly selective, specific α_2 -adrenergic receptor agonist with sedative, anxiolytic, anti-sympathetic and analgesic effects (2, 12). The analgesic effect is not very strong at any dose, and dexmedetomidine may only be applied in small surgical interventions and clinical operations with mild pain (1). At high doses, animals can also

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enter deep anesthesia, where adverse reactions such as vomiting and inhibition of the respiratory cycle often occur (20).

Ketamine does not act on the entire cerebral cortex, but only on the brain's contact pathway and the thalamic-neocortical system, selectively inhibiting certain parts of the central nervous system, causing the separation of pain and consciousness, which is why it is called a "separation anesthetic". Some scholars used ketamine alone to anesthetize cats to confirm that ketamine anesthesia was valuable (9, 16). There have been several reports on the combination of ketamine with other anesthetics, which showed that ketamine in combinations has a very positive anesthetic effect on cats (6, 10, 24).

Zoletil is an anesthetic made up of Tiletamine and Zolazepam at a ratio of 1 : 1. Tiletamine has a similar effect to ketamine, but a longer separation time, and the analgesic effects are more pronounced. Zolazepam belongs to the class of benzodiazepines. Used alone or combined with other anesthetics it can produce a positive sedative, muscle relaxant, anticonvulsant effect, and has less impact on cardiopulmonary function, making the induction of wakefulness more stable (22). Cistola et al. confirmed that zoletil, ketamine and xylazine can produce rapid onset of lateral recumbency and surgical anesthesia of sufficient duration to complete surgical procedures in 92% of adult feral cats, which does not inhibit breathing but temporarily causes the body temperature to decrease (6).

Tramadol is a synthetic drug for aniline and is listed by WHO as the second phase of treatment medication for cancer pain. At the same dose of the drug, the analgesic intensity is only 1/5 of that of morphine, but significantly stronger than other non-steroidal anti-inflammatory drugs, and it also has a certain effect on α_2 -adrenergic receptors and 5-HT receptors. The curative effect is enhanced by two mechanisms' synergistic effect, and is suitable for patients with clinical and severe cancer pain. Tramadol can specifically act on the central nervous system receptors of pain, with no smooth muscle spasm and respiratory depression in clinical trials, and can effectively relieve pain for patients for at least four hours; tramadol hydrochloride has no morphine-like serious side effects, while its adverse reactions are similar to other analgesics, mainly including nausea, stomach discomfort, vomiting, dizziness, sweating, dry mouth and other symptoms (19).

To the authors' knowledge there are no data available about the use of tramadol in combination with KDZ used in cats. It was hypothesized that tramadol combined with KDZ (KDZT) might produce a greater depth and duration of anesthesia than KDZ alone. This study on Chinese local mongrel cats was undertaken to evaluate the anesthetic and analgesic effects of KDZT and determine the magnitude of changes in some basic physiological variables.

Material and methods

Animals. Ten (5 females and 5 males) healthy local mongrel cats were enrolled in a randomized, prospective, blinded clinical study. The mean age of cats was 1.3 ± 0.39 years and the mean body weight 3.54 ± 0.68 kg. Cats with arrhythmias, respiratory abnormalities, or other systemic diseases such as kidney disease were excluded from this study. Animals didn't administrated any drugs before the experiment. Before the test, routine examinations were carried out to ensure that the cats' physiological indicators were normal, their mental condition was good, and the cats were considered healthy and then tested. The experimental animals were kept in the same environment, fed uniformly. Food, but not water, was withheld for 6 hours before the study commenced.

Time recordings and calculations. Injections were made at the quadriceps muscle of the thigh in experimental cats, and timing began after the end of the injection. The anesthesia induction period is the period from the end of the injection to the fall of the experimental animal, and the induction time was recorded. The time of the righting reflex, standing, and walking recovery upon awakening from anesthesia was recorded. The anesthesia period time was calculated by taking the sign that the experimental animal was able to walk and stand at the end of anesthesia.

Anesthetic procedure. Animals were tested twice as a comparison between the two groups ($n = 10$ in each group), and the interval between the two groups was more than a week. Drugs and fluids were given by a 5 mL syringe, which was aseptically intramuscularly injected into thigh quadriceps.

Animals were allowed to adapt to the laboratory environment before the experiment began and baseline physiologic parameters were monitored when the animals were in a peaceful state. Calculation of the dose was based on body weight. Next, animals received 10 mg/kg ketamine (Shenyang Veterinary Medicine Factory, Shenyang, China), 10 μ g/kg dexmedetomidine (Finland Orion Pharmaceutical Factory Espoo Production Plant, Espoo, Finland), 5 mg/kg zoletil (French Vic Co., Ltd., Carros, French) (Group KDZ), or 10 mg/kg ketamine, 10 μ g/kg dexmedetomidine, 5 mg/kg zoletil and 2 mg/kg tramadol (Hubei Qianjiang Pharmaceutical Co., Ltd., Qianjiang, China) (Group KDZT) intramuscularly (IM), and all of them were mixed in the same syringe and given within half a minute.

Baseline physiologic parameters included heart rate (HR), respiratory rhythm (RR), noninvasive systolic, diastolic, and mean arterial pressure (SAP, DAP, and MAP); oxygen saturation (SpO_2), and rectal temperature (RT) were measured by Generic G3F Multi-Function Animal Monitor (Shenzhen Generic Medical Instrument Co., Ltd, Shenzhen, China) before and after drugs administration, and recorded every five minutes during the period of anesthesia. Venous blood samples were also obtained from the saphenous vein by 2.5 mL heparinized syringes and immediately analyzed for venous pH, partial venous pressure of carbon dioxide ($PvCO_2$), the total amount of carbon dioxide (TCO_2), bicarbonate (HCO_3^-), ion concentration of sodium (Na), potassium (K) and calcium (Ca). Blood-gas measurements

Tab. 1. Subjective anesthesia effect score system

Observation	Score	Criteria
Analgesia	0	Normal reaction (severe struggle when acupuncture or clamping)
	1	Moderate reaction (strong reaction when acupuncture or clamping)
	2	Mild reaction (slight reaction only when acupuncture or clamping)
	3	No reaction (no reaction when acupuncture or clamping)
Sedative effect	0	Normal
	1	Mild sedation (headlifting, limb shaking, blinking, and auricular reflexes are all dull, eyeball position is normal)
	2	Moderate sedation (no reaction in head and neck, limbs, blinking, slight or disappearing ear movements, slightly inward of the eyeball)
	3	Deep sedation (no response, the position of the eyeball is completely inward)
Muscle relaxation effect	0	Opening the mouth, pulling the tongue, pulling and flexing the limbs have a strong resistance, the abdominal wall muscles are tight
	1	Opening, pulling and flexing the limbs with slight resistance; the tongue is partially dislodged and the traction feels slightly resistant
	2	There is almost no resistance to opening, pulling and flexing the limbs; the abdominal wall muscles are not completely relaxed, and the abdominal wall muscles contract when pinching and pressing; the tail is slightly drooping, and the artificial swing is slightly resistant
	3	There is no resistance to opening, pulling and flexing the limbs; the tongue is completely disengaged, and there is no resistance in pulling; the muscles in the abdominal wall are completely relaxed, and the abdominal muscles are not contracted when pinching and pressing; the tail is drooping completely, and there is no resistance in artificial swinging

Explanation: anesthesia effect score was calculated as the sum of scores for the 3 individual categories; possible scores ranged from 0 to 9

were corrected to body temperature (GEM Premier 3000, American Experimental Instruments Co., Ltd., Danmark, USA). All cats experienced general anesthesia by the same researcher. Another researcher monitored anesthesia and assessed the anesthetic effect scores.

Subjective pain analyses were performed for the assessment of anesthetic effects during the period of anesthesia. The anesthetic effect assessment was performed after the measurement of physiological parameters (HR, RR, blood pressure, RT) at the following time points: T1 = before induction, T2 = 5 mins after injection of KDZ or KDZT, T3 = 10 mins after the injection, T4 = 30 mins after the injection, T5 = 40 mins after the injection, T6 = 50 mins after the injection, T7 = 60 mins after the injection, T8 = 90 mins after the injection and T9 = 120 mins after the injection. The monitoring of cat anesthesia effects included analgesia, sedative effect, and muscle relaxation effect. The analgesic effect was evaluated by acupuncturing the animal's head and neck, trunk, abdominal wall, and fore and aft limbs, and clamping the animal's nasolabial, auricle, abdominal wall, and anterior and posterior limbs to observe the animal's response. The sedative effect was evaluated by tapping the test bench and observing whether the animal is struggling, limb twitching, blinking, or ear movement. The effect of muscle relaxation was evaluated by the degree of opening, degree of tongue dislocation, limb traction and flexion resistance, and degree of relaxation of the abdominal wall (Tab. 1).

Statistical analysis. All statistical analyses were performed using SPSS 19.0 (SPSS). The student's t-test was used to compare induction, anesthesia, standing, and walking time. Physiological parameters were analyzed using variance analysis for repeated measures to assess changes within each group and between two different treatments. The Mann-Whitney U test was used to compare the scores for sedation, analgesia, and muscle relaxation. $p < 0.05$ was considered significant. All values are reported as mean $\pm$ sd.

Results and discussion

During the period of anesthesia, no side effect such as struggling, convulsions, vomiting was observed in any of the animals. The anesthesia induction time of KDZT was relatively short, and the induction period was 1.33 ± 0.33 minutes. The induction period of KDZ was relatively long, at 1.89 ± 0.91 minutes. KDZT and KDZ's anesthesia time was 123.90 ± 49.40 minutes and 95.47 ± 37.24 minutes, respectively. The awakening period time of KDZT was shorter than KDZ. No significant differences were found among groups for the duration of anesthesia (Tab. 2).

HR was significantly different at T2 to T9, significantly lower at T6 in KDZT, and significantly lower at T4 in KDZ. RR and SpO₂ were not significantly different within groups at baseline. So changes in respiratory parameters were insignificant in KDZT and KDZ when compared to T1. Compared to T1 in KDZT, the DAP of T5 was significantly reduced. However, SAP, DAP, and MAP were lowest at T4 compared to baselines for all groups. Compared to T1 in KDZ, the SAP, DAP, and MAP of T6 were significantly reduced. Compared to T1 in KDZT, T9 has higher SAP, DAP, and MAP. At T6 and T7, the MAP of the KDZT group was significantly higher than that of the KDZ group. From T3 to T7, the rectal temperatures of all groups were significantly reduced. Rectal temperatures from T4 to T7 in KDZT and from T4 to T9 in KDZ were significantly reduced, respectively (Tab. 3).

Subjective anesthesia effect scores had no differences within groups from T1 to T5. KDZ group had lower scores compared with the KDZT group at T6 and T7. KDZT and KDZ had no differences within from T8 to T9. Rescue analgesia was not needed during this study. The minimal subjective anesthesia effect scores were

Tab. 2. Mean $\pm$ SD values for physiological parameters evaluated in cats anaesthetized with two combinations of anaesthetic drugs

Anaesthetic drugs	Time points (minutes)								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
HR (bpm)									
KDZT	184 $\pm$ 29	155 $\pm$ 39*	148 $\pm$ 31*	130 $\pm$ 32*	128 $\pm$ 19*	125 $\pm$ 16*	127 $\pm$ 16*	126 $\pm$ 19*	131 $\pm$ 18*
KDZ	193 $\pm$ 24	160 $\pm$ 12*	147 $\pm$ 5*	134 $\pm$ 8*	134 $\pm$ 8*	138 $\pm$ 11*	145 $\pm$ 19*	149 $\pm$ 23*	157 $\pm$ 28*
RR (breaths/minute)									
KDZT	41 $\pm$ 13	38 $\pm$ 8	46 $\pm$ 14	39 $\pm$ 9	35 $\pm$ 8	37 $\pm$ 9	35 $\pm$ 9	38 $\pm$ 13	39 $\pm$ 12
KDZ	35 $\pm$ 11	45 $\pm$ 13	40 $\pm$ 11	40 $\pm$ 14	39 $\pm$ 16	49 $\pm$ 26	42 $\pm$ 19	45 $\pm$ 17	43 $\pm$ 16
SAP (mmHg)									
KDZT	111 $\pm$ 15	121 $\pm$ 10	126 $\pm$ 0	106 $\pm$ 21	109 $\pm$ 20	120 $\pm$ 16	130 $\pm$ 12	122 $\pm$ 20	132 $\pm$ 5
KDZ	140 $\pm$ 7	134 $\pm$ 5	109 $\pm$ 28	125 $\pm$ 15	127 $\pm$ 12	112 $\pm$ 10*	119 $\pm$ 16	115 $\pm$ 6*	124 $\pm$ 3
DAP (mmHg)									
KDZT	86 $\pm$ 7	90 $\pm$ 3	92 $\pm$ 0	80 $\pm$ 23	71 $\pm$ 10*	85 $\pm$ 14	93 $\pm$ 12	88 $\pm$ 13	99 $\pm$ 6
KDZ	98 $\pm$ 4	96 $\pm$ 1	80 $\pm$ 21	87 $\pm$ 20	83 $\pm$ 16	76 $\pm$ 7*	82 $\pm$ 4	87 $\pm$ 4	90 $\pm$ 11
MAP (mmHg)									
KDZT	94 $\pm$ 9	101 $\pm$ 5	103 $\pm$ 0	88 $\pm$ 23	84 $\pm$ 13	96 $\pm$ 14 ^a	105 $\pm$ 12 ^a	99 $\pm$ 15	110 $\pm$ 2
KDZ	112 $\pm$ 0	109 $\pm$ 2	89 $\pm$ 23	100 $\pm$ 11	98 $\pm$ 15	88 $\pm$ 7 ^b	92 $\pm$ 7 ^b	97 $\pm$ 3	101 $\pm$ 8
RT (°C)									
KDZT	38.4 $\pm$ 1.1	38.5 $\pm$ 1.3	38.5 $\pm$ 1.3	38.1 $\pm$ 1.3*	37.9 $\pm$ 1.4*	37.7 $\pm$ 1.4*	37.5 $\pm$ 1.5*	37.3 $\pm$ 1.7	36.9 $\pm$ 3.1
KDZ	38.7 $\pm$ 0.6	38.7 $\pm$ 0.5	38.6 $\pm$ 0.5	38.0 $\pm$ 0.3*	37.7 $\pm$ 0.3*	37.5 $\pm$ 0.4*	37.3 $\pm$ 0.5*	36.9 $\pm$ 0.7*	36.8 $\pm$ 0.8*
SpO ₂ (%)									
KDZT	96 $\pm$ 3	94 $\pm$ 5	93 $\pm$ 4	92 $\pm$ 4	96 $\pm$ 2	93 $\pm$ 5	94 $\pm$ 4	93 $\pm$ 4	95 $\pm$ 3
KDZ	97 $\pm$ 1	95 $\pm$ 1	94 $\pm$ 4	95 $\pm$ 2	95 $\pm$ 2	95 $\pm$ 2	96 $\pm$ 2	95 $\pm$ 3	95 $\pm$ 2

Explanations: *statistically different from T1 within the same treatment ($p < 0.05$); different superscripts (a, b) statistically different from all other treatments at the same time point ($p < 0.05$)

observed at T9 in all groups (Fig. 1). pH, PvCO₂, and HCO₃⁻ were not significantly different within groups at baseline. KDZ were significantly lower than KDZT at T4 in PvCO₂ and HCO₃⁻ (Tab. 3).

Ketamine-dexmedetomidine-tiletamine/zolazepam-tramadol at the doses used in this study appeared to produce good anesthesia with excellent muscle relaxation, sedative effect, and analgesia in cats. Dexmedetomidine (10 μ g/kg), tiletamine/zolazepam (5 mg/kg), and tramadol (4 mg/kg) (DZT) have been reported to provide excellent immobilization and a better surgical plane of anesthesia in cats undergoing ovariohysterectomy for less than 50 minutes (4), but the addition of ketamine (10 mg/kg) in this study, despite the doses of tramadol being lower than those previously reported in cats, produced general anesthesia with excellent muscle relaxation, sedative effect, and analgesia for more than 75 minutes in these cats.

The decline of HR in the period of anesthesia is ubiquitous. The mechanism is that the anesthetics inhibit the central nervous system, which in turn excites the vagus nerve and eventually causes the fall of HR (18). Moreover, alpha-2 adrenergic agonist receptors can lead to reduced sympathetic activity and central regulation of vasoconstrictor tone (20). When the two mixtures were used for anesthesia, the animals showed

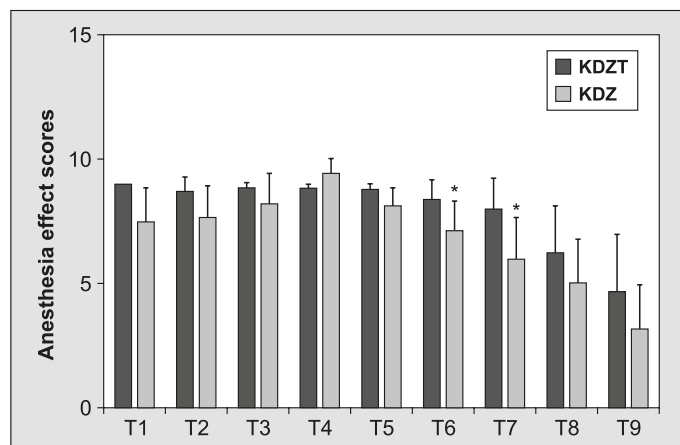


Fig. 1. Anesthesia effect scores according to subjective anesthesia effect score system after IM injection of 10 mg/kg ketamine, 10 μ g/kg dexmedetomidine and 5 mg/kg zoletil (KDZ) or 10 mg/kg ketamine, 10 μ g/kg dexmedetomidine, 5 mg/kg zoletil and 2 mg/kg tramadol (KDZT) for anesthesia. Explanations: results were resulted as mean (sd) $n = 10$ for each group; compared within the different groups at the same time-point, * $p < 0.05$

a significant change in HR after the first drop and then rose. The KDZT group reduced the HR to a minimum when the animals reached deep anesthesia but remained at 125.00 ± 16 beats/min, and the auscultation results

Tab. 3. Mean $\pm$ SD for venous pH, total amount of carbon dioxide (TCO_2), venous partial pressure of carbon dioxide (PvCO_2), bicarbonate (HCO_3^-), ion concentration of natrium (Na), potassium (K) and calcium (Ca) in cats sedated with ketamine, dexmedetomidine and zoletil (KDZ) or ketamine, dexmedetomidine, zoletil and tramadol (KDZT)

Anaesthetic drugs	Time points (minutes)			
	T1	T3	T4	T7
pH				
KDZT	7.23 $\pm$ 0.12	7.22 $\pm$ 0.06	7.26 $\pm$ 0.01	7.25 $\pm$ 0.01
KDZ	7.24 $\pm$ 0.11	7.24 $\pm$ 0.06	7.26 $\pm$ 0.01	7.21 $\pm$ 0.21
TCO_2 (mmol/L)				
KDZT	20.3 $\pm$ 6.2	22.6 $\pm$ 4.0	23.7 $\pm$ 1.0 ^a	23.0 $\pm$ 2.7
KDZ	20.4 $\pm$ 6.3	18.4 $\pm$ 0.2	18.1 $\pm$ 0.3 ^b	23.1 $\pm$ 2.8
PvCO_2 (mmHg)				
KDZT	43.9 $\pm$ 2.7	51.0 $\pm$ 2.8	49.5 $\pm$ 3.5 ^a	49.0 $\pm$ 4.2
KDZ	44.5 $\pm$ 2.1	40.5 $\pm$ 4.9	38.0 $\pm$ 0.0 ^b	54.5 $\pm$ 17.7
HCO_3^- (mmol/L)				
KDZT	18.9 $\pm$ 6.1	21.1 $\pm$ 3.9	22.2 $\pm$ 0.9 ^a	21.5 $\pm$ 2.6
KDZ	18.9 $\pm$ 6.0	17.1 $\pm$ 0.4	16.9 $\pm$ 0.3 ^b	21.4 $\pm$ 3.3
Na (mmol/L)				
KDZT	144.8 $\pm$ 1.1	144.5 $\pm$ 3.5	149.0 $\pm$ 1.4	148.0 $\pm$ 4.2
KDZ	145.3 $\pm$ 1.6	141.5 $\pm$ 12.0	140.5 $\pm$ 2.1	151.5 $\pm$ 0.7
K (mmol/L)				
KDZT	4.1 $\pm$ 0.3	3.6 $\pm$ 0.4	3.5 $\pm$ 0.2	3.7 $\pm$ 0.3
KDZ	3.9 $\pm$ 0.1	4.1 $\pm$ 0.5	3.9 $\pm$ 0.1	4.6 $\pm$ 0.8
Ca (mmol/L)				
KDZT	1.2 $\pm$ 0.1	1.2 $\pm$ 0.1	1.3 $\pm$ 0.1	1.3 $\pm$ 0.2
KDZ	1.1 $\pm$ 0.3	1.1 $\pm$ 0.2	1.2 $\pm$ 0.2	1.4 $\pm$ 0.1

Explanations: statistically different from T1 within the same treatment ($p < 0.05$); different superscripts (a, b) statistically different from all other treatments at the same time point ($p < 0.05$)

did not show abnormal heart rhythm. The combined inhibition of cardiac electrical stimulation by anesthetics and sedatives is the root cause of the decline in HR. However, this degree of decline does not adversely affect the body. It has been reported that tramadol has no significant cardiovascular inhibitory effect on cats (11). Therefore, the effects of KDZT and KDZ on the heart can be ignored.

In this study, we evaluate the effect of KDZT and KDZ on the respiratory system by monitoring RR and SpO_2 . Zoletil has a certain respiratory inhibition effect only when administered at high doses. Under normal circumstances, ketamine has few cardiopulmonary side effects; it does not inhibit the cardiovascular or respiratory system and has significant analgesic effect (3, 7, 14). Tramadol caused no significant additional respiratory depressant effect in cats (11). Our results showed that RR and SpO_2 in all treatments were not changed significantly compared with baseline, and the changes in RR and SpO_2 remained within clinically acceptable limits in all period of anesthesia. Therefore,

it can be suggested that KDZT and KDZ have little effect on the cat's respiratory system.

In the present study, we observed significant declines in SAP, DAP, and MAP at T6 in the KDZ group. Blood pressure increased at T7 could be expected as evidence of pain from painful stimulus caused by acupuncture or clamping the body due to the limited analgesic effect of KDZ without tramadol at this time. Although SAP, DAP, and MAP in the two groups changed, they all fluctuated within the cat's normal blood pressure. Therefore, it can be considered that KDZT and KDZ have only a slight influence on the cat's circulatory system, and the analgesic effect of KDZT is indeed better than KDZ.

From T4, RT values in all groups decreased significantly and remained at a low level until T7 in KDZT. This is due to the loss of thermoregulatory control following administration of alpha-2 adrenoceptor agonists, which causes a depression of the CNS (21, 22). Moreover, the decrease in RT may be due to muscle relaxation and the decrease in the body's metabolic rate (8).

Anesthesia effect score system had not been reported in cats. Therefore, a comprehensive anesthesia effect score scale was used in this study to assess subjective anesthesia effect scores (Tab. 1). The results suggest that KDZT may provide better analgesic effects in cats than KDZ in our study. Chanthawan et al. reported that DZT resulted an induction period of 2.5 ± 1 min and anesthesia time of 69 ± 15 min in cat anesthesia (4). The doses of tramadol used in our study was much lower. KDZT also had a quicker induction and longer anesthesia compared with DZT.

Values regarding blood gas were all within the feline normal physiological range and did not differ between groups at T1, T3, and T7, which indicated the absence of respiratory depression induced by KDZT and KDZ. However, it was shown that the PvCO_2 , TCO_2 , and HCO_3^- at T7 in the KDZT group were significantly higher than those at T7 in the KDZ group, which also occurred due to the risk of respiratory depression by tramadol (15). Combined with the SpO_2 at T7, the KDZT group's value is not significantly decreased from T1 but lower than that in the KDZ group, which can show the same conclusion as values regarding blood gas. Ion concentration of Na, K, and Ca have not significant differences between groups. Transient hypoxemia and respiratory acidosis can be induced by tiletamine-zolazepam injection, but the change of acid-base state is not important in the clinic (16). Previous results demonstrated that dogs given medetomidine (40 $\mu\text{g/kg}$), ketamine (10 mg/kg), and tramadol (4 mg/kg) showed no significant changes in arterial blood gasses and pH in dogs (5). Besides, after dexmedetomidine administration, systemic and pulmonary vascular resistance index, arterial oxygen concentration, and oxygen extraction increased in isoflurane-anesthetized cats (13). The results of our study were consistent with previously published results.

In conclusion, this study demonstrated that at the doses of administration via intramuscular infusion, KDZT and KDZ resulted in a great analgesia effect in cats. Moreover, the overall effect of the two programs on the cardiopulmonary function was minimal, and the acid-base balance was kept within the clinically acceptable range. KDZT has a better anesthetic effect than KDZ, and the sedative, analgesic, and muscle relaxation effects are ideal and balanced, which can provide an adequate anesthesia time of 75-175 min. In the later surgical verification, the application of KDZT allows the surgeon to complete the common clinical surgery such as male cat castration, female cat sterilization, male cat urethral foreskin surgery, gastric incision, intestinal anastomosis and bladder incision.

References

1. *Ansah O. B., Raekallio M., Vainio O.*: Comparison of three doses of dexmedetomidine with medetomidine in cats following intramuscular administration. *JVPT* 1998, 21, 380-387.
2. *Attri J. P., Bhatia T., Bhatia J., et al.*: Intrathecal dexmedetomidine to reduce shoulder tip pain in laparoscopic cholecystectomies under spinal anesthesia. *Anesthesia Essays & Researches* 2015, 9, 320-325.
3. *Boschert K., Flecknell P. A., Fosse R. T., et al.*: Ketamine and its use in the pig. Recommendations of the Consensus meeting on Ketamine Anaesthesia in Pigs, Bergen 1994. *Lab. Anim.* 1996, 30, 209-219.
4. *Chanthawan A., Durongphongtorn S.*: Comparison on the effect of tiletamine-zolazepam and tramadol combined with dexmedetomidine or xylazine in cats undergoing ovariohysterectomy. *Thai J. Vet. Med.* 2010, 111.
5. *Choi W., Jang H. S., Yun S. H., et al.*: Effect of Tramadol on Medetomidine and Ketamine Anesthesia in Dogs. *Pakistan Veterinary Journal* 2011, 31, 99-104.
6. *Cistola A. M., Golder F. J., Centonze L. A., et al.*: Anesthetic and physiologic effects of tiletamine, zolazepam, ketamine, and xylazine combination (TKX) in feral cats undergoing surgical sterilization. *J. Feline Med. Surg.* 2004, 6, 297-303.
7. *Craven R.*: Ketamine. *Anaesthesia* 2007, 62, 48-53.
8. *Doherty T. J.*: Physiologic effects of alpha 2-adrenergic receptors. *J. Am. Vet. Med. Assoc.* 1988, 192, 1612-1614.
9. *Ken, Wada, Yasuhisa, et al.*: Vocalization Induced by Electrical Brainstem Stimulation in Ketamine Anesthetized Cats An Experimental Model for Vocalization. *Koutou (The Larynx Japan)* 1993.
10. *Latifa, Khenissi, Olga, et al.*: Comparison of intramuscular alfaxalone and ketamine combined with dexmedetomidine and butorphanol for castration in cats. *Journal of Feline Medicine & Surgery* 2017.
11. *Lin, Li, Jing, et al.*: Effects of tramadol with tiletamine/zolazepam-xylazine as anaesthesia in cats. *Acta Veterinaria, Brno* 2013.
12. *Marco S., Clarissa V. H., Maria K., et al.*: Neuroprotective Effect of Dexmedetomidine on Hyperoxia-Induced Toxicity in the Neonatal Rat Brain. *Oxidative Medicine & Cellular Longevity* 2015, 1-10.
13. *Pypendop B. H., Barter L. S., Stanley S. D., et al.*: Hemodynamic effects of dexmedetomidine in isoflurane-anesthetized cats. *Veterinary Anaesthesia and Analgesia* 2011, 38, 555-567.
14. *Reves J. G., Glass P. S. A., Lubarsky D. A., et al.*: [in:] Miller R. D. (ed.): *Miller's Anesthesia*, Sixth Ed. Elsevier Churchill Livingstone, Philadelphia, PA, USA 2005, pp: 317-378.
15. *Ryan N. M., Isbister G. K.*: Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clinical Toxicology* 2015, 53, 545-550.
16. *Sakamoto T., Katada A., Kobayashi Y.*: Laryngeal reflex during electrically induced vocalization in ketamine anesthetized cats. *Neuroscience Research Supplements* 1994, 19, S183.
17. *Savvas I., Plevraki K., Raptopoulos D., et al.*: Blood gas and acid-base status during tiletamine/zolazepam anaesthesia in dogs. *Veterinary Anaesthesia and Analgesia* 2005.
18. *Schmeling W. T., Farber N. E.*: Anesthetic Actions on Cardiovascular Control Mechanisms in the Central Nervous System. *Advances in Pharmacology* 1994, 31, 617-642.
19. *Scott L. J., Perry C. M.*: Tramadol: a review of its use in perioperative pain. *Drugs* 2000, 60, 139-176.
20. *Scrollavezza P., Tambella A. M., Vullo C., et al.*: Evaluation of the muscular relaxant effect of dexmedetomidine or medetomidine in cats. *Vet. Res. Commun.* 2009, 33, 213-215.
21. *Selmi A. L., Mendes G. M., Figueiredo J. P., et al.*: Chemical restraint of peccaries with tiletamine/zolazepam and xylazine or tiletamine/zolazepam and butorphanol. *Vet. Anaesth. Analg.* 2003, 30, 24-29.
22. *Sharon R., Lewis, et al.*: Alpha-2 adrenergic agonists for the prevention of shivering following general anaesthesia. *Cochrane Database of Systematic Reviews*. 2015.
23. *Shiming P., Fen S., Wu C., et al.*: Anesthesia Effect on Captive Tigers (*Panthera tigris*) with a Combination of Tiletamine, Zolazepam and Dexmedetomidine. *Chinese Journal of Wildlife* 2015.
24. *Steagall P. V. M., Aucoin M., Monteiro B. P., et al.*: Clinical effects of a constant rate infusion of remifentanyl, alone or in combination with ketamine, in cats anesthetized with isoflurane. *Journal of the American Veterinary Medical Association*. 2015, 246, 976-981.

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