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Clinical and echocardiographic evaluations of sedative and cardiovascular effects of combination of xylazine-acepromazine versus xylazine-pregabalin in horses

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Abstract

The aim of this study was to compare the sedative and cardiovascular effects of the combination of xylazine-acepromazine versus xylazine-pregabalin - in horses. Four healthy crossbred horses were included in the study and assigned to two treatments. In treatment I (T1), the animals received xylazine hydrochloride (1.00 mg kg^{-1}) in combination with acepromazine maleate (0.05 mg kg^{-1}) intravenously. In treatment II (T2), the animals received intragastric administration of pregabalin (4.00 mg kg^{-1}) followed by xylazine hydrochloride (1.00 mg kg^{-1}) intravenously after 60 min. Head height above ground (HHAG) and echocardiographic indices were evaluated. In T1, recordings were made 5 minubefore and 5, 15, 30, 60, and 90 minu after drug administration. In T2, recordings were made 5 min before pregabalin, 55 minu after pregabalin administration, and then 5, 15, 30, 60, and 90 min after xylazine hydrochloride acepromazine injection. Analyses of the data showed there were no significant differences regarding HHAG and echocardiographic indices between the two treatments. Intragastric administration of pregabalin prior to xylazine could be considered as an alternative premedication regimen when acepromazine administration is contraindicated or undesirable.

Introduction

In equine surgery, various techniques and modalities have been adopted to safely sedate and anesthetize horses with minimal side effects in order to help maintain their previous services.[1-3]

Clinical and echocardiographic evaluations of sedatives and their cardiovascular effects have been studied in horses.[4] Echocardiography is a valuable and noninvasive procedure that is increasingly used in the assessment of congenital and acquired heart diseases in horses. While echocardiography is well tolerated by most horses, it may be necessary to restrain nervous and restless horses with sedative drugs. Echocardiography is able to determine the cardiovascular effects of drug-induced sedation and establish the degree of compromised cardiac function, allowing for inferences about the efficacy, safety, and viability of drugs and their possible procedural risks.[5]

The most commonly used drugs for standing sedation in horses are the alpha-2 agonists, which can be used alone or in combination with other drugs such as opioids or phenothiazines. Acepromazine, a phenothiazine derivative, is commonly used in horses as a sedative during transportation and for clinical or surgical procedures. However, it can lead to cardiorespiratory depression, severe hypotension and continued paralysis of the penis retractor muscle.[6,7] Moreover, acepromazine is categorized as a controlled substance in many racing and equestrian jurisdictions, limiting its usage in horses.[8]

Pregabalin has antiepileptic, analgesic, and anxiolytic activity.[9] It is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid. The mechanism of action of pregabalin, for either its anticonvulsant or analgesic actions is not fully understood, but it appears to bind to CaVa2-d (alpha2-delta subunit of the voltage-gated calcium channels). By decreasing calcium influx, release of excitatory neurotransmitters (e.g., substance P, glutamate, norepinephrine) is inhibited. Mullen *et al.* studied pharmacokinetics of single-dose intragastric pregabalin administration in clinically normal horses and observed minimal adverse effects of pregabalin.[10]

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The aim of this study was to compare the sedative and cardiovascular effects of a combination of xylazine and acepromazine versus xylazine and pregabalin in healthy horses. Head height above ground (HHAG) and echocardiographic indices were evaluated.

Materials and Methods

Procedures. Four healthy crossbred horses (two males and two females weighing 385 - 450 kg, and 8 - 10 years old were included in this study. In this crossover clinical trial, animals were randomly assigned to receive two different treatment protocols, with a washout period between the two treatment periods to allow any effects of the first treatment to subside before the second treatment was administered. . Due to the small sample size each protocol was repeated twice. In other words, eight horses were examined for each treatment protocol. All horses underwent clinical, hematological and parasitological examinations and were considered normal. The horses were placed together in stocks during the study period, with free access to hay and water. The solid fasting period was 12 hr. Experimental protocols were performed for each horse on fixed days and periods (morning), with and a three-week washout period between the experiments. For jugular injection of treatments, the region of the neck was clipped. For echocardiography, the region between the 3rd and 5th intercostal spaces, was clipped and washed with surgical spirit and covered with acoustic coupling gel.[10] The study was carried out in two treatment settings. In treatment I (T1), the animals received cocktail of xylazine hydrochloride (1.00 mg kg^{-1}, Alfasan, Woerden, The Netherlands) and acepromazine maleate (0.05 mg kg^{-1}; Alfasan) intravenously (IV) in one syringe, with volumes equalized using normal saline. In treatment II (T2), the animals received intragastric administration of pregabalin (4.00 mg kg^{-1}; Tolid Darou, Tehran, Iran) followed by xylazine hydrochloride (1.00 mg kg^{-1}) intravenously after 60 min. The tablets of pregabalin were completely dissolved in 100 mL of warm water and administered as a slurry via a nasogastric tube, followed by approximately 1,000 mL of warm water to rinse any remaining medication from the tube into the stomach. The pharmaceutical product of pregabalin for IV injection was not available, therefore, we used intragastric administration based on a method described by Mullen *et al.*[10] Head height above ground and echocardiographic indices were recorded as follows: In T1, the parameters were evaluated 5 min before, and 5, 15, 30, 60, and 90 min after the administrations. In T2, the parameters were evaluated 5 min before, and 55 min after pregabalin administration and then 5, 15, 30, 60, and 90 min after xylazine injection were recorded. The time points were based on a modified protocol described by Dezfouli *et al.*[11] The present study was conducted following the standard animal experimentation protocol of the Veterinary Ethics Committee of Urmia University. It was approved under ethical code# IR-UU-AEC-3/16- 28/05/2023.

Assessment of the HHAG. Ringer *et al.* adopted the HHAG as a marker of depth of sedation.[12] The HHAG is defined as the position of the nose in relation to a scale marked on the wall. The scale is individual to each horse, with 100% indicating the normal head position (± 10.00%) of the particular horse while completely awake. An HHAG ≤ 50.00% indicates sufficient sedation.[10] We used a modified method of Ringer *et al.*[12] and assessed sedation depth by measuring the degree of head drop following drug administration. The floor to chin height was determined at all times during both treatments and recorded.

Echocardiography. Echocardiographic images were acquired with an ultrasound device (Q9Vet; Chison Medical Technologies Co., Wuxi, China) with a phased array transducer (2.50 MHz). The region between the 4th and 5th intercostal spaces was used for echocardiography. The lack of cardiac anomalies was confirmed through right parasternal long and short axis echocardiography before starting the treatment protocol. M-mode echocardiography was performed via the right parasternal short axis view at the level of the chordae tendinea to record the following parameters by the built-in software (Fig. 1): Left ventricular internal diameter at end diastole (LVIDd), left ventricular internal diameter at end systole (LVIDs), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and fractional shortening (FS). The LVIDd was measured using the beginning of the QRS complex as the reference point, and the LVIDs was measured at the maximum upswing of the left ventricular free wall.[8]

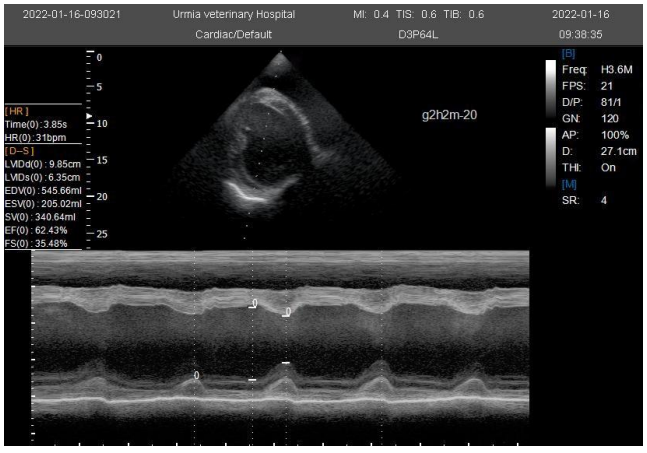

Fig. 1. M-mode echocardiography of the right parasternal short axis view at the level of the chordae tendinea in one of the horses undergoing sedation. HR: Heart rate, LVIDd: Left ventricular internal diameter at end diastole, LVIDs: Left ventricular internal diameter at end systole, EDV: End-diastolic volume, ESV: End-systolic volume, SV: Stroke volume, EF: Ejection fraction, FS: Fractional shortening.

Statistical analysis. Data were presented as mean ± standard deviation. Statistical analysis was conducted using SPSS Software (version 22.0; IBM Corp., Armonk, USA). The Shapiro-Wilk test was used to check for normal distribution. For comparisons between groups, independent samples *t*-tests was used, and for within-group comparisons, paired samples *t*-tests was employed. The qualitative data between groups were compared with chi-square and Kruskal-Wallis tests. Statistical differences with $p < 0.05$ were considered significant.

Results

HHAG. The results of HHAG for determining the degree of sedation are shown in Table 1. In group T1, there was a decreasing trend until 5 min after xylazine-acepromazine administration, followed by an increasing trend. In the second group, the trend was downward until 5 min after the injection, then turned upward. Overall, the lowest head height in both groups was observed at 5 min after drug administration. Statistical analysis revealed no significant difference between groups at 5, 30, and 60 min after drug administration ($p > 0.05$).

Heart rate and echocardiographic indices. Results for heart rate and echocardiographic indices including LVIDd, LVIDs, SV, EDV, ESV, EF and FS are shown in Table 2. The results in T1 and T2 showed that in both groups, there was a decrease in heart rate 5 min after the injection, which then increased significantly at the 15-min time point. In T2 the heart rate was higher than in T1 at all time points; however, no significant differences were observed ($p > 0.05$).

LVIDd findings. The results of LVIDd in T1 and T2 showed that in the first group, there was a downward trend until the 15th min after the injection, followed by an upward trend until the 90th min. In the second group, there was a decrease in the internal diameter of the left ventricle at the end of diastole from the 5th min after the injection to the 30th min. Then, from the 60th min after the injection in the second group, there was an increase followed by another decrease at the 90th min. The intensity of the decline was greater in the first group compared to the second group. The smallest internal diameter of the left ventricle at the end of diastole was observed in the first group at 15 min after injection and in the second group at 30 min after injection. According to the statistical tests, there were no significant differences between the two groups at 5, 15, 30, 60 and 90 min after injection ($p > 0.05$).

LVIDs findings. The results of LVIDs in T1 and T2 showed that in both groups, until 15 min after injection, the trend was downward and then upward. The severity of the decline in the first group was more than the second group. In the first group, the internal diameter of the left ventricle at the end of systole was the lowest at 15 min after injection, and in the second group at 60 min after injection. The smallest internal diameter of the left ventricle at the end of systole was observed in the second group. The statistical tests indicated that there was no significant difference between the two groups ($p > 0.05$).

EDV findings. The results of EDV in T1 and T2 showed that in the first group, until 15 min after injection, the trend was downward and then upward. But in the second group, until the 30th min after the injection, the trend was downward, then it was upward until the 60th min, and then it was downward again at the 90th min. The severity of the decline in the first group was greater than in the second group. In the first group, the volume of blood in the left or right ventricle at the end of diastole was the lowest in 15 min after injection and in the second group at 90 min after injection. The lowest amount of blood volume in the ventricle at the end of diastole was found in the first group ($p > 0.05$).

ESV findings. The results of ESV in T1 and T2 showed that in both groups, until the 15th min after injection, the trend was downward and then it became upward. The severity of the decline in the first group was more than the second group. In the first group, the volume of blood in the ventricle, at the end of systole, was the lowest at 15 min after the injection and in the second group at the 60th min. The lowest volume in the ventricle at the end of systole was observed in the first group. The statistical tests indicated that there was no significant difference between the two groups ($p > 0.05$).

SV findings. The results of SV in T1 and T2 showed that in the first group, until the 15th min after the injection, there was a downward trend, and then until the 30th min after the injection, the trend was upward, and from the 30th to the 60th min after the injection, it was downward and then upward. The changes were not significant and noticeable, but in the second group, until the 30th min after the injection, there was a downward trend, and then until the 60th min after the injection, and then at the 90th min after the injection, it became a downward trend. The statistical tests revealed no significant difference between two groups ($p > 0.05$).

Table 1. Mean ± SD values of head height above the ground (cm) for four research horses at various time points in groups T1 and T2.

Treatments	Time (min)					
	– 5	5	15	30	60	90
T1	100.00 [a]	31.66 ± 3.89 [b]	43.75 ± 2.26 [c]	54.58 ± 3.96 [d]	85.00 ± 3.69 [e]	100.00 [a]
T2	100.00 [a]	40.00 ± 5.22 [b]	41.66 ± 4.92 [b]	44.16 ± 5.57 [b]	75.83 ± 5.14 [c]	100.00 [a]

[abcde] Different superscripts in each row indicate significant differences among time points ($p < 0.05$).

Table 2: Mean ± SD values of heart rate and echocardiographic indices including LVIDd, LVIDs, SV, EDV, ESV, EF, and FS in different time points in animals from groups T1 and T2.

Indices	Treatments	Time (min)					
		– 5	5	15	30	60	90
Heart rate (min)	T1	26.25 ± 4.09	12.91 ± 2.31	23.50 ± 4.29	22.00 ± 4.63	20.83 ± 4.40	22.41 ± 3.60
	T2	29.35 ± 40.17	13.83 ± 1.46	26.83 ± 1.19	29.58 ± 1.15	28.33 ± 4.57	30.75± 3.19
LVIDd (cm)	T1	11.31 ± 1.00	8.63 ± 1.01	8.08 ± 0.98	10.57 ± 0.95	11.13 ± 0.95	11.51 ± 0.93
	T2	11.35 ± 0.44	10.26 ± 0.29	9.85 ± 0.17	9.49 ± 0.13	9.77 ± 0.13	9.37± 0.19
LVIDs (cm)	T1	8.58 ± 0.56	7.33 ± 0.55	6.92 ± 0.55	7.23 ± 0.42	7.52 ± 0.44	8.18 ± 0.44
	T2	8.73 ± 0.24	7.59 ± 0.18	7.26 ± 0.20	7.39 ± 0.11	6.67 ± 0.10	7.72 ± 0.22
EDV (mL)	T1	740.73 ± 138.72	523.12 ± 129.02	430.27 ± 132.29	481.26 ± 130.82	535.24 ± 131.06	630.59 ± 131.87
	T2	746.16 ± 63.89	596.59 ± 39.18	547.02 ± 21.91	503.28 ± 15.91	536.9 ± 16.04	490.31 ± 22.18
ESV (mL)	T1	413.81 ± 56.83	199.93 ± 54.18	110.66 ± 31.06	155.45 ± 31.34	214.39 ± 36.21	299.96 ± 32.86
	T2	419.12 ± 25.63	307.34 ± 17.19	227.62 ± 17.84	289.45 ± 10.34	230.36 ± 9.12	318.82 ± 20.59
SV (mL)	T1	326.92 ± 101.25	323.19 ± 84.15	319.61 ± 110.23	325.8 ± 109.66	320.85 ± 104.93	330.63 ± 107.76
	T2	327.04 ± 60.21	289.24 ± 27.78	269.39 ± 24.73	214.01 ± 12.95	306.53 ± 16.13	171.48 ± 30.34
EF (%)	T1	43.18 ± 8.01	61.74 ± 5.18	73.07 ± 7.61	66.11 ± 8.86	58.47 ± 8.71	51.00 ± 8.84
	T2	43.56 ± 4.72	48.4 ± 2.14	49.19 ± 3.42	42.03 ± 2.29	57.06 ± 1.80	34.84 ± 5.17
FS (%)	T1	23.88 ± 4.17	14.59 ± 6.31	13.84 ± 7.12	31.33 ± 3.44	32.23 ± 3.23	28.72 ± 2.92
	T2	23.14 ± 3.12	25.94 ± 1.24	26.29 ± 2.21	22.02 ± 1.08	31.68±1.26	17.56 ± 2.96

LVIDd: Left ventricular internal diameter at end diastole, LVIDs: Left ventricular internal diameter at end systole, EDV: End -diastolic volume, ESV: End-systolic volume, SV: Stroke volume, EF: Ejection fraction, FS: Fractional shortening. T1: Treatment 1, T2: Treatment 2. There were not significant differences between two treatment protocols ($p > 0.05$).

EF findings. The results of EF in T1 and T2 showed that in the first group, until 15 min after the injection, the trend was upward and then downward. In the second group, there was an upward trend until 15 min after the injection, followed by a slight decrease at the 30th min, an increase at the 60th min, and a final decrease at the 90th min. The highest ratio of the volume of blood removed from the left ventricle to the volume of blood in the left ventricle at the end of diastole was at its peak in the first group at 15 min after injection and in the second group at 60 min after injection. According to the statistical tests, there was no significant difference between the two groups ($p > 0.05$).

FS findings. The results of FS in T1 and T2 showed that in the first group, there was a downward trend until 15 days after the injection, then it increased until the 60th min. The percentage of left ventricular diameter changes during systole in the second group increased at 15 min, decreased at 30 min, increased at 60 min, and decreased at 90 min. The intensity of changes in the second group is not high. The highest percentage of left ventricular changes during systole belonged to the first group at the 60th min after injection. The severity of changes in left ventricular diameter during systole was greater in the first group than in the second group. According to the statistical tests, there was no significant difference between the two groups ($p > 0.05$).

Discussion

Acepromazine is known to cause penile prolapse in male horses, although the mechanism is unknown.[7] Acepromazine injection is metabolized in the liver and should be used cautiously in animals with a history of liver dysfunction or leukopenia. Rapid intravenous injection can result in hypotension, causing cardiovascular collapse. Accidental intracarotid injection can cause a range of clinical signs, from disorientation to convulsive seizures and death. Acepromazine is Food and Drug Administration approved for use in horses and US federal law restricts its use to a lawful written or oral order from a licensed veterinarian. Acepromazine is a prohibited substance in most sanctioned competitions.[6-8] In search of introducing of a substitution for acepromazine where its usage is contraindicated, this study evaluated pregabalin to determine whether it could be used as an alternative agent. Since the pharmaceutical product of pregabalin for IV injection was not available, intragastric administration was used instead. The evaluations were based on behavioral and echocardiographic parameters.

The HHAG is a marker of depth of sedation.[13] The HHAG is defined as the position of the chin in relation to a scale marked on the wall. The scale is unique to each horse, with 100% indicating the normal head position of the horse while completely awake, with a margin of ± 10.00%. Reductions of the HHAG by 50.00% or more represent a sufficiently sedated animal.[14,15] In this study, the same index was used to assess the level of sedation. It was found that 55 min after oral administration of pregabalin, there was no significant reduction in head height. However, but 5 min after injection in both groups, the height of the head from the ground level reached its lowest percentage, which means that 5 min after injection in both groups the maximum amount of sedation was occurred. Also, in both groups from the 15th min after the injection, we saw an upward trend in the height of the

head above the ground, and at the 90th min, this percentage returned to normal (100%). According to these results, the first group in min 5 and 15 and the second group in min 5, 15 and 30, experienced acceptable sedation (altitude below 50.00%); Therefore, it could be said that the duration of acceptable sedation in the T2 was longer than the T1. In addition, the amount of sedation based on HHAG in the second group was higher than the first group only at the 5th min after injection, and in other min the amount of sedation was slightly higher in the first group. Echocardiography, an invaluable tool for the assessment of cardiac structure, chamber size and function, is ultrasonography of heart. Equine echocardiography uses ultrasound technology to provide images of a horse's heart and has become a standard diagnostic procedure in equine cardiology.[11] Echocardiography is an indispensable diagnostic procedure in equine cardiology.[16] Four views of the heart are captured- a long and short view from both the right and left sternal areas. While structural information remains accurate in a sedated horse, certain cardiac dimensions (e.g., end systolic left ventricular diameter, interventricular septal thickness, and free wall thickness) and indices of cardiac function (e.g., FS and fractional area change) may be altered.[17,18]

Real-time two-dimensional (2D) or B-mode ("brightness" mode), M-mode (motion mode), color flow Doppler, pulsed-wave Doppler, and continuous-wave Doppler are some of the possible modes employed for the procedure. M-mode and 2D equine echocardiography allow users to visualize the heart structure and function.[19]

Two-dimensional (2D) gray-scale imaging and M-mode echocardiography provide the foundation for noninvasive evaluation of cardiac structures, chamber dimensions, and chamber function. Acepromazine has been reported to either increase or decrease cardiac output.[15] Acepromazine induced increases in arterial diameter and volumetric flow rate, with a trend towards increased blood velocity.[20] A similar result was seen by Muir and Mason, where acepromazine caused a decrease in blood pressure and vascular resistance due to vasodilation.[21] The findings of this study showed that intragastric administration of pregabalin had the similar effects on arterial diameter compared to acepromazine. Buhl *et al.* [5] and Menzies-Gow[22] found no effect of acepromazine administration on LVIDs, LVIDd. Similarly, Dezfuoli *et al*. reported no changes in LVIDd, LVIDs, EF, and SF. These results were consistent with the findings of the current study.

The effect of acepromazine on heart rate remains unclear, with some studies suggesting a reflexive increase in heart rate due to decreased arterial blood pressure following acepromazine injection.[23-25] However, another study found the minimal effects of acepromazine on heart rate.[5] Accordingly, in this study, in both groups, 5 min after injection, we saw a decrease in heart rate, likely due to the effect of xylazine. The severity of the decrease in the T1 group was insignificantly more than the T2 group. Then, from 15 min after the injection a gradual increase in heart rate was observed in both groups. Although the lowest heart rate was observed in the first group, the differences were not significant at 5-, 15-, 30-, 60-, and 90-min post-injection. The echocardiographic indices showed that intragastric administration of pregabalin had a similar effect on cardiac function compared to acepromazine. Pregabalin showed no adverse effects of acepromazine and could be considered a safer alternative in cases where acepromazine is contraindicated.

Our findings indicate that the sedative and cardiovascular effects of intragastric pregabalin administration and intravenous acepromazine administration are comparable to those of acepromazine-xylazine IV administration. Hence, these options could serve as viable alternatives for premedication in situations where acepromazine use is contraindicated.

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Conflict of interest

There is no conflict of interest to declare.

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