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A Comparison of Two Intramuscular Doses of a Xylazine-Diazepam-Ketamine Combination in Dogs

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Abstract : Many drugs are administered intramuscularly to immobilize and anesthetize dogs. There are many established intramuscular (IM) anesthetic combinations for dogs; however, little information is available on the effects of a xylazine-diazepam-ketamine (XDK) combination. The purpose of this study was to investigate the anesthetic effects of the XDK combination in dogs. Twelve adult mixed bred dogs were used. All dogs were anesthetized with an IM injection of diazepam (0.5 mg/kg) and xylazine (1.1 mg/kg) with low-dose ketamine (5 mg/kg; group 1) or high-dose ketamine (10 mg/kg; group 2) in one syringe. After administration of the test dose, the animals were positioned in a right lateral recumbency, and analgesia and cardiopulmonary data were collected and recorded. The duration of anesthesia in group 2 was significantly longer than that of group 1 (mean [sd] 68.0 [7.6] v 51.3 [2.7] minutes). Blood pressure increased significantly after XDK administration in both groups, and S_aO_2 levels decreased significantly from baseline at 10, 20, and 30 minutes in both groups. XDK administration produced satisfactory sedation and analgesia in all dogs. In conclusion, intramuscular administration of xylazine-diazepam-ketamine combination at a doses of 1.1 mg/kg xylazine, 0.5 mg/kg diazepam, and 5 or 10 mg/kg ketamine appeared to be effective short duration anesthetic protocols in dogs.

Key words **:** anesthesia, dogs, diazepam, ketamine, xylazine.

Introduction

Knowledge of anesthetic agents alone, or in combination with preanesthetics is a prerequisite to understand the changes taking place in anesthetized patients. Each drug has its own peculiarities and acts differently when combined with another (6). Ketamine hydrochloride is a dissociative cyclohexylamine group anesthetic used for chemical restraint and to induce and maintain anesthesia in a number of species (8). Ketamine has been used in combination with various drugs including benzodiazepines, e.g., diazepam (10) and alpha-2 agonists (7). Diazepam is not a reliable sedative, but is a good muscle relaxant and anticonvulsant in most species. Diazepam can be administered prior to inducing anesthesia with thiopental, propofol, etomidate, or an opioid. Benzodiazepines induce a central muscle relaxant effect that decreases the muscle hypertonus associated with ketamine (3). Although diazepam produces limited effects on cardiovascular and pulmonary function in animals, there are published and anecdotal reports of cardiovascular dysfunction associated with diazepam-ketamine combination anesthesia in dogs, cats, and other species (1).

Xylazine hydrochloride is a typical non-opioid alpha-2 agonist, with analgesic, sedative, and muscle relaxant effects (11). Xylazine is commonly used in combination with ketamine. Many established intramuscular (IM) anesthetic combinations are available for dogs; however, little information is available on the effects of a xylazine-diazepam-ketamine (XDK) combination in dogs.

The purpose of this study was to investigate the anesthetic effects of two intramuscular doses of a XDK combination in dogs.

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Materials and Methods

Experimental animals

Twelve adult mixed breed dogs (six male and six female, mean ages, 1.8 ± 0.7 years; mean body weight, 5.2 ± 0.9 kg) were used. All dogs were raised in appropriate animal management facilities and fed a standard commercial dry canine food (Science Diet Adult, Hill's Pet Nutrition, Inc, Topeka, KS, USA). Routine hematological tests were performed before the experiment commenced, and all values were within normal physiological ranges. This experiment was conducted under the supervision of the Chungnam National University Animal Care and Use Committee. The dogs were fasted for 12 hours before the experiment, and water was withheld for 2 hours before anesthesia to prevent any possible adverse effects, such as vomiting during the anesthesia or recovery period.

Experimental group

All dogs were anesthetized with an IM injection of diazepam (0.5 mg/kg, Merod®, Donghwa Co, Seoul, Korea) and xylazine (1.1 mg/kg, Rompum®, Bayer Co, Seoul, Korea) with

low-dose ketamine (5 mg/kg, Ketamin 50®, Yuhan Co, Seoul, Korea, group 1) or high-dose ketamine (10 mg/kg, group 2) in one syringe. After administration of the test dose, the animals were positioned in a right lateral recumbency, and analgesia and cardiopulmonary data were collected and recorded.

Instrumentation and drug administration

Before the each experiment, a sterile 22-gauge arterial catheter (BD IV Catheter, Becton Dickinson Korea Ltd., Seoul, Korea) was inserted percutaneously into the left dorsal pedal artery of each dog masked with isoflurane (Forane®, Choong Wae Pharma Corp., Seoul, Korea) anesthesia for several minutes to measure arterial blood pressure and to obtain arterial blood samples. The catheter was flushed with heparinized saline (2 IU/ml), secured in place, and connected to a pressure transducer with a noncompliant tube. The transducer was attached to a physiological monitor (Pulscan-Component, Scionic, Seoul, Korea). After inserting the catheter, the isoflurane was discontinued, and the dogs were allowed to recover for 10 minutes prior to administration of the treatment drugs. The dogs were restrained to collect the arterial blood samples and to measure baseline data. Each of the 12 dogs received two different treatments with a 14 days withdrawal time in randomized order.

Induction and recovery

Induction time, anesthesia time, sternal recumbency time, standing time, and walking time were recorded for each dog. Induction time was the time from XDK administration to complete immobilization. Complete immobilization was defined as the lack of response to handling. Anesthesia time was the time interval between complete immobilization and the first attempt made by the animal to lift its head a few centimeters above the ground. Sternal recumbency time was the time from XDK administration to when the dog achieved sternal recumbency. Standing time was the time from XDK administration to when the dog stood up without assistance for longer than 10 seconds. Walking time was the time from XDK administration to when the dog was able to walk without knuckling.

Evaluation of sedation, response to a noxious stimulus, and posture

Level of sedation (spontaneous posture) and response to noxious stimuli (pedal withdrawal) were assessed at designated times during anesthesia (Table 1).

Heart rate, blood pressures, and rectal temperature

Heart rate (HR), blood pressure (BP), and rectal temperature were measured at time 0 (pre-injection) and at 5, 10, 20, 30, 40, 50, 60, and 70 minutes after drug administration. HR was measured by a transducer attached to a physiological monitor. Mean arterial pressure (MAP), systolic arterial pressure (SAP), and diastolic arterial pressure (DAP) were measured using a monitor and were recorded. The BP device was calibrated before each experiment. The left scapulohumeral joint was used as the zero reference point for MAP measurement. Rectal temperature (RT) was continuously recorded using a thermocouple probe (Pulscan-Component, Scionic), which was placed deep into the rectum.

Respiratory rate and blood gases

Respiratory rate (RR) and blood gases were also measured at time 0 (pre-injection) and at 5, 10, 20, 30, 40, 50, 60, and 70 minutes after drug administration. RR was measured by observing thoracic movement. Arterial blood samples were collected anaerobically and analyzed immediately using a por-

Table 1. Subjective criteria used to score levels of sedation and response to noxious stimulus in dogs after administration of xylazine/diazepam/ketamine

Variable	Score	Criteria
Sedative score	0-5	
Spontaneous posture		
	0	Normal
	1	Being able to stand or sit on their hind legs
	2	Keeping the position of ventral recumbency
	3	Lateral recumbency with apparent spontaneous movement (head lifting or struggling)
	4	Lateral recumbency with subtle spontaneous movement (ear and nose twitching or blink)
	5	Lateral recumbency without spontaneous movement
Score of response to noxious stimulus	0-3	
Pedal withdrawal response to pinching of a digit or interdigital web		
	0	Hypersensitive or normal
	1	Slightly impaired
	2	Clearly weak
	3	Absent

table analyzer (i-STAT Portable Clinical Analyzer, Abbott Laboratories, Abbott Park, USA). The analyzer calculated arterial pH, carbon dioxide partial pressure ($PaCO_2$), arterial oxygen partial pressure (PaO_2), and arterial oxygen saturation (SaO_2).

Statistical analysis

Immobilization characteristics were compared using the paired *t*-test. A repeated-measures two-way analysis of variance (ANOVA) was used to compare the physiological responses between treatments. A repeated-measures one-way ANOVA was used to compare physiological parameters over time. Bonferroni's correction for multiple comparisons was used to determine when significant differences occurred. The significance level was set at $P < 0.05$.

Results

Induction and recovery

Dogs in both groups were sedated rapidly after the intramuscular injection of drugs, and they all became laterally recumbent within 2 minutes without any signs of excitement. Induction time in group 1 was similar to that in group 2. The duration of anesthesia in group 2 was longer than that of group 1.

Sternal recumbency and standing and walking times were longer in group 2 than those in group 1. Significant differences in recovery times were observed between the groups (Table 2).

Table 2. Time for induction, duration of anesthesia, and recovery times in dogs after the administration of xylazine/diazepam/ketamine

	Group 1	Group 2
Induction time	1.3 ± 0.5	1.4 ± 0.6
Duration of anesthesia	51.3 ± 2.7	68.0 ± 7.6*
Time to sternal recumbency	65.3 ± 5.3	86.7 ± 18.6*
Time to standing	72.6 ± 9.5	98.6 ± 18.7*
Time to walking	81.6 ± 12.3	113.0 ± 12.6*

Data are expressed as mean ± SD (n = 12).
*Significantly different ($p < 0.05$) from group 1.

Evaluation of sedation and analgesia

XDK administration produced satisfactory sedation and analgesia in all dogs. However, the posture and response scores to noxious stimuli were significantly higher in group 2 than those in group 1 at 50 minutes after drug administration (Table 3).

HR, BPs, and RT

HR, SAP, MAP, DAP, and rectal temperature data are summarized in Table 4. Mean HR tended to decrease after drug

Table 3. Scores of sedation (spontaneous posture) and response to noxious stimulus (pedal withdrawal) after the administration of xylazine/diazepam/ketamine

	Group	10 min	20 min	30 min	40 min	50 min
spontaneous posture	Group 1	4.7 ± 0.8	4.5 ± 0.9	4.3 ± 0.7	4.3 ± 0.8	3.3 ± 0.8
	Group 2	4.7 ± 0.8	4.7 ± 0.5	4.2 ± 0.8	4.3 ± 0.5	4.3 ± 0.0*
Response to noxious stimulus	Group 1	2.7 ± 0.8	2.7 ± 0.8	2.2 ± 0.8	1.8 ± 0.4	1.2 ± 0.4
	Group 2	2.7 ± 0.8	2.7 ± 0.5	2.5 ± 0.8	2.3 ± 0.0[a]	2.3 ± 0.0*

Data are expressed as mean ± SD (n = 12).
*Significantly different ($p < 0.05$) from group 1.

Table 4. Blood pressures, heart rate and rectal temperature in dogs after administration of xylazine/diazepam/ketamine

	Group	Pre	10 min	20 min	30 min	40 min	50 min	60 min	70 min
HR (beats/minutes)	Group 1	112.3 ± 19.9	89.7 ± 22.4	94.3 ± 21.0	89.3 ± 20.7	83.8 ± 19.3	85.3 ± 18.2	NT	NT
	Group 2	112.7 ± 21.6	93.3 ± 20.1	79.3 ± 16.5	76.5 ± 13.1	68.5 ± 12.5*	69.3 ± 9.9*	69.3 ± 9.7*	68.3 ± 7.7*
SAP (mmHg)	Group 1	120.3 ± 12.8	160.8 ± 20.2*	158.9 ± 9.6*	157.9 ± 13.1*	140.5 ± 10.4	139.9 ± 9.4	NT	NT
	Group 2	119.3 ± 11.8	153.0 ± 11.9*	154.0 ± 3.5*	155.3 ± 4.7*	137.8 ± 5.3	144.3 ± 8.9	129.5 ± 7.9	125.0 ± 6.9
MAP (mmHg)	Group 1	81.0 ± 8.8	128.4 ± 10.1*	125.0 ± 6.9*	122.8 ± 9.2*	110.9 ± 10.1	112.1 ± 8.1	NT	NT
	Group 2	80.3 ± 9.1	126.3 ± 12.7*	122.5 ± 5.7*	120.8 ± 4.6*	107.5 ± 2.6	110.8 ± 3.9	102.0 ± 11.1	97.3 ± 6.7
DAP (mmHg)	Group 1	62.8 ± 11.0	111.3 ± 12.4*	110.3 ± 6.5*	97.9 ± 12.3*	93.5 ± 5.7	90.5 ± 6.9	NT	NT
	Group 2	62.8 ± 11.0	109.3 ± 13.6*	106.3 ± 6.5*	95.9 ± 5.3*	96.5 ± 5.0*	89.5 ± 7.9	79.0 ± 16.5	76.5 ± 12.4
RT (°C)	Group 1	38.7 ± 1.4	38.6 ± 1.4	38.6 ± 1.4	38.5 ± 1.4	38.3 ± 1.4	38.1 ± 1.5	NT	NT
	Group 2	37.9 ± 0.6	37.9 ± 0.6	37.8 ± 0.5	37.8 ± 0.5	37.7 ± 0.7	37.6 ± 0.7	37.5 ± 0.7	37.4 ± 0.8

Data are expressed as mean ± SD (n = 12)
*Significantly different ($p < 0.05$) from baseline.

administration in group 1, but the difference was not significant. Mean HR decreased significantly at 40 minutes following XDK administration and remained consistently below the baseline for 70 minutes in group 2. Both groups showed their lowest HR 40 minutes after administration of the drug combination. No significant difference in HRs was observed between the groups.

BP (MAP, SAP, and DAP) increased significantly within 10 minutes after XDK administration and remained consistently above the baseline value for anesthesia in both groups. No significant differences in BP were observed between the groups. RT did not change significantly at any time point in either group.

RR and blood gases

RR and blood gas (pH_a, P_aCO_2, P_aO_2, and S_aO_2) data are summarized in Table 5. No significant differences in RR were observed in group 1, but RR decreased significantly at 10 and 20 minutes compared to that at baseline in group 2. Significant differences were observed in the RR at 10 and 20 minutes between the two groups. No significant differences in P_aCO_2 were observed in group 1, but P_aCO_2 increased significantly at 10 and 20 minutes compared to that at baseline in group 2. P_aO_2 decreased significantly within 10 minutes after drug administration in both groups and remained consistently below the anesthesia baseline. S_aO_2 levels decreased significantly from baseline at 10, 20, and 30 minutes after drug administration in both groups .

Discussion

The clinical efficacy of the high-dose ketamine used in this study was superior to that of the low-dose ketamine. Both doses were apparently well absorbed after intramuscular injection, and sedation and lateral recumbency were fairly rapid in both treatments.

All dogs in group 1 remained in a lateral recumbent position and retained analgesia for at least 48 minutes, which is an adequate amount of time to do most procedures that require general anesthesia. Dogs in group 2 remained in a lateral recumbent position and retained analgesia for 60-75 minutes, indicating that this dose could be used when a longer duration of anesthesia is desired.

HR tended to decrease below baseline values in all dogs that received the XDK combination, but a significant decrease was observed only in group 2. These findings are consistent with other reports of the cardiac effects of xylazine in dogs (9). Treatment with atropine (0.04 mg/kg) is recommended for treating cardiovascular side-effects of anesthetic drugs in dogs (5), although the use of anticholinergics in conjunction with alpha-2 agonists in other species is controversial (4). The bradycardia we observed was not considered clinically significant, and no treatment was deemed necessary. BP significantly increased in both groups after treatment, and hypertension was a consistent complication in both groups of dogs. Alpha-2 adrenoceptor agents may initially increase and then decrease systemic BP in dogs (2). The dogs remained hypertensive, as measured directly during anesthesia in both groups. This response may have been due to the sustained, alpha-2 agent-mediated vasoconstriction producing increased systemic vascular resistance. This sustained effect may also have been due to the centrally mediated sympathomimetic effects produced by the concurrent administration of ketamine. Although no detrimental clinical signs were noted, hypertension may increase afterload, resulting in decreased cardiac output and leading to decreased tissue perfusion.

The most significant finding in the respiration and gas exchange portion of this study was the bradypnea following

Table 5. Respiratory rate and blood gases in dogs after administration of xylazine/diazepam/ketamine

	Group	Pre	10 min	20 min	30 min	40 min	50 min	60 min	70 min
RR (breaths/ minute)	Group 1	24.0 ± 5.9	15.0 ± 10.4	16.3 ± 7.8	24.3 ± 8.4	27.0 ± 7.4	39.0 ± 8.8	NT	NT
	Group 2	27.0 ± 6.0	8.5 ± 2.4*∫	6.0 ± 1.7*∫	13.8 ± 2.3	15.0 ± 3.3	14.3 ± 4.4	16.5 ± 3.3	22.3 ± 9.5
pH_a	Group 1	7.45 ± 0.1	7.45 ± 0.1	7.43 ± 0.0	7.42 ± 0.0	7.42 ± 0.0	7.42 ± 0.0	NT	NT
	Group 2	7.35 ± 0.1	7.26 ± 0.1*	7.24 ± 0.1*	7.25 ± 0.1*	7.34 ± 0.0	7.36 ± 0.1	7.36 ± 0.0	7.35 ± 0.1
P_aCO_2 (mm Hg)	Group 1	43.3 ± 6.0	47.1 ± 6.8	48.7 ± 7.6	48.7 ± 8.5	45.8 ± 6.8	45.4 ± 6.1	N.E	N.E
	Group 2	46.9 ± 6.9	58.3 ± 3.4*	57.5 ± 3.2*	48.6 ± 5.4	45.7 ± 4.5	45.1 ± 4.3	44.0 ± 6.4	40.5 ± 5.8
P_aO_2 (mm Hg)	Group 1	108.8 ± 32.0	70.0 ± 17.5*	67.3 ± 14.2*	66.8 ± 12.1*	69.8 ± 14.0*	69.0 ± 18.2*	N.E	N.E
	Group 2	102.0 ± 43.5	60.5 ± 12.8*	60.0 ± 12.8*	65.0 ± 18.8*	71.8 ± 16.3*	76.0 ± 18.3*	74.5 ± 18.5*	81.8 ± 19.2*
SO_2 (%)	Group 1	97.5 ± 2.1	92.5 ± 1.9*	92.3 ± 1.0*	92.3 ± 1.0*	93.3 ± 1.7	93.0 ± 2.2	N.E	N.E
	Group 2	98.3 ± 2.1	92.5 ± 5.3*	92.5 ± 2.6*	92.8 ± 3.3*	94.5 ± 1.9	95.3 ± 1.7	95.0 ± 1.8	96.5 ± 1.3

Data are expressed as mean ± SD (n = 12), N.E; Not examined.
*Significantly different ($P < 0.05$) from baseline.
∫Significantly different from group 1 ($P < 0.05$).

administration of high-dose ketamine in group 2.

The increased P_aCO_2 and decreased P_aO_2 and SpO_2 values in both groups indicated dose-dependent respiratory depression. Hypoxemia was observed in both groups, and an increase in P_aCO_2 levels was observed in group 2. Hypoxemia might have been caused by hypoventilation, as there was an increase in P_aCO_2 after drug administration. Although hypoventilation was not severe (P_aCO_2 remained < 60 mmHg), it would have contributed to hypoxemia. The pH values observed in group 2 were significantly lower at 10, 20, and 30 min after drug administration, whereas those seen in group 1 were still within the reported reference ranges for dogs (12). No dogs in the current study had any clinically apparent problems following the hypoxemia induced by the drug combination. However, as a result of the hypoxemia, supplementary oxygen should be provided to dogs receiving the high dose used in this study.

A case of acute pulmonary edema after diazepam-ketamine anesthesia has been reported in a dog that received 0.25 mg/kg diazepam and 5 mg/kg ketamine (1). The clinical symptoms included generalized weakness, seizures, dyspnea, severe hypotension, tachycardia, and diarrhea. No adverse clinical signs were observed in any of the dogs in this study. However, cardiopulmonary parameters significantly changed during anesthesia in both groups.

In conclusion, a XDK combination at dosage of 1.1 mg/kg xylazine, 0.5 mg/kg diazepam, and 5-10 mg/kg ketamine IM appeared to be very effective for dog anesthesia. The clinical efficacy of the high-dose ketamine used was superior to that of the low-dose ketamine in the XLD combination. However, some dogs may experience a dose-dependent, transient hypoxemia, and supplemental oxygen may be necessary during anesthesia.

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개에서 Xylazine-diazepam-ketamine 병용마취 시 두 가지 근육내 투여 용량 비교

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요 약 : 많은 약물들이 개의 진정 및 마취를 위해 근육내 투여를 통해 사용되고 있다. 개 마취를 위한 많은 근육내 병용투여 방법이 정립되었으나 xylazine-diazepam-ketamine 병용투여에 대한 연구는 미흡하다. 따라서 본 연구의 목적은 개에서 xylazine-diazepam-ketamine 병용투여의 영향을 연구하는 것이다. 12 마리의 혼혈 종 개를 사용하였으며 diazepam (0.5 mg/kg), xylazine (1.1 mg/kg)에 두 가지 용량의 ketamine (5 mg/kg; group 1, 10 mg/kg; group 2)을 근육내로 투여하여 비교하였다. 마취 시간은 group 2에서 group 1과 비교 시 유의적으로 길었으며 혈압은 약물 투여 후 두 군에서 모두 유의적으로 증가 하였다. S_aO_2 수준도 약물 투여 후 두 군에서 모두 유의적으로 감소 하였다. 마취는 두 군에서 모두 적절히 이루어졌다. 본 실험 결과 diazepam (0.5 mg/kg), xylazine (1.1 mg/kg)에 두 가지 용량의 ketamine (5 mg/kg, 10 mg/kg)의 병용투여는 개에서 짧은 시간의 깊은 진정 및 마취 시에 사용할 수 있는 효과적인 방법으로 생각된다.

주요어 : 마취, diazepam, ketamine, xylazine, 개