Article

The effects of xylazine or detomidine when used as a pre-anesthetic sedative on recovery quality and duration in horses undergoing elective equine castration

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Abstract — The purpose of this prospective, blinded, randomized clinical trial was to compare the effects of low dose detomidine to xylazine on recovery quality and duration in a castration procedure. Horses were administered either detomidine [0.015 mg/kg body weight (BW)] or xylazine (1.1 mg/kg BW) intravenously (IV) before IV induction with ketamine (2.2 mg/kg BW) and diazepam (0.05 mg/kg BW). Two anesthesiologists who were unaware of treatment allocation scored the recoveries using a simple descriptive scale (with a low number representing the most desirable recovery) and recoveries were timed. Horses in the detomidine group (n = 16) had a median recovery score of 16 (range: 11 to 26), whereas horses in the xylazine group (n = 12) had a median recovery score of 12 (range: 10 to 16) (P = 0.001). There was no difference in surgery time (P = 0.52), time from the end of surgery to standing (P = 0.45), or time from induction to standing (P = 0.48) between the groups.

Résumé — Les effets de la xylazine ou de la détomidine lors d'utilisation comme sédatif pré-anesthésique sur la qualité et la durée de la récupération chez les chevaux soumis à une castration équine élective. Le but de cet essai clinique prospectif, en aveugle et randomisé était de comparer les effets de la détomidine à faible dose à la xylazine sur la qualité et la durée de la récupération dans une procédure de castration. Les chevaux ont reçu soit de la détomidine [0,015 mg/kg de poids corporel (PC)] soit de la xylazine (1,1 mg/kg de PC) par voie intraveineuse (IV) avant l'induction IV avec de la kétamine (2,2 mg/kg de PC) et du diazépam (0,05 mg/kg de PC). Deux anesthésistes qui ignoraient l'attribution du traitement ont noté les récupérations à l'aide d'une échelle descriptive simple (avec un petit nombre représentant la récupération la plus souhaitable) et les récupérations ont été chronométrées. Les chevaux du groupe détomidine (n = 16) avaient un score de récupération médian de 16 (éventail de valeurs : 11 à 26), tandis que les chevaux du groupe xylazine (n = 12) avaient un score de récupération médian de 12 (éventail de valeurs : 10 à 16) (P = 0,001). Il n'y avait aucune différence dans le temps de chirurgie (P = 0,52), le temps entre la fin de la chirurgie et la position debout (P = 0,45) ou le temps entre l'induction et la position debout (P = 0,48) entre les groupes.

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Introduction

Alpha-2-adrenoreceptor agonist drugs such as xylazine and detomidine are commonly used for sedation, analgesia, and premedication in horses. Because of differences in receptor affinity and duration of action, these drugs may affect recovery time and quality when used as premedication prior to induction for short anesthetic procedures. Detomidine has greater potency and specificity for the alpha-2-adrenoreceptor, with 100 times the affinity compared to xylazine (1,2). Pharmacokinetic factors such as plasma clearance and half-life may also play a role in each drug's effect upon recovery. The mean plasma clearance of xylazine [15.8 mL/min/kg body weight (BW)] is faster than that of detomidine (7.1 mL/min/kg BW) (3,4), and detomidine's half-life is longer (1.19 h) than xylazine's (50 min) (3–5). These factors likely contribute to the degree and duration of sedation and analgesia provided by each drug, and their selection for use in anesthetic protocols.

There are relatively few studies comparing the effects of detomidine and xylazine on recovery quality and time when used as a premedication prior to induction of general anesthesia in horses (6–9). The results of previously published work are difficult to compare as studies employed a range of detomidine

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dosages, drug combinations, intervals between sedation and induction, and surgical models (10–12). As castration is the most often performed procedure using injectable anesthesia in our clinic, the authors sought to better understand the effects of two commonly used alpha-2 agonists on recovery. The objective of this study was to compare the quality and duration of recovery in horses using detomidine and xylazine before induction of general anesthesia in an equine castration model.

Materials and methods

Animals

All procedures were reviewed and approved by the Institutional Animal Care and Use and the Clinical Research Review Committees at the College of Veterinary Medicine and Biomedical Sciences at Texas A&M University. Inclusion criteria were healthy stallions with 2 descended testicles, older than 1 y, and halter-broken. All horses were client-owned and maintained their normal routine and feeding schedule prior to admission. Informed consent was obtained from all owners before enrollment. Horses were determined to be healthy based on history, physical examination, packed cell volume, and total protein.

Anesthetic protocol

A 14-gauge, 13.3-cm catheter (BD, Angiocath; Becton Dickinson, Sandy, Utah, USA) was placed percutaneously in an external jugular vein for intravenous (IV) drug administration. Thirty minutes before surgery, all horses were administered the following medications: IV flunixin meglumine (1.1 mg/kg BW), intramuscular (IM) procaine penicillin G (22 000 IU/kg BW), and IM tetanus toxoid (1 mL). Horses were walked to a 3.65 × 3.65 m padded recovery stall. The first study patient was randomly selected using an online software (www.randomizer.org) to receive either IV detomidine (Zoetis, Parsippany, New Jersey, USA), 0.015 mg/kg BW or xylazine (VetOne, Boise, Idaho, USA), 1.1 mg/kg BW for premedication. The premedication protocol was alternated for each study patient thereafter. Five minutes following IV premedication, anesthesia was induced with the administration of IV ketamine (VetOne), 2.2 mg/kg BW and IV diazepam (Pfizer, Lake Forest, Illinois, USA), 0.05 mg/kg BW.

Following induction, horses were placed in dorsal recumbency with the assistance of forelimb hobbles and a hoist. The scrotum was aseptically prepared with betadine scrub and solution in routine fashion. Two percent lidocaine HCl (VetOne) was administered directly into the testicular parenchyma (0.88 mg/kg BW) to provide local anesthesia. All castrations were performed by one of the authors (RH) with the assistance of a 4th-year veterinary student. The ventral aspect of the scrotum was removed using a #10 scalpel blade. A closed castration was performed by manually stripping fascia from each testicle but leaving the parietal tunic intact. Reimer emasculators were applied to each cremaster and spermatic cord for 2 min. In horses > 2 y of age, a ligature of #2 polyglactin 910 was applied prior to use of the emasculators. Scrotal skin incisions were stretched manually and left open. Monitoring of anesthesia was performed by a veterinarian or veterinary technician who sat at the head of the horse and observed movement, respiratory rate, heart rate, and pulse quality *via* digital palpation of the facial artery. Horses that were deemed too light to complete the procedure were given a combination of 20% of the induction dose of ketamine and 20% of the pre-induction sedation dose of the assigned sedative IV. The number of times that horses required additional sedation/analgesia was recorded. Following the completion of surgery, horses were placed in lateral recumbency. A towel was placed over the eyes to reduce external stimuli. Horses were allowed to recover unassisted.

Table 1. Timed elements (median ± standard deviation in minutes) of surgery, anesthesia, and recovery.

Segment	Xylazine (n = 12)	Detomidine (n = 16)	P-value
Surgery	10.05 ± 2.5	10.2 ± 2.7	0.952
Induction to standing	43 ± 11.1	46.5 ± 13.1	0.455
End of surgery to standing	26.5 ± 12.3	29.5 ± 12.9	0.4865
Maintenance of anesthesia	16.5 ± 3.4	16.6 ± 3.4	0.9027

Recovery scoring

A camcorder was placed in a catwalk approximately 4.6 m above the recovery stall to record all recoveries. Video recordings were edited to remove patient information at the start of each procedure and the videos were randomized according to publicly available software (www.randomizer.org). The recovery videos were evaluated and scored by 2 blinded, Board-certified anesthesiologists. The evaluations were based on a modified version of a previously established recovery scale (13). Numerical scores were assigned based on observations of the horse's demeanor, coordination, and strength, as well as quantifying the number of attempts to become sternal and stand. A low score, with a minimal value of 10, represents the most desirable recovery encompassing a quiet phase in lateral recumbency, methodical movements, and 1 attempt each for sternal and standing. Undesirable recoveries included those horses that were frantic, ricocheting off walls, made multiple attempts to stand or fell during recovery. Undesirable recoveries could produce very high scores depending on the number of attempts to become sternal or stand. The time from induction of general anesthesia to standing, the end of surgery to standing, duration of surgery, and maintenance of anesthesia were recorded.

Statistical analysis

Statistical analysis of timed elements and recovery scores was performed using the software package PRISM (PRISM 8; GraphPad Software, San Diego, California, USA). Data were tested for normality using the Shapiro-Wilk test. All timed components, except time to first bump dose and last re-dose to standing, had a normal distribution and an unpaired t-test was used to determine differences between the timed elements. A Mann-Whitney U-test was used to evaluate the recovery scores and 2 timed elements that were not normally distributed. Results were considered significant if $P < 0.05$. A Fisher's exact test was used to determine if the percentage of horses requiring additional top-up doses of sedation was different between horses given xylazine or detomidine. Cohen's *kappa* (Microsoft Excel, 2016; https://office.microsoft.com/excel) was used to calculate inter-rater agreement with a κ = 0.81 to 1.0 representing very

Table 2. Total (overall) recovery scores and individual components of recovery (median and range) of horses administered xylazine or detomidine for pre-anesthetic sedation.

	Xylazine (n = 12)		Detomidine (n = 16)		
Category	Median	Range	Median	Range	P-value
Total recovery	11	10 to 16	16	11 to 26	0.0014
Overall attitude	1	1 to 2	1	1 to 2	0.20
Activity in recumbency	1	1	1	1	> 0.99
Move to sternal	1	1 to 3	1	1 to 3	> 0.99
Number attempts to sternal	1	1 to 2	1	1 to 2.5	0.85
Quality of sternal phase	1	1 to 3	1	1 to 3.5	0.22
Move to stand	1	1 to 2	2	1 to 2.5	0.0009
Strength	1	1 to 5	2.5	1 to 6.5	0.04
Number of attempts to stand	1	1 to 1.5	1.25	1 to 5	0.02
Balance and coordination	1	1 to 2	2.33	1 to 5.5	0.03
Knuckling	1	1 to 2	1.333	1 to 2	0.01

good agreement, κ = 0.61 to 0.8 representing good agreement, κ = 0.41 to 0.6 representing moderate agreement, κ = 0.21 to 0.4 representing fair agreement, and κ < 0.2 representing poor agreement.

Results

Twenty-eight healthy stallions, median: 4 y (range: 1 to 13 y) and 321 kg (range: 118 to 498 kg), were enrolled and finished the study with complete data sets and video footage. The study population consisted of 15 Quarter Horses, 4 American Paint horses, 5 donkeys, 1 mustang, 1 Andalusian, 1 Dutch Warmblood, and 1 American miniature horse. All horses were successfully castrated and recovered from surgery and anesthesia with no complications.

None of the 4 timed recovery components was statistically different in horses receiving detomidine and xylazine. There was no difference in surgery time, time from induction to standing, time from the end of surgery to standing, or time spent under anesthesia maintenance between the groups of horses receiving xylazine *versus* detomidine (Table 1).

In terms of recovery score, horses in the xylazine group had a median recovery quality score of 11 (range: 10 to 16), whereas those in the detomidine group had a median recovery quality score of 16 (range: 11 to 26). The lower score represents a better recovery. The difference between the total recovery scores was significant at P = 0.0014.

In regard to the recovery scale, there was no significant difference between the detomidine and xylazine groups for overall attitude, activity in recumbency, movement to sternal, number of attempts to move to sternal, and quality of sternal phase. Horses in the detomidine group differed significantly from horses in the xylazine group in the following categories: move to standing, strength once standing, number of attempts to stand, balance and coordination once standing, and knuckling once standing (Table 2).

Some horses required administration of additional drugs to remain anesthetized during the procedure. Two out of sixteen horses (12.5%) in the detomidine group and 8 out of 12 horses (66.7%) in the xylazine group required additional drugs to remain anesthetized. The 2 horses in the detomidine group only required 1 additional top-up dose, whereas 6 of the 8 horses in the xylazine group required 1 additional top-up dose and the remaining 2 required 2 additional top-up doses. The number of additional top-up doses administered to horses receiving xylazine was significantly higher than those required by horses receiving detomidine (P = 0.005). The median time from induction to the first top-up in the xylazine group was 9.75 min (range: 7.2 to 19.8 min) compared to 11.2 min (range: 10.4 to 12 min) for the detomidine group (P = 0.7111). The median time from the last top-up to standing was 30.4 min (range: 15.1 to 59.6 min) in the xylazine group *versus* 34.2 min (range: 19.1 to 49.3 min) in the detomidine group (P > 0.9999). Inter-rater agreement was very good (κ = 0.81 to 1.0) for the following evaluation criteria: overall attitude (xylazine), activity in recumbency (detomidine and xylazine), move to sternal (detomidine and xylazine), number of attempts to sternal (detomidine and xylazine), sternal phase (detomidine and xylazine), move to stand (xylazine), number of attempts to stand (detomidine and xylazine), and knuckling (detomidine and xylazine). Agreement was good in the following evaluation criteria: overall attitude (detomidine), strength (xylazine), and balance and coordination (xylazine). Agreement was moderate in the following evaluation criteria: move to stand (detomidine), strength (detomidine), and balance and coordination (detomidine). There were no evaluation criteria in which inter-rater agreement was fair or poor.

Discussion

In the present study, horses castrated using xylazine and detomidine premedication all had safe recoveries. However, xylazine premedication produced a significantly better recovery compared to detomidine premedication (Table 1) with a lower overall score, and lower scores for the following recovery elements: movement to standing, strength once standing, number of attempts to stand, and degree of knuckling after standing. These results may be due to detomidine's increased affinity for the alpha-adrenoceptor or to a more prolonged sedative action than xylazine, with the result being more ataxia and incoordination during the recovery period.

Although it is reported that xylazine, 1 mg/kg BW, IV, and detomidine, 20 μg/kg BW, IV, provide equipotent sedation (14), studies investigating the use of these 2 drugs as premedication before induction have reported contradictory results. One

reported that detomidine was associated with longer periods of recumbency but provided recoveries equal to that of xylazine (8). Another reported recovery quality to be similar for both drugs, but recovery times were longer for horses premedicated with detomidine (12). Differences between the studies include the dose of detomidine used, time from administration of premedication and induction, surgical model, and recovery score. Authors from these studies comment that their results were likely influenced by the doses of detomidine, potency for alpha-2-adrenoreceptor, half-life, and plasma clearance.

In the current study, the authors used the lower end of the reported dose range (0.005 to 0.03 mg/kg BW, IV) based on the results of previous studies and manufacturer and pharmaceutical textbook recommendations (8,10,14,15). The authors also desired to find drug dosages that produced equivalent results on recovery score and time. Because detomidine is not frequently chosen as premedication for short surgical procedures in our clinic, doses of 0.01 mg/kg BW, 0.015 mg/kg BW and 0.02 mg/kg BW were used in a small pilot study using the described anesthetic protocol and castration model. The horses which were administered 0.01 mg/kg BW were judged to be insufficiently sedated for induction, and those given a 0.02 mg/kg BW dose had profound sedation. The dose of 0.015 mg/kg BW was the lowest dose that could provide adequate sedation before induction in our patient population and operating protocols.

The authors attempted to control for sources of variability in the environment and subjects. The authors recognize that most horses presented for castration are young, naïve to handling and novel environments, factors that could affect sedation. Our study protocol used the same technical staff and procedures for unloading from the trailer, acquisition of weight, catheter placement, preoperative antibiotics, and placement in the recovery stall. The same veterinarian (RH) performed each castration to minimize differences in operative techniques and times. Castration times never exceeded 15 min per procedure, and there were no intra-operative complications experienced by any of the study participants that required additional surgery time. The same surgical personnel were used to ensure consistent preoperative handling of the horses; therefore, it is likely that differences in recovery characteristics observed were due to differences in the drugs used for premedication.

The authors used a published equine recovery scale to evaluate recovery quality (13). This scale included important aspects of recovery such as coordination, strength, reflexes, and demeanor, while quantifying the number of attempts made to move sternal or standing. Two blinded, experienced anesthesiologists reviewed the videotaped recordings and scored the recoveries. The agreement between reviewers was very good for most components on the scale, and never fell below moderate for any of the categories. These factors provided a high level of confidence in the evaluation of recovery quality.

There was a statistically significant difference in the number of top-up doses administered between the xylazine and detomidine groups, but no significant difference between the timing of administration of the top-up doses relative to the start of surgery or to recovery. The need for repeated administration of alpha-2 agonists during surgery may indicate that an appropriate level of anesthesia was not achieved or maintained. Horses in the xylazine group required more top-up doses, presumably due to its shorter half-life and receptor affinity. This factor may have had a positive influence on recovery quality. Ideally, a horse should sufficiently eliminate ketamine before attempting to stand. Horses in recovery that display nystagmus are often given additional sedation to allow ketamine and other anesthetic agents time to metabolize. However, a horse that has been administered excessive xylazine or detomidine may have a prolonged recovery or experience increased ataxia when standing in recovery. Furthermore, the repeated administration of sedative agents has been associated with a higher rate of complications (16). In this study, only 2 horses in the detomidine group received top-up doses, which may have skewed results for the timed elements regarding additional dosages. Further study is indicated to determine the effects of repeated boluses of xylazine or detomidine in combination with ketamine.

Limitations of this study include patient variability as to previous handling, demeanor, drug metabolism, and an unequal group size. Although more than 28 stallions were enrolled in this study, complications related to technical difficulties (battery life) with the camera resulted in incomplete data sets and, therefore, uneven group size. These limitations should be taken into consideration when interpreting the results.

This study demonstrates that xylazine at a dose of 1.1 mg/kg BW, IV, and detomidine at a dose of 0.015 mg/kg BW, IV, can be used as a premedication for general anesthesia with ketamine. Recovery time, but not quality, associated with detomidine was equivalent to that produced by xylazine. All horses that received detomidine recovered safely but showed symptoms of ataxia compared to those that received xylazine.

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SK Jarosinski was involved in writing the manuscript. NS Matthews and CE Arnold were involved in the study design and in conducting the study. CE Arnold and SK Jarosinski performed data analysis. BT Simon and NS Matthews were involved in reviewing recovery videos and scoring each recovery. BT Simon, NS Matthews, and CE Arnold were involved in reviewing the manuscript before submission. CVJ

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