

Anesthetic and Cardiorespiratory Effects of Medetomidine-Ketamine-Butorphanol and Xylazine-Ketamine-Butorphanol in Dogs

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Abstracts : This study examined the anesthetic and cardiopulmonary effects of xylazine or medetomidine in combination with ketamine-butorphanol in dogs. Five dogs were used in both the medetomidine-ketamine-butorphanol (MKB) group and the xylazine-ketamine-butorphanol (XKB) group. The procedures for the two groups were performed 4 weeks apart. MKB group showed a shorter duration for anesthesia than XKB group. Other factors were not statistically significant between the two groups. The MKB group showed signs of bradycardia, therefore cautious patient monitoring is necessary. The XKB showed a longer anesthetic time and less adverse effects, however the MKB combination was more expensive and had less advantages. In conclusion, the results suggested the recommended use of both MKB and XKB in procedures that need approximately 50 minutes. If patients have a risk of bradycardia, one should be cautious of using a medetomidine-xylazine-butorphanol combination. Both MKB and XKB did not have much adverse effects; however MKB did not have advantages when compared to XKB. Therefore, XKB may be more effective when compared to MKB.

Key words: medetomidine, xylazine, ketamine, butorphanol, dogs.

Introduction

The anesthetic combination of ketamine and medetomidine is widely used for a variety of species. The addition of butorphanol to this combination can affect smoother anesthesia, while allowing decreases in the doses of both ketamine and medetomidine (7).

Medetomidine, which is the most widely used α_2 -agonist in small animals (5,12) and it is a more selective and full agonist for the central α_2 -adrenoceptor agonist, was introduced as a sedative analgesic agent for use in large and small animals (5,9). The pharmacological effects of medetomidine include CNS depression, peripheral and cardiac vasoconstriction, bradycardia, respiratory depression and hypothermia. Its effects on blood pressure are variable (5,10,12).

Xylazine depresses the CNS thermoregulatory mechanisms, and may cause either hypothermia or hyperthermia or an initial increase in total peripheral resistance and blood pressure, followed by a longer period of lowered blood pressure (5). The respiratory effects of xylazine are usually clinically insignificant, but at high doses the drug can cause respiratory depression, with a decrease in tidal volume and respiratory rate (RR) (5).

Ketamine has been used in many mammalian species. It is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist routinely used as an anesthetic in veterinary medicine (10,12). Ketamine induces a dose-dependent CNS depression which leads to a dissociative state, characterized by profound analgesia and amnesia with maintained ocular, laryngeal, pharyngeal, pinnal and pedal reflexes (10).

Butorphanol has agonist activity at the kappa receptor and antagonist activity at the mu receptor, for which it has high affinity. It is considered effective for mild to moderate visceral pain and is a popular pre-anesthetic and postoperative analgesic for minor elective surgical procedures (10).

Anesthesia is an essential procedure in a veterinary clinic; therefore deciding which appropriate anesthetic agent to use for different conditions is very important. Medetomidine, xylazine, ketamine and butorphanol have commonly been used in practice and have been used alone or in combination. Many established intramuscular (IM) anesthetic combinations are available for dogs; however, little information is available on the effects of medetomidine, or xylazine, ketamine and butorphanol combination in dogs.

The purpose of this study was to evaluate the cardiopulmonary effect of a combination of medetomidine-ketaminebutorphanol (MKB) and to compare its efficacy as an anesthetic with that of xylazine-ketamine-butorphanol (XKB).

Materials and Methods

Experimental animals

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Committee approved this study design. A total of five clinically healthy mongrel dogs (5 ± 2 years old, 3 ± 0.5 kg body weight, 2 female and 3 male) were used in this study. The dogs were fed with commercial dog food (ANF, ANF Specialties, Inc., USA) for 2 weeks before the experiment. The dogs 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 animals were assigned to the MKB group (n = 5); 20 µg/kg medetomidine (Domitor[®]; Orion Pharma, Finland), 5 mg/kg ketamine (Yuhan Ketamine 50 Injection[®]; Yuhan Co., Korea) and 0.2 mg/kg butorphanol (Buphanol Inj[®]; Hana Pharm Co., Korea) and XKB group (n = 5); 1.5 mg/kg xylazine (Rompun[®]; Bayer Korea Ltd., Korea), 5 mg/kg ketamine and 0.2 mg/kg butorphanol by intramuscular injection. After administration of the test dose, the animals were positioned in a right lateral recumbent position, and analgesia and cardiop-ulmonary data were collected and recorded.

Instrumentation and drug administration

Before the experiment began, each of the animals were anesthetized with isoflurane (Foranel[®]; Choongwae, Korea), and a sterile 24-guage catheter (BD IV Catheter; Becton Dickinson Korea, LTD., Korea) was inserted percutaneously into the left dorsal pedal artery, to measure arterial blood pressure and obtain arterial blood samples. The catheter was flushed with heparinized saline, secured in place and connected to a pressure transducer with a non-compliant tube (Pulscan-Component; Scionic, Austria). The transducer was attached to a physiological monitor (Pulscan-Component; Scionic, Austria). After inserting the catheter, isoflurane was discontinued and the dogs were allowed to recover before the anesthetic agent

Table 1. Criteria used score of the anesthetic effects

were administered. The dogs were restrained physically during the collection of arterial blood samples and the measurement of baseline data. All the injections were administered into biceps femoris muscles. To comply with a crossover study design, each of the five dogs received two different treatments at the rate of one treatment per 4 weeks, in a randomized order.

Anesthesia and recovery

Induction time, anesthesia time, sternal recumbent position time, standing time, walking time and recovery time were recorded for each dog. Induction time was defined as the time from the injection of XKB or MKB to complete immobilization (defined as a lack of response to being handled). Anesthesia time was defined as the time between complete immobilization and the first attempt the animal made to lift its head a few centimeters. Sternal recumbent position time was defined as the time from the injection of XKB or MKB to when the animal achieved a sternal recumbent position. Standing time was defined as the time from the injection of XKB or MKB to when the animal stood up without assistance for longer than 10 seconds. Walking time was defined as the time from the injection of XKB or MKB to when the animal was able to walk without knuckling. Recovery time was defined as the time from the first attempt made by the animal to lift its head a few centimeters until when the animal was able to walk without knuckling.

Evaluation of spontaneous posture and response to noxious stimulus

Spontaneous posture was evaluated according to Table 1. To evaluate the response a to noxious stimulus, pedal withdrawal response (the presence or absence of pelvic limb withdrawal in response to clamping the interdigital space) was recorded according to Table 1.

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	e to pinchin	g of a digit or interdigital web
	0	Hypersensitive or normal
	1	Slightly impaired
	2	Clearly weak
	3	Absent

Heart rate, blood pressure and rectal temperature

The heart rate (HR), blood pressure and rectal temperature (RT) were measured at time 0 (the time before the injection of the drugs) and 5, 10, 20, 30, 40, 50 and 60 minutes after the administration of the drugs. HR was measured by a transducer attached to an ananesthetic patient monitor (Pulscan-Component; Scionic, Austria). The systolic arterial pressure (SAP), mean arterial pressure (MAP) and diastolic arterial pressure (DAP) were measured using an anesthetic patient monitor and recorded. The blood pressure device was calibrated every time to ensure an accurate measurement of blood pressure. RT was continuously recorded using a monitor and a thermocouple probe placed deep into the rectum.

Respiratory rate, blood gases and lactate

The RR (respiratory rate) was also measured at time 0 (the time before the injection of the drugs) and 10, 20, 30, 40, 50 and 60 minutes after administration of the drugs. The RR was measured based on the thoracic movements of the animal.

The blood gas variables and level of lactate (Lac) were also measured at time 0 (before injection of the drugs), 10, 20, 40 and 60 minutes after administration of the drugs. Arterial blood samples were collected anaerobically and analyzed immediately using a portable analyzer (i-STAT Portable Clinical Analyzer; Heska, USA). The analyzer calculated arterial oxygen partial pressure (PaO₂), carbon dioxide partial pressure (PaCO₂), arterial oxygen saturation (SaO₂) and arterial pH.

Statistical analysis

Values are expressed as means and standard deviation. Kruskal-Wallis analysis of variance was used for group comparison. Between-group differences were compared by the Mann-Whitney U-test. Differences within groups were tested with a one-way analysis of variance (ANOVA) and Duncan's post hoc tests if ANOVA gave significant results. P < 0.05 was considered statistically significant. All statistics were performed using a computer statistical package (Statistics Package for the Social Sciences, version 18.0; SPSS Inc., IL, USA).

Results

Anesthesia and recovery

Sedation was achieved rapidly in both groups of dogs after intramuscular injection of the drugs, and they all were laterally recumbent within three minutes without any signs of

excitement. The induction time in the MKB group (1.4 ± 0.5) minutes) was longer than in the XKB group $(1.2 \pm 0.4 \text{ min-}$ utes) (Table 2), but it was not statistically significant. The duration of anesthesia in the XKB group $(87.4 \pm 18.9 \text{ min-}$ utes) was longer than in the MKB group (62.6 ± 15.0 minutes), and it was statistically significant (p < 0.05) (Table 2). The sternal recumbent position time in the MKB group $(75.0 \pm$ 24.1 minutes) was shorter than in the XKB group (91.0 \pm 19.6 minutes), but it was not statistically significant. In results for movement from a sternal recumbent position to standing, the MKB group $(77.2 \pm 24.3 \text{ minutes})$ was shorter than in the XKB group (95.4 \pm 22.7 minutes), but it was not statistically significant. For the time between the animal standing to walking, the MKB group (80.0 ± 23.0 minutes) was found to be shorter than in the XKB group (98.8 ± 24.0 minutes), and it was statistically significant.

Evaluation of spontaneous posture and response to noxious stimulus

Scores for the anesthetic effects are shown in Table 3. Both drug combinations produced satisfactory general anesthesia in all of the dogs. The total scores for spontaneous posture and response to noxious stimulus were similar in both groups, with no statistically significant differences in any of the parameters. There were no statistically significant differences between the groups in the scores relating to spontaneous posture and response to noxious stimulus.

Heart rate, blood pressure and rectal temperature

Data relating to HR, SAP, MAP, DAP and rectal temperature are summarized in Table 4. The mean HR decreased sig-

 Table 3. Scores for the anesthetic effects (spontaneous posture and response to noxious stimulus)

	Crown	Before injection	Time after injection (minutes)			
	Group		20	40	60	
Posture	MKB	0	5.0	4.0 ± 1.2	$2.2\pm1.9*$	
	XKB	0	5.0	4.8 ± 0.4	4.2 ± 0.8	
Analgesia	MKB	0	3.0	2.2 ± 0.8	$1.2 \pm .10*$	
	XKB	0	3.0	3.0	2.6 ± 0.9	

(minutes)

Data are expressed as mean \pm SD (n = 5)

*Significantly different (P < 0.05) from baseline.

Table 2. The time for induction, duration of anesthesia and stages of recovery in dogs after the administration of medetomidineketamine-butorphanol (MKB) and xylazine-ketamine-butorphanol (XKB)

Group	Induction time	Anesthesia time	Sternal recumbency time	Standing time	Walking time	Recovery time
MKB	1.4 ± 0.5	$62.6\pm15.0^{\text{a}}$	75.0 ± 24.1	77.2 ± 24.3	80.0 ± 23.0	17.4 ± 17.9
XKB	1.2 ± 0.4	$87.4 \pm 18.9^{\text{a}}$	91.0 ± 19.6	95.4 ± 22.7	98.8 ± 24.0	11.4 ± 5.8

Data are expressed as mean \pm SD (n = 5)

^aStatistical difference (P < 0.05) between MKB and XKB.

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Time after injection (minutes) Before injection 10 20 Group 5 30 40 50 60 $60.0(22.0)^*$ $52.2(15.4)^*, 47.6(12.8)^*, 46.8(11.0)^*, 46.2(13.2)^*$ 49.4(21.3)* MKB 104.0(20.0) 73.8(34.0) HR (bpm) 78.0(24.0) 54.0(21.4)* XKB 116.2(21.3) 68.6(22.8)* 68.4(22.5)* 68.8(22.0)* 62.0(21.2)* 55.8(20.6)* MKB 104.4(14.4)130.6(6.8)* 132.0(6.4)* 124.2(11.3)* 123.8(13.9) 119.0(12.9) 118.0(15.8) 115.8(19.1) SAP(mmHg) XKB 111.6(15.7) 113.2(30.6) 121.0(31.5) 124.8(33.4) 119.0(36.1) 114.2(33.9) 108.2(30.0) 105.8(30.1) MKB 98.0(11.5)* 86.8(1.8)* 76.6(8.1) 95.6(26.7)* 84.8(4.5) 79.6(4.6) 79.4(4.3) 78.0(6.4) MAP (mmHg) XKB 84.6(12.6) 87.4(26.5) 91.8(30.0) 90.6(28.5) 84.8(26.3) 75.3(22.8) 73.0(21.8) 69.8(20.5) MKB 62.4(107) 80.0(28.3)* 79.4(7.1) 69.2(6.6) 66.8(7.1) 62.4(9.5) 63.0(7.9) 61.6(7.3) DAP (mmHg) XKB 70.4(13.0) 73.8(26.1) 76.6(28.7) 71.2(23.4) 68.2(24.6) 57.6(21.1) 53.2(16.1) 52.4(17.0) MKB 38.2(0.4) 38.0(0.6) 37.9(0.4) 37.7(0.4) 37.5(0.5) 37.2(1.0) 37.8(0.4) 37.4(0.7) RT(°C) XKB 38.3(0.3) 37.9(0.5) 37.7(0.4) 38.2(0.3) 38.1(0.4) 38.0(0.5) 37.5(0.7) 37.5(0.6)

Table 4. Blood pressures, heart rates (HR) and rectal temperatures (RT) in dogs after the administration of medetomidine-ketaminebutorphanol (MKB) and xylazine-ketamine-butorphanol (XKB)

DAP Diastolic arterial pressure, MAP Mean arterial pressure, SAP Systolic arterial pressure

Data are expressed as mean(SD), n = 5,

*Significantly different (P < 0.05) from baseline. Statistical difference (P < 0.05) between MKB and XKB.

 Table 5. Respiratory rate (RR) and blood gases in dogs after the administration of medetomidine-ketamine-butorphanol (MKB) and xylazine-ketamine-butorphanol (XKB)

 (minutes)

								(minutes)
	Group	Pre	10	20	30	40	50	60
RR (breaths/ minute)	MKB	27.0 ± 12.6	$14.2\pm4.5^{\boldsymbol{*}}$	$13.6\pm3.0*$	$15.0\pm3.3*$	$14.4\pm3.6\texttt{*}$	$16.0\pm4.7*$	18.0 ± 6.6
	XKB	22.8 ± 5.0	19.4 ± 3.1	17.8 ± 3.9	18.2 ± 4.3	18.0 ± 3.7	17.4 ± 4.4	$13.8\pm1.8*$
pH _a	MKB	7.30 ± 0.11	7.25 ± 0.05	7.26 ± 0.03	NE	7.30 ± 0.04	NE	7.28 ± 0.04
	XKB	7.30 ± 0.10	7.24 ± 0.06	7.26 ± 0.07	NE	7.30 ± 0.06	NE	7.31 ± 0.07
P _a CO ₂ (mm Hg)	MKB	46.3 ± 12.4	49.1 ± 2.3	50.5 ± 7.3	NE	49.7 ± 10.2	NE	49.3 ± 9.6
	XKB	49.2 ± 13.0	55.7 ± 7.7	51.0 ± 6.4	NE	44.4 ± 12.3	NE	46.3 ± 7.5
P _a O ₂ (mm Hg)	MKB	477.0 ± 82.6	485.2 ± 67.9	$\textbf{481.8} \pm \textbf{48.8}$	NE	486.6 ± 134.4	NE	469.2 ± 111.1
	XKB	516.2 ± 29.8	519.4 ± 30.1	509.8 ± 61.0	NE	478.6 ± 117.2	NE	411.5 ± 215.1
SaO ₂ (%)	MKB	100 ± 0	100 ± 0	100 ± 0	NE	100 ± 0	NE	100 ± 0
	XKB	100 ± 0	100 ± 0	100 ± 0	NE	100 ± 0	NE	100 ± 0

Data are expressed as mean \pm SD, n = 5,

*Significantly different (P < 0.05) from baseline.

nificantly within 10 minutes of the administration of both the MKB and the XKB groups, and remained consistently below baseline for 60 minutes. In the MKB and the XKB group, the lowest HR was at 50 and 60 minutes, respectively. There was significant difference in HR values between the XKB and the MKB groups at the time of 20, 30 and 40 minutes.

There were no significant differences in arterial pressure between the two treatment groups. In the MKB group, the SAP and MAP were significantly higher than the baseline measurements at 5, 10 and 20 minutes and DAP was significantly higher than the baseline measurement at 5 minutes.

Rectal temperature decreased relative to the baseline mea-

surement after the administration of either XKB or MKB, but not to a statistically significant extent.

Respiratory rates, blood gases and lactate

Data for RR and blood gases (pH_a, PaCO₂, PaO₂ and SaO₂) are summarized in Table 5. In the MKB group, RR was significantly lower than the baseline measurment at 10, 20, 30, 40 and 50 minutes. In both groups, there were no statistically significant differences in pH, PaCO₂, PaO₂ and SaO₂. There was no significant difference between the two groups in terms of RR and blood gases.

Discussion

Ketamine is a broadly used dissociative agent with a wide margin of safety. It produces anesthesia without muscle relaxation, is not reversible, and provides only somatic analgesia (6,10,12). When it is used alone, it has been associated with rough inductions, lack of muscle relaxation, and/or prolonged recoveries. If sedatives or tranquilizers are used concomitantly, a lower dose of ketamine can affect anesthesia and its adverse effects can be minimized (6). Ketamine combinations that include α_2 -adrenoceptor agonists, such as medetomidine, provide smooth inductions and recoveries, good muscle relaxation and additional analgesia (13). Alpha₂-adrenoceptor agonists may cause dose-dependent hypertension, bradycardia, cardiopulmonary depression, and peripheral vasoconstriction, but these effects might be reduced if lower doses of medetomidine are used (6). Butorphanol, a synthetic opioid agonistantagonist, provides analgesia, sedation, and muscle relaxation while further decreasing the effective dose of other concurrently administered anesthetic agents (2,3). Ketamine, medetomidine and butorphanol combinations create almost completely reversible anesthesia because low doses of ketamine can be used effectively and effects of medetomidine and butorphanol can be reversed with atipamezole and naloxone, respectively (6,13). Medetomidine has been used extensively for the immobilization of captive and free-ranging carnivores, because it is rapidly and completely antagonized by the administration of atipamezole, a specific α_2 -adrenoceptor antagonist (4,13). Marked cardiopulmonary changes, such as decreased heart rate, elevated blood pressure, and profound hypoxemia, have been reported in wild and domestic artiodactylids that were administered medetomidine or a medetomidine/ketamine combination (1). To lower the dose of medetomidine and minimize the likelihood of medetomidineinduced cardiopulmonary side effects, the synthetic opioid butorphanol was added. Medetomidine-butorphanol and medetomidine-ketamine-butorphanol combinations have been used successfully in dogs, ferrets, redwolves, pigs, and Thomson's gazelles (1-4,8,11). Medetomidine is commonly used in combination with ketamine or butorphanol for the short-term immobilization of dogs (2). Ko et al. (2000) suggested that a combination of medetomidine with either butorphanol or ketamine resulted in a more reliable and uniform sedation in dogs as compared to medetomidine alone (2).

Blood gas analysis is the gold standard method for the evaluation of gas exchange. It provides invaluable information about the oxygenation, ventilation and acid-base status of the patient (10). Normal values of blood gases are: pH 7.35-7.45, P_aCO_2 35-45 (mmHg), HCO₃ 22-26 (mmol/l), P_aO_2 80-100 (mmHg) and S_aO_2 95-100 (%), respectively (10). The gold standard to evaluate the efficiency of ventilation is P_aCO_2 (10). Arterial blood pressure is one of the most useful measures of cardiovascular function available to a veterinary surgeon and invasive blood pressure measurement is considered the gold standard technique (10). Generally, arterial blood pressure

gives an indication of the adequacy of cardiovascular function. There is a wide range in blood pressure encountered in anesthetized dogs, therefore ranges commonly seen are between 90 and 120 mmHg for systolic, between 55 and 90 mmHg for diastolic, and between 60 and 120 mmHg for mean blood pressure. The systolic blood pressure is determined by a combination of peripheral vascular resistance, stroke volume and intravascular volume, whereas diastolic blood pressure primarily arises from peripheral vascular resistance. Mean blood pressure is an important factor in relation to general tissue perfusion (10). Blood flow to the major organs of the body is autoregulated across a range of mean blood pressures from about 60 mmHg to about 120 mmHg. When mean blood pressure falls below this range, blood flow to the major organs is jeopardized. This results in inadequate oxygen delivery and the accumulation of lactic acid, leading to acidosis. Changes in blood pressure and heart rate can be seen with inadequate anesthetic depth, anesthetic agent overdose, hypovolemia and overhydration. Perioperative monitoring of body temperature is important to detect hypothermia, which commonly develops during anesthesia.

In this study, we compared the anesthetic and cardiopulmonary effects for recipients of MKB and XKB. The cardiopulmonary effects and arterial blood gas analyses were similar in both groups. However, the duration of anesthesia was significantly longer in XKB group (87.4 ± 18.9 minutes).

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개에서 Medetomidine-Ketamine-Butorphanol과 Xylazine-Ketamine-Butorphanol의 마취 효과 및 심폐에 미치는 영향

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요 약: Medetomidine과 xylazine은 수의 임상에서 많이 이용되고 있는 마취약물이다. Medetomidine-ketaminebutorphanol과 xylazine-ketamine-butorphanol의 개에 미치는 마취효과와 심폐 효과를 비교 연구하였다. Medetomidineketamine-butorphanol를 MKB군으로 xylazine-ketamine-butorphanol를 XKB군으로 분류하고 각각 5두의 개를 4주간의 휴약기간을 거쳐 실험하였다. 각각의 군에서 마취효과 점수는 자세와 진통에 대한 반응을 통해 평가하였고, 마취 시간 은 XKB군 (87.4±18.9분)이 MKB군 (62.6±15.0분)에 비하여 유의성 있게 높은 시간의 결과를 보였다. 하지만, 기타 심폐 효과에서는 두 군 사이에 통계적으로 유의성 있는 차이를 보이지 않았다. 하지만 MKB군에서는 서맥을 보였으 므로, 마취 모니터링 시 주의하여야 한다. 만약 서맥의 위험이 있는 환자라면 MKB 합제는 선택을 안 하는 것이 요구 된다. 결론적으로, XKB군에서 더 긴 마취시간과 더 적은 부작용을 보였으며, MKB 합제 약물은 XKB군에 비하여 특 별한 장점이 없으므로 XKB 합제가 더욱 유용한 것으로 판단하였다. 하지만 XKB군과 MKB군 모두에서 적절한 체온 유지와 산소공급이 필요하다.

주요어 : medetomidine, xylazine, ketamine, butorphanol, 개