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Effect of Medetomidine and Combination of Medetomidine/tiletamine/zolazepam and Medetomidine/tiletamine/zolazepam/tramadol on Echocardiographic Cardiac Contractility in Dogs

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Abstract : This study evaluated the myocardial performance on echocardiography after the sedation/anesthesia of medetomidine (D), the combination of medetomidine and tiletamine/zolazepam (DZ), and the combination of medetomidine, tiletamine/zolazepam and tramadol (DZT) in Beagle dogs. Ten healthy adult Beagle dogs (weighing 8.6 ± 1.0 kg) were enrolled in this study. Heart rate (HR), fractional shortening (%FS), left ventricular ejection fraction (%LVEF), stroke volume (SV), cardiac output (CO), left ventricular internal diameter in systole (LVIDs) and left ventricular internal diameter in diastole (LVIDd) using M-mode echocardiography were measured prior to anesthesia, then every 10 min for 60 min. The HR, %FS, %LVEF, SV and CO were significantly decreased during sedation/anesthesia with D, DZ and DZT combination of anesthesia. Although those anesthetic protocols provided acceptable quality of sedation/anesthesia, levels of cardiovascular suppression were substantial and persistent and thus the continuous monitoring on vital signs should be accompanied in any situation. Close attention is required for dogs with pre-existing heart diseases, when those anesthetic protocols were applied.

Key words **:** medetomidine, anesthesia, Domitor, tiletamine, tramadol, dog.

Introduction

Medetomidine is a potent and selective α2-adrenoreceptor agonist and provides deep sedation and analgesia, which can be rapidly and completely reversed by α2-antagonist atipamezole (3). Medetomidine is generally used in combinations with opioids (butorphanol, buprenorphine) and other sedatives as premedication in healthy dogs. However, it caused marked peripheral vasoconstriction and bradycardia in dogs (10). Therefore it is contraindicated in patients with cardiac disease. Since medetomidine can induce transient hyperglycemia from reduced secretion of insulin, it is not recommended for diabetic dogs. Furthermore, recent feline study found rare cases of delayed pulmonary edema, some resulting in death, after received medetomidine (usually in conjunction with anesthesia; unpublished data). In these cases, dyspnea due to the delayed onset of pulmonary edema developed up to three days after medetomidine administration. Therefore medetomidine should be used with other premedicants, to lower the dose of medetomidine (5).

Tiletamine-zolazepam is a combination of equal parts of tiletamine HCl and zolazepam HCl and is widely used for preanesthetic medication, sedation and general anesthesia for diagnostic and minor surgical procedures in dogs. Unlike other induction agents (e.g. propofol and alfaxalone), it provides smooth muscle relaxation and minimal analgesic effect (8). One study found that tiletamine-zolazepam caused significant increases in heart rate after injection doses (6.6 mg/kg) and significant increases in cardiac output after the larger doses (13.2 mg/kg) (8). All doses caused significant decreases in arterial blood pressure at 1 minute. Arterial blood pressures returned to baseline and then increased significantly above baseline values. It results in a reliable and predictable immobilization, has a little physiological adverse effect and also is safe to handle. However, it has only few antagonists and causes lengthy and poor recovery. Therefore it is generally used with other sedatives and analgesics in dogs (2,6,11).

Tramadol is synthetic codeine analog, is a weak μ opioid receptor agonist (12) and is widely used for acute and chronic pain of moderate to severe intensity. Although few clinical studies have examined the use of tramadol in dogs, it has been reported that tramadol had an analgesic effect after ovariohysterectomy similar to that of morphine (12). Therefore, tramadol is generally used alone to treat mild pain and adjunctively in a multimodal pain therapy for moderate to severe pain. It is also used as a premedicant for general anesthesia, especially with the combination of medetomidine and tiletamine/zolazepam.

Some reason, the combination of tiletamine/zolazepam-medetomidine with tramadol anesthesia is popular in Korea and causes sudden death in dogs and cats. The purpose of this study is to evaluate how severely affects myocardial performance even after lowering dose of medetomidine in dogs. Therefore in this study, we evaluated the left ventricular (LV) contractility and LV indices on echocardiography after the sedation/anesthesia of medetomidine (D), the combination of medetomidine and tiletamine/zolazepam (DZ), and the com-

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bination of medetomidine, tiletamine/zolazepam and tramadol (DZT) in Beagle dogs.

Materials and Methods

Approval of the animal ethics committee of Kangwon National University was obtained for this experiment prior to the commencement of the study. Ten adult Beagle dogs (five male, five female, mean body weight 8.6 ± 1.0 kg, 4.2 ± 1.0 yrs) were used for this study. All dogs were healthy based upon physical examination, evaluation of an electrocardiogram (ECG), serum chemistry and hematologic analyses.

Three different anesthetic protocols were evaluated in this study: 1) medetomidine (30 ug/kg; Domitor®, Pfizer, USA), 2) medetomidine (15 μg/kg) + tiletamine/zolazepam (3 mg/kg, Zoletil®, Virbac, France), 3) medetomidine (15 μg/kg) + tiletamine/zolazepam (3 mg/kg) + tramadol (3 mg/kg, Shinpoong, Tramdol HCl, Korea). All drugs were mixed in a single syringe and then were injected slowly into the dorsal lumbar muscle of the dog by using a syringe with a 23-gauge, 1-inch needle (Becton Dickinson, New Jersey, USA). Each experiment was repeated in 3-days interval to clear out previous medications.

Heart rate (HR) was recorded before administration of anesthesia (T0), and then every 10 min for 60 min. The 3-lead digital electrocardiogram (VH-1, CU-medical, Korea) was recorded prior to study and during anesthesia. Echocardiographic left ventricular (LV) indices were measured in all dogs using M-mode echocardiography at the right parasternal short axis of left ventricular papillary muscle level with an ultrasound unit (X300; Simens, Germany) equipped with 3.0-9.0 MHz phased-array transducers. All echocardiographic measurements were performed by the same experienced person (Kim). Left ventricular internal diameter in systole (LVIDs), left ventricular internal diameter in diastole (LVIDd), % fractional shortening (%FS), % ejection fraction (%LVEF), stroke volume (SV, m*l*) and cardiac output (CO, ml min^{-1}) were measured by M-mode echocardiography at LV papillary muscle level before administration of any medications (T0) and every 10 min after administration for 60 min, as described previously (1). The CO was calculated as SV x HR.

The statistical software used in statistical analysis was SPSS 15.0 for Windows (IBM, NY, USA). Normality was tested by the Kolmogorov-Smirnov test. One-way ANOVA repeated measures were performed with the same parameters between baseline and post-induction values with Dunnett's

Table 1. Changes in left ventricular echocardiographical measurement before (T0), and after intramuscular administration of medetomidine (30 ug/kg), medetomidine (15 μg/kg) and tiletamine/zolazepam (3 mg/kg), and medetomidine (15 μg/kg), tiletamine/zolazepam (3 mg/kg) and tramadol (3 mg/kg) in Beagles. Mean ± SD. *Significant difference from baseline (T0; $P < 0.05$). $^{\$}$Significant difference among study group ($P < 0.05$)

Time (min)		0	10	20	30	40	50	60
HR (beats/min)	D	114 ± 31	62 ± 32*	63 ± 40*	65 ± 37*	66 ± 35*	70 ± 37*	74 ± 37*
	DZ	112 ± 31	93 ± 25*$^{\$}$	80 ± 9*$^{\$}$	84 ± 11*$^{\$}$	86 ± 12*$^{\$}$	99 ± 22*$^{\$}$	109 ± 25$^{\$}$
	DZT	93 ± 18	83 ± 26$^{\$}$	79 ± 20*$^{\$}$	75 ± 19*$^{\$}$	79 ± 25*$^{\$}$	93 ± 35$^{\$}$	89 ± 25$^{\$}$
%FS	D	36.4 ± 6.3	24.3 ± 6.3*	28.9 ± 9.2*	28.6 ± 4.6*	26.8 ± 6.3*	22.7 ± 9.1*	29.0 ± 10.2*
	DZ	38.4 ± 112.	22.7 ± 12.6*	24.7 ± 7.3*	23.7 ± 5.2*	26.9 ± 9.1*	29.1 ± 8.3*	32.7 ± 20.2
	DZT	32.8 ± 7.3	17.7 ± 8.6*$^{\$}$	21.4 ± 8.0*	22.0 ± 4.1*$^{\$}$	25.3 ± 10.7*	26.8 ± 12.1*	28.7 ± 12.5
%LVEF	D	67.3 ± 8.9	49.3 ± 10.0*	56.2 ± 13.3*	56.6 ± 7.1*	53.5 ± 10.3*	46.1 ± 15.3*	55.9 ± 16.2*
	DZ	69.4 ± 13.6	45.1 ± 20.3*	50.0 ± 12.2*	49.3 ± 9.3*	50.1 ± 14.0*	52.0 ± 12.0*	54.9 ± 19.1*
	DZT	62.4 ± 10.1	37.2 ± 15.7*$^{\$}$	44.0 ± 14.2*	49.3 ± 10.8*	50.1 ± 16.7*	52.0 ± 17.3*	54.9 ± 18.7*
SV (mL)	D	23.2 ± 7.3	19.7 ± 9.8*	18.0 ± 6.8*	20.1 ± 8.4*	19.9 ± 7.9*	16.1 ± 4.2*	21.1 ± 11.1
	DZ	19.7 ± 6.4	14.8 ± 5.2$^{\$}$	17.1 ± 5.7	15.3 ± 7.4$^{\$}$	16.5 ± 4.8$^{\$}$	17.9 ± 5.2	16.1 ± 7.9$^{\$}$
	DZT	19.5 ± 6.4	14.4 ± 5.9*$^{\$}$	17.7 ± 6.3	17.5 ± 5.2	16.3 ± 6.4*	18.8 ± 6.0	19.3 ± 6.4
CO (mL/min)	D	2615 ± 997	1370 ± 1294*	1243 ± 1269*	1518 ± 1683*	1430 ± 1340*	1444 ± 386*	1664 ± 1416*
	DZ	1920 ± 1200	1456 ± 967*	1346 ± 371*	1328 ± 783*	1455 ± 631*	1692 ± 284*	1639 ± 664*
	DZT	1781 ± 635	1120 ± 391*$^{\$}$	1358 ± 562*	1349 ± 536*	1305 ± 691*	1740 ± 888	1697 ± 698
LVIDd (mm)	D	28.8 ± 4.1	30.0 ± 4.1	28.2 ± 5.9	28.9 ± 3.2	29.6 ± 4.1	29.5 ± 3.2	29.5 ± 4.7
	DZ	24.7 ± 3.5	29.0 ± 3.2*	28.9 ± 4.9*	27.3 ± 4.8*	28.1 ± 3.0*	27.9 ± 3.8*	24.1 ± 6.4*$^{\$}$
	DZT	27.6 ± 3.1	30.7 ± 4.0*	31.2 ± 4.6*	29.8 ± 5.0	28.4 ± 3.6	29.8 ± 2.9	29.4 ± 2.7
LVIDs (mm)	D	18.2 ± 3.2	22.3 ± 2.9*	20.2 ± 6.0	20.4 ± 3.0*	21.5 ± 3.9*	22.8 ± 4.1*	20.8 ± 4.2
	DZ	17.7 ± 3.8	22.5 ± 6.1*	21.7 ± 5.3*	20.7 ± 4.5*	20.5 ± 4.3*	19.7 ± 4.2*	23.8 ± 8.1
	DZT	18.3 ± 2.4	25.3 ± 4.9*	24.5 ± 5.4*	22.2 ± 5.4*	21.1 ± 4.7*	21.7 ± 5.0*	20.9 ± 4.8

LVIDs, Left ventricular internal diameter in systole; LVIDd, left ventricular internal diameter in diastole; %FS, % fractional shortening; %LVEF, %ejection fraction; SV, stroke volume; CO, cardiac output; HR, heart rate

test for post hoc analysis. Significance was set at $p < 0.05$.

Results

Although no morphological alterations in ECG were detected, sinus bradycardias were recorded in all dogs sedated with D, DZ and DZT combination from T10 to T60, depending on the medication (Table1). There were also statistically significant changes in HR after the administration of D, DZ and DZT combination (Table 1). The HR was significantly decreased from T10 to recovery ($p < 0.05$) in dogs sedated with D only, while the HR was gradually returned to baseline levels in dogs sedated with DZ and DZT combination. The %FS and %LVEF were statistically significantly decreased after the administration of D, DZ and DZT combination (Table 1). The reduction of D and DZT was persisted, even after recovery, while the %FS and %LVEF were gradually returned to baseline levels in dogs sedated with DZ (Table 1). The CO was statistically significantly decreased after the administration of D, DZ and DZT combination, while statistically significant decrease of SV was only noticed in D (T10-T50) and DZ (T10 and T40) combination (Table 1). There was significant and persistent increase in LVIDs after the administration of D, DZ and DZT combination, while the LVIDd was significantly and persistently increased only in DZ group. The LVIDs and LVIDd were returned to the baseline level at T60 in all study groups (Table 1).

Discussion

The recommended dose of medetomidine in dogs is 10-30 (slight sedation) and 10-20 (premedication) ug/kg. Therefore 30 ug/kg of medetomidine was used for the experiment in evaluating the effect of medetomidine (D) only, while 15 ug/kg for the experiment in evaluating the effect of DZ and DZT combination. The recommended dose of tiletamine/zolazepam in dogs is 5-7 (unpremedicated) and 3-5 (premedicated) mg/kg. Therefore 3 mg/kg of tiletamine/zolazepam was used for the experiment in evaluating the effect of DZ and DZT combination.

The HR was significantly decreased from the administration to recovery in dogs sedated with D only. However, the HR in dogs sedated with DZ and DZT combination was initially decreased after administration but later gradually increased from T20 ~T30 and then returned to the baseline levels. Medetomidine caused marked peripheral vasoconstriction and bradycardia in dogs (10), while tiletamine-zolazepam caused significant increases in heart rate after administration with dose-dependent manner (8). Tramadol can also increase HR (12). One study also found the combination of tiletamine with anticholinergic agent (glycopyrrolate) could not fully prevent reflex bradycardia from medetomidine (9). That study found the reflex bradycardia could prevent when glycopyrrolate started to take effect (9). However, in this study, we did not use anticholinergics. Therefore, the increase in HR might be from the effect of either/both tiletamine or/and tramadol. This result implies that the reflex bradycardia from medetomidine might be dose-dependent and lessen with time, and thus be suppressed by the chronotrophic effect from tiletamine/tramadol. Therefore the combination of DZ or DZT might be better for preventing adverse effects from medetomidine in practice.

SV is the blood volume pumping out from the heart with each beat. Using M-mode echocardiography, the SV can be calculated by subtracting the end-systolic volume from the end-diastolic volume. SV is an important determinant of CO, because the CO is calculated by multiplying SV with HR. Because SV tends to decrease in certain conditions and disease states, the SV is closely correlated with cardiac function. Major determinants of SV are the end-diastolic volume (residual blood volume in ventricles after pumping out), afterload (systemic and peripheral vascular resistance) and myocardial contractility. Myocardial contractility represents the intrinsic ability of the heart/myocardium to contract. It can be affected by heart rate, conduction velocity, preload, afterload and autonomic nerve stimulation. Myocardial contractility can be indirectly assessed by %FS and %EF. In this study, all echocardiographic LV indices for myocardial contractility (%FS, %LVEF, SV, CO) were decreased after the initiation of anesthesia in D, DZ and DZT groups. However, echocardiographic LV indices were gradually returned to baseline levels in DZ group, since the tiletamine might improve cardiac performance, as noticed in other study (9). Interestingly, this study found tramadol might have certain degree of cardiovascular suppression, because the level of improvement in %FS and %LVEF in DZT group was much lower than DZ group, although the %FS and %LVEF were also improved in DZT group with time. SV and CO were also significantly decreased in all groups in this study after the initiation of anesthesia in all groups (T10). The reduction of CO in this study might be due to the decrease in HR, increase in vascular resistance and/or a direct depression of myocardial contractility. One study found the reduction of CO in dogs sedated with medetomidine was mainly due to the decrease in HR and increase in vascular resistance, not due to a direct depression of myocardial contractility (7). However, it was difficult to identify the exact cause for CO reduction in this study, since many factors contributed the CO reduction in this study, besides the reflex bradycardia from medetomidine. Because all dogs breathed room air without endotracheal intubation, hypoxia might be one of factors for the CO reduction in this study. Because SV is a major determinants for CO, the decreased myocardial contractility evidenced by decreased %FS and %LVEF also contributed for the CO reduction in this study. The degree of reduction in SV and CO was more severe and steady in D only group, suggested the tiletamine/zolazepam might improve myocardial performance, especially in dogs sedated with medetomidine. Interestingly, one study found medetomidine increases inotropy and vascular resistance in autonomic-blocked dogs (4). However, this study found the medetomidine and its combination could directly depress myocardial contractility evidenced by the increased LVIDs and decreased SV during anesthesia, although it was unclear which drug was more attributable for this myocardial depression, because many contributing factors were involved in myocardial contractility. Despite this, it was clearly observed there was significant suppression in myocardial

contractility in dogs sedated with medetomidine and its combination, although the combination with other sedatives and perioperative drugs could lessen the degree of this suppression. Therefore, it is not advisable to sedate dogs with medetomidine only. Furthermore, levels of cardiorvascular suppression from medetomidine and its combination was substantial and persistent, the continuous monitoring on vital signs should be accompanied in any situation. Also any anesthetic method combined with medetomidine should not be used in dogs with pre-existing heart disease and high risk of cardiorespiratory suppression.

There are several study limitations for applying the results to clinical practice. The study population was limited to a small number of healthy colony dogs and not capable of obtaining sufficient statistical power to prove minimal cardiovascular detrimental effects. Secondly, there is a potential error from non-invasive measurement of CO by the M-mode echocardiography (1).

In conclusion, this study evaluated the myocardial performance on echocardiography after the administration of D, DZ and DZT combination in dogs. Although those anesthetic protocols provided acceptable quality of anesthesia, levels of cardiovascular suppression were substantial and persistent and thus the continuous monitoring on vital signs should be accompanied in any situation.

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개에서 Medetomidine, Medetomidine/tiletamine/zolazepam 합제, Medetomidine/tiletamine/zolazepam/tramadol 합제가 심장초음파 상 심장 수축력에 미치는 영향

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요 약 : 이번 연구는 비글 개에서 medetomidine(D), medetomidine, tiletamine/zolazepam(DZ) 합제, medetomidine, tiletamine/zolazepam, tramadol(DZT) 합제를 이용한 진정/마취 후 심근 기능을 평가하였다. 10 마리의 건강한 성견 비글(체중 8.6 ± 1.0 kg)를 이번 연구에 사용하였다. M-mode 심장초음파를 사용하여 심박수(HR), 구획단축률(%FS), 좌심실 박출기계수(%LVEF), 박출량(SV), 심박출량(CO), 수축기 좌심실 내강 직경 (LVIDs), 이완기 좌심실 내강 직경 (LVIDd)을 마취 전, 그리고 마취 후 10분 간격으로 60분 동안 측정하였다. HR, %FS, %LVEF, SV, CO 는 D, DZ 합제, DZT 합제 로 진정된 동안 심각하게 감소하였다. 이번 실험에 사용된 마취 프로토콜은 사용 가능할 정도의 진정/마취가 이뤄졌지만, 심혈관계 압박의 정도가 심했고 지속적이었고, 따라서, 어떠한 상황에서도 생체지수에 대한 모니터링이 동반되어야 한다. 본 마취 프로토콜은 심장질환을 가지고 있어서 심맥관계 억압의 가능성이 높은 환자에서는 주의해서 사용해야 한다.

주요어 : 메데토미딘, 마취, 틸레타민, 트라마돌, 개