

Effect of nalbuphine or ketamine on xylazine requirements in standing sedated horses

Ahmed Sharshar¹, Amal Hammad^{1*}, Shaaban Gadallah¹, Nahed Thabet², and Tarek Misk¹

¹Department of Surgery, Anesthesiology and Radiology, Faculty of Veterinary Medicine, University of Sadat city, Egypt

²Department of clinical pathology, Faculty of Veterinary Medicine, University of Sadat city, Egypt

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ABSTRACT

Despite the pivotal role of α_2 -agonists for standing sedation in horses, these drugs possess several dose-dependent side effects. Therefore, this study aimed to determine the effect of nalbuphine or ketamine on xylazine requirements necessary to provide constantly moderate sedation in horses. Five healthy adult horses were subjected to three randomized treatments at one-week intervals as follows: xylazine (XYL) (xylazine: 0.55 mg/kg, IV; saline: bolus & CRI); xylazine/nalbuphine (XYL/NAL) (xylazine: 0.55 mg/kg, IV; nalbuphine: 0.3 mg/kg, IV & 0.23 mg/kg/hour CRI) and xylazine/ketamine (XYL/KET) (xylazine: 0.55 mg/kg, IV; ketamine: 0.1 mg/kg, IV & 0.5 mg/kg/hour CRI). On all occasions, moderate sedation was maintained for 120 minutes by administering additional xylazine boluses (0.14 mg/kg, IV) whenever lower sedation was demonstrated. All treatments were assessed in terms of the degree of sedation, the time of administering the first additional xylazine bolus, and xylazine requirements (presented as mg/kg/hour) for maintaining moderate sedation for 120 minutes. The degree of ataxia and adverse events were also monitored. Sedation scores were significantly higher than the baseline for all treatments over 120 minutes. A longer time before the first additional xylazine bolus and lower xylazine requirements (lower calculated infusion rates) for maintaining moderate sedation were evident following the XYL/NAL and XYL/KET treatments compared to the XYL treatment. All treatments were associated with an acceptable degree of ataxia and limited behavioral effects. In conclusion, both nalbuphine and ketamine were efficient in reducing xylazine requirements for constant sedation in horses. Further study is required for comprehensive testing of all studied combinations to elucidate the potential advantages of the demonstrated xylazine sparing effect.

Keywords: constant sedation; horses; ketamine; nalbuphine; xylazine

Introduction

General anesthesia in horses may be complicated with high mortality rates as well as various adverse

events, such as cardiopulmonary dysfunction, nerve and ischemic muscle damage and traumatic

*Corresponding author:

Amal Hammad, BVSc, master degree of veterinary medical sciences. Department of Animal surgery, Anesthesiology and Radiology, Faculty of veterinary medicine, University of Sadat City, Sadat City, Egypt, Postal code: 32511, Tel: 00201007971657; Fax: 0020482612225; E-mail: amal.abdelhakam@vet.usc.edu.eg

injuries during the recovery period (KLEIN, 1990; JOHNSTON et al. 2004; BIDWELL et al. 2007 and CLARKE et al. 2014). In order to enhance patient safety and to avoid the expense of general anesthesia, many diagnostic and surgical procedures may be conducted in sedated standing horses (MUIR, 2009 and WAGNER et al. 2011).

The α_2 -adrenergic agonists, including xylazine, detomidine, romifidine and medetomidine, are the main components of any sedative protocol in horses (VIGANI and GARCIA-PEREIRA, 2014). Despite their inevitable role in increasing the success rate of standing procedures by means of their sedative and analgesic effects (MOENS et al. 2003; MUIR, 2009 and PEȘTEAN et al. 2010), their administration is usually accompanied with significant drawbacks, such as bradycardia, decreased cardiac output, and variable changes in arterial blood gases, with a tendency for these events to be more severe at higher doses (CLARKE et al. 1991; WAGNER et al. 1991; YAMASHITA et al. 2000; FREEMAN et al. 2002). Ataxia, intestinal hypomotility, hyperglycemia and decreased hematocrit are other adverse events (BRYANT et al. 1991; MAMA et al. 2009 and GRIMSRUD et al. 2012). Administration of opioids along with α_2 -agonists is recommended to reduce the required doses and to overcome the drawbacks associated with higher doses (RINGER et al., 2012). Moreover, opioids improved and prolonged the sedative and analgesic effects of α_2 -agonists in horses (SEO et al. 2011; KULKARNI et al. 2015; RUIZ et al. 2015 and GOZALO-MARCILLA et al. 2017). A ketamine/opioid mixture was also found to be effective in improving the sedation quality of α_2 -agonists (WAGNER et al. 2011). On the basis of the previously mentioned dose-dependent side effects of α_2 -agonists and the virtues of administering opioids and ketamine in association with them, this study aimed to determine the effect of nalbuphine or ketamine on the xylazine requirements necessary to provide constantly moderate sedation in horses. We hypothesized that coadministration of nalbuphine or ketamine with xylazine would reduce its required dose for stable sedation in horses compared to its use alone.

Materials and methods

Animals. Five adult research horses (four stallions and one mare) of mixed breeds, weighing 286.33 ± 16.01 kg and aged 15.60 ± 5.77 years were enrolled in this study. The horses were considered healthy and free from painful conditions on the basis of physical examination, complete blood count and serum biochemistry analyses. This study was approved by the Institutional Animal Care and Use Committee (IACUC) of the Faculty of Veterinary Medicine, University of Sadat City, Egypt (protocol no VUSC-015-1-19). During the study period, the horses were housed in their usual stall at the University of Sadat City, where they were fed hay and allowed free access to water.

Study design. The present study was designed as a randomized, blinded and crossover study. At the end of the day prior to the experiment, the horses were weighed and the hair over their right jugular vein was shaved for placement of an intravenous catheter. Food but not water was withheld for 12 hours before the experiment. On the day of the study, the horses were kept in a stock in a quiet room and allowed at least two hours to acclimatize to their surroundings. Fly repellent was also applied to the skin of the horses to decrease external stimulation. For administration of the tested drugs, the right jugular vein was catheterized under local anesthesia with subcutaneous lidocaine 2% (2mL) using a 16-gauge catheter. The horses were randomly subjected to three treatments with a week wash out period in between. The assigned treatments were:

Xylazine (XYL) treatment. The horses received an IV bolus of xylazine (Xyla-Ject 20 mg/mL, Adwia Co, 10th of Ramadan city, Egypt) at a dose of 0.55 mg/kg (loading dose) over 1 minute (FERNANDES DE SOUZA et al. 2012). After 5 minutes, saline (El-Nile Co, Cairo, Egypt) was administered as an IV bolus followed by a constant rate infusion (CRI).

Xylazine/Nalbuphine (XYL/NAL) treatment. The horses received an IV bolus of xylazine at a dose of 0.55 mg/kg over 1 minute. After 5 minutes, nalbuphine (Nalufin 20 mg/mL, Amoun pharmaceutical Co, Cairo, Egypt) was administered

as an IV bolus at a dose of 0.3 mg/kg (TAYLOR et al. 1990) followed by a CRI of 0.23 mg/kg/hour. The nalbuphine CRI was calculated according to the equation previously described by THOMSON (2000) as follows:

Infusion rate IV (mg/h) = desired concentration (mg/L) × Debugging (L/h)

For this equation, 79.64 ng/ml was specified as the target plasma concentration while 2.88 L/h was used as the debugging or clearance rate, according to a study conducted in our laboratory (unpublished work). For the CRI of nalbuphine, the required solution was created by adding 178.75 ± 18.37 mg of nalbuphine into a 500-mL bag of 0.9% saline.

Xylazine/ketamine (XYL/KET) treatment. The horses received an IV bolus of xylazine at a dose of 0.55 mg/kg over 1 minute. After 5 minutes, ketamine (KETAMAX 50 mg/mL, Troikaa pharmaceuticals Ltd, Uttarakhand, India) was administered as an IV bolus at a dose of 0.1 mg/kg (based on a pilot study that was conducted on two horses prior to the experiment to evaluate the degree of ataxia associated with administration of 0.1, 0.3 and 0.5 mg/kg of ketamine in combination with 0.55 mg/kg of xylazine). Subsequently, the ketamine infusion (0.5 mg/kg/hour) was started according to SANCHEZ and ROBERTSON (2014). For the CRI of ketamine, the required solution was created by

adding 396.76 ± 12.60 mg of ketamine to a 500-mL bag of 0.9% saline.

To preserve blinding, in all treatments, the saline or nalbuphine or ketamine bolus used was adjusted to 10 ml (saline solution was used as vehicle) and administered over 2 minutes. Additionally, CRI of either saline, nalbuphine or ketamine was administered at a similar rate (1 drop/second) using 20 drops/mL infusion set (Jiangsu Kanghua Medical Equipment Co, Jiangsu, China).

Evaluation of the degree of sedation. The degree of sedation was evaluated by determination of the head-drop percentage, as well as the horses' response to auditory, visual, and tactile stimuli. At each recording time, the head drop % was estimated by measuring the change in head height (the distance from the most ventral bony portion of the chin to the ground, in centimeters) with respect to the baseline (baseline head height), using a measuring tape attached to the chin region (SOLANO et al. 2009 and REZENDE et al. 2014). For determination of baseline head height, the horses were observed for 15 minutes before drug administration, and the most frequently observed head position was recorded as the baseline head height. A numerical rating scale (NRS) ranging from 0-3 was used to score the head drop % determined at each observation time using a modification of the scoring system previously listed by SOLANO et al. (2009)

Table 1. The multifactorial sedation scale (MFSS) used to score the degree of sedation (scores of head-drop% and the horse's response to auditory, visual and tactile stimuli)

Variable	Score	Description
Head drop %	0	No head lowering (head height was equal or higher than baseline)
	1	Head slightly lowered (<40%)
	2	Head moderately lowered (40–60%)
	3	Head markedly lowered >60%
Response To auditory stimulation	0	Horse raised its head briskly and ears were erect or laid back
	1	Horse calmly raised its head
	2	Ear twitched or horse moved slightly
	3	No observable response

Table 1. The multifactorial sedation scale (MFSS) used to score the degree of sedation (scores of head-drop% and the horse's response to auditory, visual and tactile stimuli) (continued)

Response to visual stimulation	0	Undiminished response, animal moved away vigorously
	1	Muted response or subdued reaction and movements
	2	Reaction significantly subdued (elevates head slightly)
	3	No signs of visual arousal
Response to tactile stimulation	0	Rapid and marked response (head shake) to stimulation. It was also awarded when test was extremely difficult to perform
	1	The response was easily elucidated but was slower
	2	The response was sluggish and only elicited by prolonged stimulation
	3	No response
Total score of sedation degree	0-3	No sedation
	4-6	Mild sedation
	7-9	Moderate sedation
	10-12	Intense sedation

At different recording times, the studied horses were subjected to auditory, visual and tactile stimulation. Auditory stimulation was performed by clapping hands approximately 60 centimeters from the horse's head (LOVE et al. 2011). The horse's response was subsequently scored using a scale modified from WAGNER et al. (2011). Visual stimulation was done by waving a piece of cloth towards the animal's head (PEȘTEAN et al. 2010) with scoring of its reaction using the scoring system described by RINGER et al. (2013). Tactile stimulation was carried out by touching inside the pinna of the ear using a pen (GOZALO-MARCILLA et al. 2017) with scoring for the resultant response using a scale modified from CLARKE et al. (1991). The response of the horses to the different stimuli was scored subjectively from 0-3 (Table 1). For overall scoring of the degree of sedation exhibited by each horse at each observation period, the head-drop % score and the response scores to the different stimuli were summated to develop a

multifactorial sedation scale (MFSS), as presented in Table 1. With all treatments, moderate sedation (7-9 sedation score) was maintained for 120 minutes by repeated injection of a xylazine bolus at a dose of 0.14 mg/kg, IV (VIGANI and GARCIA-PEREIRA, 2014) when a lower sedation level was exhibited by the horses. For this, head-drop % and the horse's response to auditory, visual and tactile stimuli were assessed before (baseline) and every 10 minutes after xylazine administration for the 120 minute observation period. Furthermore, if the head was elevated by about 10 cm in periods between the assessments, the horse's response to different stimuli was evaluated to ensure that moderate sedation was being maintained, and to allow dosing of the animal once the sedation score was lower than needed.

Determination of the time for administering the first additional xylazine bolus. The time for administration of the first additional xylazine bolus was the first time when a moderate degree of

sedation (7-9 sedation score) was exhibited by the horses after administration of the xylazine loading dose (0.55mg/kg) was reduced to lower sedation (4-6 sedation score).

Determination of xylazine requirements for maintaining moderate sedation. The amount of xylazine required for maintaining a moderate sedation for 120 minutes was represented as the CRI (mg/kg/hour). This infusion rate was calculated for all treatments as the total dose of additional xylazine used after the initial loading dose, divided by the total time the horses showed the intended degree of sedation (starting with loading dose administration

and ending with the first observation of mild sedation after the 120 minute observation period).

Evaluation of the degree of ataxia. The degree of ataxia was evaluated at baseline and every 10 minutes after xylazine administration for 120 minutes, using the NRS previously used by FERNANDES DE SOUZA et al. (2012) (Table 2). Throughout the entire observation period, the horses were monitored for any CNS excitatory signs, such as muscle tremors. A single blinded investigator was responsible for assessing all the studied variables throughout the study.

Table 2. Numerical rating scale (NRS) used to assess degree of ataxia

NRS	Degree of ataxia
0	No ataxia
1	Mild ataxia. the horse was stable but swaying slightly
2	Moderate ataxia - the horse was swaying and leaning against the stock
3	Intense ataxia - the horse was leaning against the stock and swaying with its hind limbs crossed and its forelimbs buckling at the carpal joints

Statistical analysis. Statistical analysis was performed with SPSS 16.0 software (SPSS, USA). Head-drop % was analyzed using one-way analysis of variance (ANOVA) with Dunnett's post-test for comparisons of means within each group in relation to the baseline. Comparisons between groups at each time were performed with one-way ANOVA followed by Tukey's test. The Friedman test was used for the non-parametric variables including the horses' responses to auditory, visual and tactile stimuli, as well as ataxia. The results of head-drop % were expressed as mean \pm SD whereas the non-parametric results were expressed as the median (range). The level of significance was set at $P < 0.05$.

Results

Regardless of the treatment given, typical signs of sedation (head dropping, eyelid ptosis, ear tip and lip separation and ataxia) were evident immediately after xylazine administration. Relative to the baseline, the head dropped significantly with all treatments from 10 minutes into the observation period ($59.71 \pm 4.98\%$ with XYL; $64.20 \pm 6.76\%$ with XYL/NAL and 67 ± 6.63 with XYL/KET) up to 120 minutes. Throughout this period, no significant differences were detected in head-drop % between treatments, however at all time points, the heads were slightly lower with the XYL/NAL and XYL/KET treatments compared to the XYL treatment. All data are presented in Fig. 1.

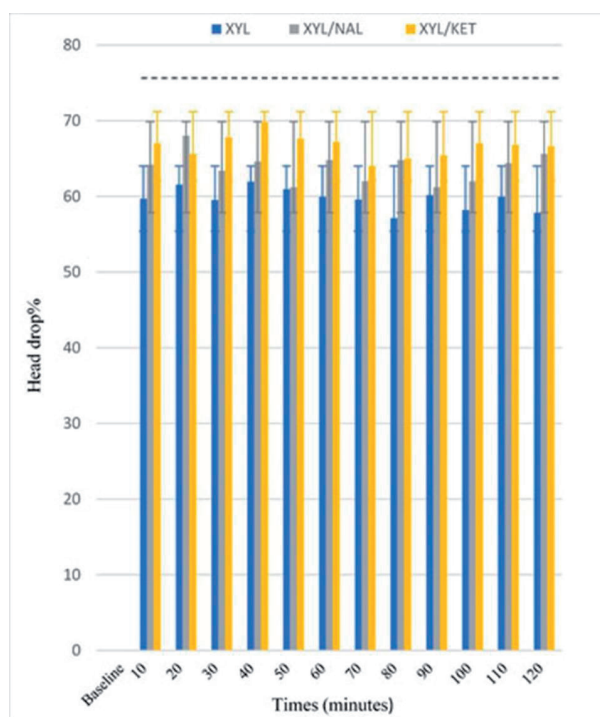


Fig. 1. Mean \pm SD of head drop % in five horses after receiving xylazine (XYL), xylazine/nalbuphine (XYL/NAL) and xylazine/ketamine (XYL/KET) treatments. ----- Significant difference ($P < 0.05$) between each treatment and the corresponding baseline value.

Following all treatments, significantly reduced responses to auditory, visual and tactile stimuli were exhibited by the horses at all time points compared to the baseline. Comparing treatments, no significant difference was detected in the horses' response to the stimuli. Nevertheless, at some time points, the XYL/NAL and XYL/KET treatments resulted in a slightly poorer reaction to auditory stimulation compared to the XYL treatment. Furthermore, an inferior response to visual and tactile stimuli was occasionally observed following XYL/NAL treatment than after XYL treatment (Table 3).

A significant increase in the overall sedation scores relative to the baseline was detected following all treatments from 10 minutes up until the end of the observation period (120 minutes). Significantly greater sedation was exhibited by the

horses that received the XYL/NAL treatment than those who received the XYL (at 10, 20, 30 and 80 minutes) and XYL/KET (at 10 and 20 minutes) treatments (Table 3). Slightly (insignificantly) deeper sedation was also recorded following the XYL/KET treatment compared to the XYL treatment.

The time point of administration of the first additional xylazine bolus was 12.67 ± 2.08 , 25 ± 2.65 and 18 ± 3.46 minutes with the XYL, XYL/NAL and XYL/KET treatments, respectively. For maintenance of moderate sedation for 120 minutes, xylazine requirements (expressed as CRI) were 1.08, 0.64 and 0.87 mg/kg/hour with the XYL, XYL/NAL and XYL/KET treatments, respectively. With respect to ataxia, the pilot study conducted to select the suitable loading dose of ketamine revealed that intravenous administration of 0.5 mg/kg of ketamine, in association with xylazine caused one horse to fall down and intense ataxia in the other, while 0.3 mg/kg of ketamine combined with xylazine resulted in moderate ataxia in one and intense ataxia in the other. As a result, a ketamine loading dose of 0.1 mg/kg was selected as it resulted in mild ataxia in the two horses studied, when given in combination with xylazine.

The data presented in Table 3 revealed that, at the 10 minute observation period, ataxia scores were significantly higher than the baseline following all treatments. At this time point, the XYL and XYL/KET treatments resulted in mild ataxia in four horses, and moderate ataxia in only one horse while, the XYL/NAL treatment induced moderate ataxia in three horses and mild ataxia in two horses. A significant increase in ataxia scores from the baseline was also detected at 20 minutes following all treatments. At the same recording time, the XYL treatment induced mild ataxia in four horses, with no ataxia in the remaining horse, while the other treatments induced mild ataxia in three horses, moderate ataxia in one horse, and no ataxia in the remaining horse. Comparing treatments, no significant difference was detected in the degree of ataxia at any time point. Throughout the study period, the horses were never severely ataxic or in danger of falling.

Table 3: Median (range) of response scores to auditory, visual and tactile stimuli, and sedation and ataxia scores in five horses after receiving xylazine (XYL, xylazine/nalbuphine (XYL/NAL) and xylazine/ketamine (XYL/KET) treatments

Variable	Treatment	Time (minutes)												
		Baseline	10	20	30	40	50	60	70	80	90	100	110	120
Response to auditory stimulation	XYL	1(0-1)	2(1-3)	2(2-3)	2(2-3)	2(2-3)	2(1-3)	2(2-3)	2(1-3)	2(2-3)	2(1-3)	2(2-3)	2(2-3)	2(2-3)
	XYL/NAL	1(0-1)	2(2-3)	2(2-3)	3(2-3)	3(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)
	XYL/KET	1(0-1)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(2-3)	2(1-3)	2(2-3)	2(2-3)	2(2-3)
Response to visual stimulation	XYL	0(0-1)	2(1-2)	2(1-2)	1(1-2)	2(1-2)	1(1-2)	2(1-2)	2(1-2)	2(1-2)	2(0-2)	2(1-2)	2(1-2)	2(1-2)
	XYL/NAL	0(0-1)	2(1-3)	2(1-3)	1(1-3)	2(1-3)	2(1-3)	2(1-3)	2(1-3)	2(1-2)	2(1-3)	2(1-2)	2(1-3)	2(1-2)
	XYL/KET	0(0-1)	2(1-2)	2(1-2)	2(1-2)	2(1-2)	1(1-2)	1(1-2)	2(0-2)	1(0-2)	2(1-2)	2(1-2)	2(1-2)	2(1-2)
Response to tactile stimulation	XYL	0(0-1)	1(1-2)	1(1-2)	1(0-2)	1(0-2)	1(1-2)	1(1-2)	1(1-2)	1(0-2)	1(1-2)	1(1-2)	1(1-2)	1(0-2)
	XYL/NAL	0(0-1)	2(1-3)	2(1-3)	2(1-2)	1(1-2)	1(1-2)	2(1-2)	1(1-2)	2(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-2)
	XYL/KET	0(0-1)	1(1-2)	1(1-2)	1(1-2)	1(-12)	1(1-2)	1(1-2)	1(0-2)	1(1-2)	1(0-2)	1(1-2)	1(1-2)	1(1-2)
Sedation score	XYL	1(1-2)	7(7-8)	8(7-8)	7(7-8)	8(7-9)	7(7-8)	7(7-8)	7(7-8)	7(7-7)	7(7-8)	7(7-8)	8(7-8)	7(7-7)
	XYL/NAL	1(1-2)	9(8-9) [‡]	9(9-9) [‡]	8(7-9) ^δ	9(7-9)	8(7-9)	8(8-9)	8(7-9)	9(7-9) ^δ	8(7-9)	9(7-9)	8(7-9)	8(7-9)
	XYL/KET	1(1-2)	8(7-8)	8(7-8)	8(7-9)	8(7-9)	8(7-8)	7(7-8)	7(7-8)	7(7-8)	8(7-8)	8(7-8)	8(7-8)	8(7-8)
Ataxia score	XYL	0(0-0)	1(1-2)	1(0-1)	1(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)
	XYL/NAL	0(0-0)	2(1-2)	1(0-2)	1(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)
	XYL/KET	0(0-0)	1(1-2)	1(0-2)	1(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)	0(0-1)

Shaded timepoints indicate significant differences (P<0.05) from baseline values.

[‡] Significant difference between XYL/NAL and other treatments.

^δ Significant difference between XYL/NAL and XYL.

Minor excitatory signs were observed during the monitoring of the animals over the study period, whereas muzzle tremors were detected in one horse following the XYL and XYL/KET treatments, and in two horses following the XYL/NAL treatment.

Discussion

Under the conditions of the present study, the sedative protocols tested were efficient in producing adequately moderate sedation in the studied horses. Following xylazine administration, the classical signs of sedation were demonstrated, such as head dropping, eyelid ptosis, ear tip and lip separation, and ataxia. Similarly, these signs were described by many authors following administration of α_2 -agonists to horses (HEWES et al. 2007; VALVERDE, 2010 and GUILHEN et al. 2015). To assess the degree of sedation provided by α_2 -agonists, either given alone or combined with opioids, different variables could be evaluated. Alterations in head height or head drop are most frequently adopted (FIGUEIREDO

et al. 2005; GUILHEN et al. 2015 and CENANI et al. 2017). In the current study, head-drop % was used in the MFSS designed for evaluating the studied protocols. Inclusion of this variable in the scale was intended to decrease its subjectivity as head height is an approved objective variable in evaluating sedation (RINGER et al. 2013). In a previous report, head height was significantly lower following administration of 0.6 mg/kg of xylazine intravenously to horses (SANTONASTASO et al. 2014). Consistently, in the present study, the head was noticeably lower following intravenous administration of the xylazine loading dose (0.55 mg/kg). This could be attributed to the muscle relaxation, sedation and reduced awareness induced by α_2 -agonists (FREEMAN and ENGLAND, 1999 and FIGUEIREDO et al. 2005).

Alteration in head height does not reasonably predict the response of horses to stimulation (SCHAUVLIEGE et al. 2019) as it may be considered as an indicator of the degree rather than the quality of sedation (HAMM et al.

1995). Consequently, in order to establish a more reliable way to evaluate the sedative effect of the combinations studied, we designed an MFSS involving head-drop % and the horses' response to auditory, visual and tactile stimuli, as the commonly used variables for assessing sedation quality in horses (RINGER et al. 2013 and SCHAUVLIEGE et al. 2019).

The models adopted for audiovisual and tactile stimulation of the studied horses were selected as satisfactory in evaluating the degree as well as the quality of sedation in horses (CLARKE et al. 1991; PEȘTEAN et al. 2010; GOZALO-MARCILLA et al. 2017 and MEDEIROS et al. 2017). Following xylazine administration, the reaction of the horses to auditory, visual and tactile stimuli was greatly reduced. In agreement with these findings, administration of xylazine as a loading dose of 1mg/kg, followed by a CRI of 0.69 mg/kg/hour also significantly reduced horses' reaction to different stimuli (RINGER et al. 2013). In contrast, SANTONASTASO et al. (2014) reported that, intravenous injection of xylazine did not induce a significant alteration in the horses' response to visual tests. Although the dose used in our study was very near to the used one in the latter study, individual variations might be the cause of the conflicting results.

In a previous report by POLLER et al. (2013), an MFSS was used and described to be a successful system for scoring sedation in horses. The efficiency of an MFSS was further ascertained in the current study, whereas higher sedation scores were recorded following XYL/NAL and XYL/KET treatments relative to XYL treatment. Despite this agreement, compared to the previously described scale of POLLER et al. (2013), response to tactile stimulation was also considered in ours to decrease the subjectivity of the scale and increase its reliability.

The greater sedation associated with the XYL/NAL and XYL/KET treatments could be explained by the ability of these combinations to induce more head drop and a reduction in the horse's response to the stimuli used compared to the XYL treatment. These actions might be attributed to the synergistic sedative effect of opioid and α_2 -agonists

combinations (TAYLOR et al. 1990; CLARKE et al. 1991 and CORLETTI et al. 2005) and the reported ability of ketamine to enhance sedation quality exerted by α_2 -agonists (MÜLLER et al. 2017).

Achievement of more than 60 % of the maximum sedation (LOVE et al. 2011) was previously used as an indicator for optimal sedation for clinical procedures in horses. On this basis, moderate sedation (which required attaining at least 58 % of the maximum sedation score) was the intended degree of sedation in our study. We speculated that this degree could enable practitioners to perform various procedures in standing horses successfully.

In a previous study by FERNANDES DE SOUZA et al. (2012), a CRI of 1.1 mg/kg/hour of xylazine was sufficient to maintain moderate to intense sedation in their horses. In line with this in the present study, for maintaining moderate sedation, a very similar CRI of xylazine (1.08 mg/kg/hour) was calculated following XYL treatment. To produce the same degree of sedation, the XYL/NAL and XYL/KET treatments were found to be effective in reducing the required xylazine infusion rate by 41% and 19%, respectively. In agreement with our findings, ketamine reduced the required infusion rate of romifidine during standing procedures in horses (MÜLLER et al. 2017). In contrary to our observations regarding nalbuphine, a CRI of butorphanol (another agonist-antagonist opioid) at 25 μ g/kg/hour, following an intravenous bolus dose of 18 μ g/kg, was found to be ineffective in reducing the required xylazine infusion rate (RINGER et al. 2012). The authors attributed their results to the assessment model, which was only dependent on head height and did not involve any stimulation of the horses studied.

During this study, it was obvious that administration of nalbuphine in association with xylazine (XYL/NAL treatment) delayed the time until the administration of the first additional xylazine bolus. In agreement with these findings, butorphanol was found to be effective in prolonging the sedative effect of romifidine in horses (DEROSSI et al. 2009).

Concerning ataxia, it is inappropriate to judge the quality of sedation without considering the degree

of ataxia especially following administration of α_2 -agonists (CORLETTTO et al. 2005). Consequently, the degree of ataxia was assessed in the current work. Furthermore, to limit the deleterious ataxic effect of xylazine, a dose of 0.55mg/kg was selected (FERNANDES DE SOUZA et al. 2012). Selection of this dose seemed successful in reducing xylazine-associated ataxia whereas mild ataxia was exhibited by most horses following XYL treatment.

Administration of the XYL/NAL treatment was associated with slight increment in the resultant ataxia comparing to XYL treatment. In agreement with our findings, romifidine/butorphanol combination induced slightly increased ataxia in horses compared to romifidine alone (CLARKE et al. 1991). Despite the increased ataxia noted following XYL/NAL protocol, moderate ataxia was the highest observed degree. This degree of ataxia can be still acceptable as it did not negatively impact performance of different procedures in standing horses (WILSON et al. 2002 and SOLANO et al., 2009). In the study reported here, mild ataxia was most commonly observed following XYL/KET treatment. In contrast, severe ataxia was described following administration of ketamine (0.06 mg/kg, IV) along with romifidine (0.05 mg/kg, IV) to horses (IBURG, 2014). The degree of ataxia did not show any significant difference between the XYL/KET and XYL treatments. Similarly, a ketamine/romifidine combination did not induce greater ataxia compared to romifidine alone (MÜLLER et al. 2017).

In agreement with our findings, the xylazine/opioid combination induced a higher incidence of muscle tremors compared to xylazine alone (RINGER et al. 2012). This could be attributed to the repeatedly reported excitement in healthy and pain-free horses receiving opioid analgesics (VALVERDE and GUNKEL, 2005 and CRUZ et al. 2011). Despite this, in the present study the overall incidence of this side effect appeared to be low as it confined to muzzle tremors in two of the horses that received the XYL/NAL treatment. Administration of xylazine prior to nalbuphine could limit its associated excitatory signs (CORLETTTO et al. 2005 and LOVE et al. 2011). Ketamine did not induce adverse behavioral effects in horses (FIELDING et

al. 2006). Consistently, in our study the XYL/KET treatment did not induce any side effects beyond those induced by XYL treatment.

Conclusion

Throughout the study period, all treatments induced a significant increase in sedation scores, which represented maintenance of moderate sedation. An acceptable degree of ataxia and limited behavioral effects were associated with all the evaluated treatments. The time before the administration of the first additional xylazine bolus was prolonged, and xylazine requirements for maintaining moderate sedation were reduced following the XYL/NAL and XYL/KET treatments compared to the XYL treatment. Both nalbuphine and ketamine seemed efficient in reducing xylazine requirements for constant sedation in horses. To determine the potential advantages of this finding, further study is needed for testing the effect of the combinations studied on different cardiorespiratory and hematobiochemical parameters in horses.

Conflict of interest

The authors declare that there is no conflict of interest.

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SHARSHAR, A., A. HAMMAD, S. GADALLAH, N. THABET, T. MISK: Učinak nalbufina ili ketamina na sposobnost ksilazina da održi sedaciju konja u stojećem stavu. *Vet. arhiv* 92, 369-380, 2022

SAŽETAK

Unatoč ključnoj ulozi α_2 -agonista u sedaciji konja u stojećem stavu, ovi lijekovi imaju nekoliko nuspojava koje ovise o njihovoj dozi. Cilj je istraživanja bio odrediti učinak nalbufina ili ketamina na sposobnost ksilazina da održi umjerenu sedaciju u konja. Pet zdravih odraslih konja podvrgnuto je trima randomiziranim pokusima u intervalima od tjedan dana prema sljedećem protokolu: ksilazin (XYL; ksilazin 0,55 mg/kg, iv., fiziološka otopina bolus i CRI); ksilazin/nalbufin (XYL/NAL ksilazin 0,55 mg/kg, iv., nalbufin 0.3 mg/kg, iv. i 0,23 mg/kg/h CRI) i ksilazin/ketamin (XYL/KET; ksilazin 0,55 mg/kg, iv., ketamin 0.1 mg/kg, iv. i 0,5 mg/kg/h CRI). U sve je tri skupine održana umjerena sedacija tijekom 120 minuta. Kad god se pokazala niža sedacija, dodavan je bolus ksilazina (0,14 mg/kg, iv.). Procjenjivan je stupanj sedacije, vrijeme primjene prvog dodatnog bolusa ksilazina i potrebe za ksilazinom (prikazane u mg/kg/h) kako bi se održala umjerena sedacija tijekom 120 minuta. Praćeni su i stupanj ataksije odnosno štetnih događaja. Pokazatelji sedacije bili su znakovito veći u sva tri pokusa tijekom 120 minuta. Dulje vrijeme prije prvog dodatnog bolusa ksilazina i manje potrebe za ksilazinom (niža stopa infuzije) kako bi se održala umjerena sedacija uočeni su nakon primjene XYL/NAL i XYL/KET lijekova u usporedbi sa skupinom koja je primila samo XYL. U sve je tri skupine zapažen prihvatljiv stupanj ataksije i ograničeni učinci na ponašanje. Zaključeno je da su i nalbufin i ketamin učinkoviti u smanjenju potreba za ksilazinom kako bi se održala sedacija u konja. Potrebna su daljnja istraživanja i sveobuhvatno testiranje ovih kombinacija kako bi se ustanovile potencijalne prednosti smanjene primjene ksilazina uočene u ovom istraživanju.

Ključne riječi: održavanje sedacije; konji; ketamine; nalbufin; ksilazin
