# Evaluation of sedative and analgesic effects of intravenous sub anesthetic doses of ketamine in horses

by

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# Abstract

**Background**: Sedation and analgesia in emergency or refractory cases of pain in standing equids is of clinical importance. There are limited reports investigating the effects of administering sub-anesthetic doses of ketamine to the standing horse.

**Objective:** To evaluate the sedative and analgesic effects of a single intravenous sub-anesthetic bolus of ketamine at two doses with detomidine as compared to a detomidine control.

**Study design:** Prospective, blinded, placebo-controlled

**Methods**: Monitoring of heart rate, sedation level, ataxia, procedural condition, and algometry scores of horses administered two sub-anesthetic doses of ketamine with detomidine compared to detomidine controls.

**Results**: Eight horses were administered detomidine alone, or in combination with two sub-anesthetic doses of ketamine. A dose dependent ataxia was observed in all ketamine treated horses immediately after intravenous bolus, lasting 3-5 minutes compared to control. Horses in ketamine treated groups had an extended duration of sedation and increased threshold to stimuli in the first 8 minutes after administration when compared to control horses. Hypersalivation in 25% (4/16) ketamine treated groups, AV block in 33% (8/24) of all groups, aberrant aggression in one horse (1/8) control horses, and recumbency in one ketamine treated horse (1/16) was observed.

**Main limitations**: The small sample size and use of non-clinically affected animals.

**Conclusion:** Use of sub-anesthetic doses of ketamine with detomidine administered as a single, intravenous, bolus resulted in superior sedation, prolonged increase in nociceptive threshold, and a dose dependent increase in ataxia scores.

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# Acknowledgements

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# Introduction

Standing sedation in equids is commonly performed for routine medical procedures such as dental or ophthalmic interventions, as well as in emergency situations to provide anxiolysis and pain relief in cases of colic, injury and lacerations, and for emergency transportation. Alpha-2 adrenoreceptor agonists, the most common sedative class used in horses, are often combined with opioids to offer a balanced standing sedation (Fielding et al. 2006). Alpha-2 adrenoreceptor agonists can however cause deleterious cardiopulmonary depression, therefore, are often combined with an opioid or other class of drug. The addition of an opioid such as butorphanol tartrate lessens the cardiopulmonary effects and extends the duration of sedation. The use of opioids alone, or in high doses is limited by the risk of inducing central stimulation and excitement that is undesirable and dangerous in the standing horse. These effects are seen as head shaking, unsteadiness, and pressing forward. (Müller et al. 2017; Gorlin, Rosenfeld, and Ramakrishna 2016)

# Background

Ketamine is a commonly available N-methyl- D-aspartate (NMDA) receptor antagonist used as an anesthetic agent. Ketamine has clinical application in standing and anesthetized horses; however limited evidence is available on its use in the standing horse. Administration of subanesthetic doses of ketamine, referred to as a “ketamine stun” is used anecdotally to facilitate short procedures, or to obtain diagnostics in painful or noncompliant large animal patients such as those suffering from colic (Peterbauer et al. 2008; Coetzee et al. 2010).

The analgesic properties of subanesthetic doses of ketamine has long since been utilized in a multitude of painful statuses and species including postoperative pain in rats, cats and dogs, chronic regional pain syndrome (CRPS) and phantom limb pain in humans (Meenan 2010), induced pain in ponies (Peterbauer et al. 2008), castration associated discomfort in calves (Coetzee et al. 2010), and to provide superior sedation quality in standing horses undergoing cheek tooth removal or carotid translocation (Benredouane et al. 2011).

Although administration of sub-anesthetic doses of ketamine is commonplace in both standing procedures and in emergency immobilization, there is a lack of standardized dosing and route of administration, that results in an unpredictable response to this medication. Therefore, the objective of this study is to assess the level, and duration of sedative effects, and any complications of adult horses administered the combination of two commonly used and readily available sedatives; detomidine and ketamine at two sub-anesthetic doses as compared to a detomidine control.

# Methodology

## Study Design

A prospective, randomized, blinded, placebo-controlled investigation of the sedative and analgesic effects of two sub-anesthetic doses of ketamine with detomidine sedation, compared to a detomidine control in 8 university-owned horses. The protocol was approved by the Institutional Animal Case and Use Committee at Kansas State University (Protocol Number: IACUC-5036).

## Animals

A sample size calculation revealed a total sample size of 8 horses was calculated to achieve a 95% confidence interval, with a Type I error of 5%. Eight, apparently healthy, Quarter Horse type horses ranging in age from 2.5-26 years of age, with a mean body weight of 480kgs (-/+ 67 kgs) were used. Included were 6 mares and 2 geldings. There was no clinical evidence of lameness, pain, respiratory, cardiac, or ocular pathology prior to or during any session. Horses were transported in cohort groups to the study facility and allowed a stall acclimation period with limited external stimuli such as noise and movement in the surrounding area. All horses had free choice hay and water prior to each trial. No management changes were made throughout the study period.

## Sedation Protocol

Each horse received either detomidine (0.01mg/kg) intravenously; treatment control, detomidine (0.01mg/kg) plus ketamine (0.2mg/kg) intravenously; treatment DK1, or detomidine (0.01mg/kg) plus ketamine (0.4mg/kg), treatment DK2. The drugs were combined and diluted to 5mL with 0.9% sodium chloride for blinding purposes by a licensed pharmacist and administered immediately intravenously via 19g, 1.25-inch needle by the same investigator (DC). Horses were monitored and recordings were obtained for 30 minutes post injection. Each horse underwent

three sedative events in total, one in each group, with a minimum washout period of one week between each sedation event.

**Algometry**

Response to noxious stimuli was recorded at baseline, and every 5 minutes throughout the study period using a 2mm pneumatic pin limb mounted algometer, using the Topcat Metrology Ltd ProdPro GBP 2500 automated algometry testing system (Figure 1a, 1b). Pin advancement in the pneumatic cylinder was set at a rate of 2N/second. A positive response was recorded only when the tested limb was lifted completely off the weight bearing surface. Measurements were obtained and recorded in Newtons (N) by a boarded veterinary anesthesiologist (DH).

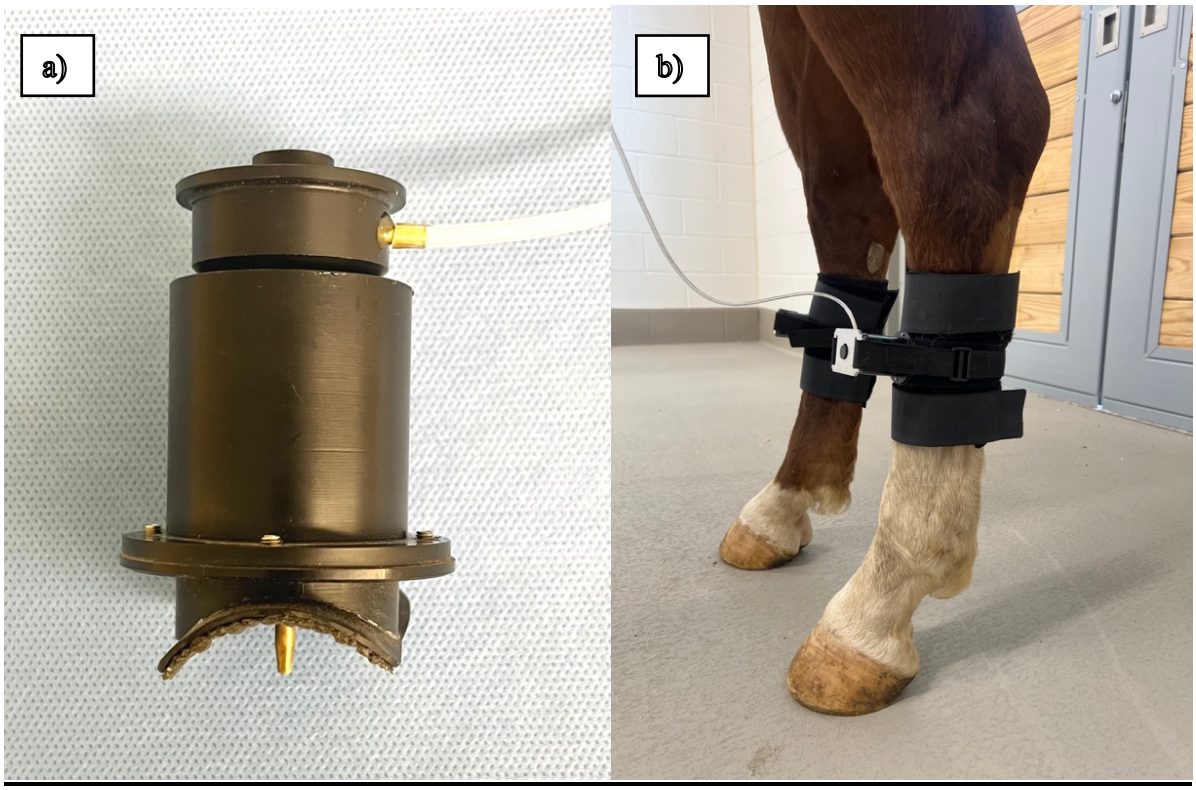


**Figure 1 a)** Topcat Metrology Ltd ProdPro GBP 2500 automated algometry testing system. b) ProdPro GBP 2500 automated algometry testing system mounted to the hind limbs of Horse 2.

**Cardiac Telemetry**

An equine specific wearable heart rate and rhythm monitoring unit (*POLAR Equine Heart Rate Monitor)* was affixed to each horse prior to the start of each trial (Figure 2a, 2b). The band was applied to moistened skin over the left heart. The coat was clipped to increase contact with the monitor in one horse that had an unusually thick hair coat. Continuous heart rate and rhythm monitoring was recorded by a boarded large animal internist (LB) throughout the study period. Heart rate was recorded every 60 seconds. Changes in rhythm were monitored and recorded throughout the trial period.

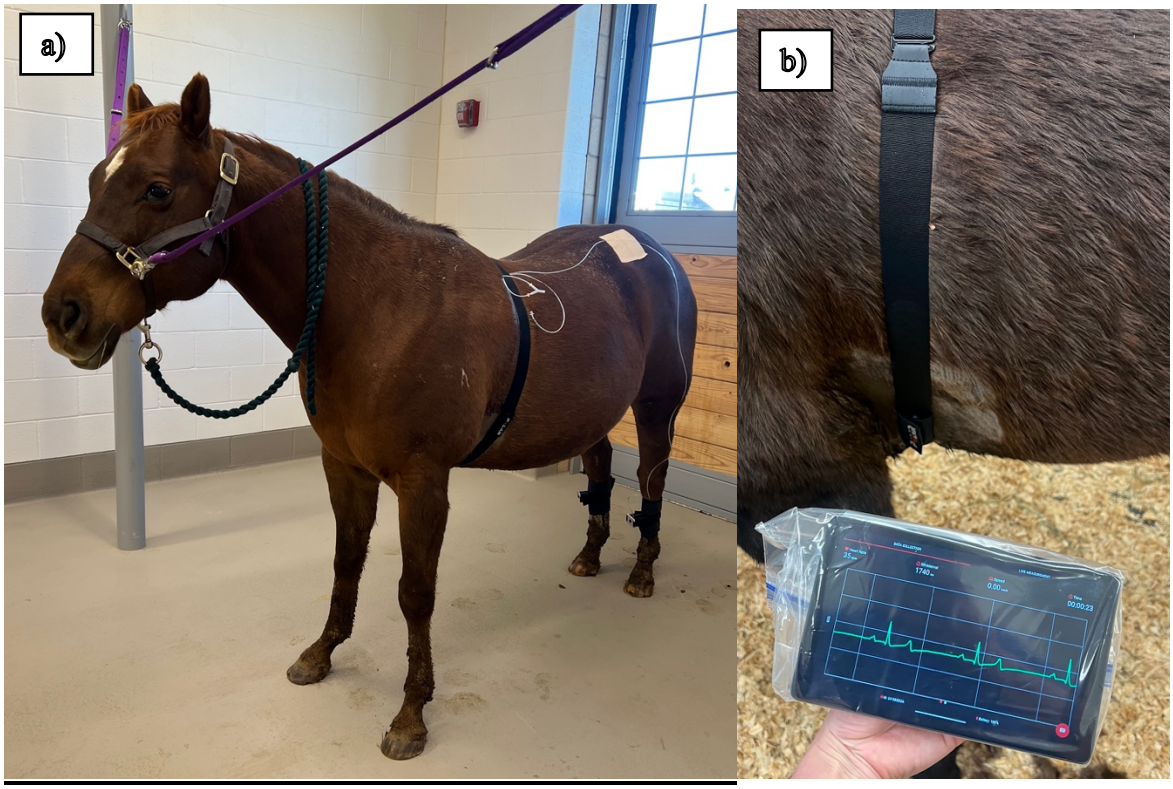


**Figure 2 a) POLAR Equine Heart Rate Monitor affixed to horse 7 and b) mobile ECG and heart rate telemetry**

**Sedation Algorithm**

The Ghent Sedation Algorithm (Figure 3) was used to assess the animal's overall sedation plane. An ataxia score, sedation depth, and surgical condition were recorded at baseline, and every 60

seconds after administration of the study drug for a period of 30 minutes. Scores were recorded by a boarded large animal internist (LB) throughout the study period.

| Position/ataxia | Clinical signs |
|---|---|
| 0 | Standing square, bearing equal weight on all four legs. |
| 1 | One hind limb in resting position and/or slight swaying. |
| 2 | Clear swaying or leaning against the stocks (not bearing weight on maximally one of the four limbs) |
| 3 | Very pronounced leaning (possibly not bearing weight on several limbs) and/or attempts to become recumbent. |
| Sedation depth | |
| 0 | No sedation. Animal is alert with normal posture and response to environment/contact with assessor. Normal objection to intervention. Ears responsive to surroundings (moving). |
| 1 | Mild sedation. May or may not lean on head support, relaxed facial muscles. Reduced responses to background activity in the room. Ears partially responsive to surroundings. Light or no ptosis of the ears. |
| 2 | Good sedation. Leans on head support. No response to background activity in the room. Pendulous lower lip. Ears mildly responsive to surroundings. Moderate ear ptosis. Eyelids partially closed. |
| 3 | Marked sedation. Leans strongly on head support. No response to background activity in the room. Pendulous lower lip. Pronounced ear ptosis, minimal/no movement of ears. Eyelids partially or fully closed. Eye may be rotated, little to no movements of the eye. |
| Surgical condition | |
| 0 | Excessive interference from the horse. Impossible to perform surgery. |
| 1 | Moderate interference from the horse. Strong movements, heavy chewing and movement of the tongue. Repeated attempts to pull away or lift the head. |
| 2 | Acceptable interference from the horse. Small movements, moving the tongue or chewing. Little or no attempts to pull away or lift the head. |
| 3 | No interference from the horse. Hardly any movement. |

Figure 3 Ghent Sedation Algorithm

**Statistical Analysis**

Data were entered into a statistical software package (Microsoft Excel, Microsoft Office Professional, 2019) prior to data review and analysis. Statistical analysis was performed using a commercially available software package (JMP® Pro 17.0.0, JMP Statistical Discovery LLC). Given the repeated measures nature of the data collected, a mixed effects model was used with animals nested in treatment and designated as a random effect. Treatment, timepoint, and the interaction between treatment and time were designated as fixed effects. Where a time X treatment interaction was noted ($P<=0.1$) interactions were clarified using test slices. Statistical significance was assigned a-priori as $P<0.05$.

# Results

## Results

There was a statistically significant difference in observations between animals and between treatment groups for algometry values (P-value - <.001), ataxia scores (P-values = <.0001), and time (P-value = <.0001). Additional findings noted included hypersalivation seen in 25% (4/16) of ketamine treated horses. Aberrant aggression was observed in one horse (Horse 3) in the control group in the form of ear pinning and attempts to bite the handler. One horse (Horse 6) in the DK2 group became recumbent during minute 2 of the study due to severe ataxia. She recovered uneventfully with one coordinated effort at minute 12. All but one horse returned to baseline values by 30 minutes. Horse 6 required 4 additional minutes of monitoring until all vital parameters retuned to pre-sedation values.

### Algometry

Statistically significant differences in individual animal algometry readings were seen. These differences subjectively correlated to the animal's pre-sedation behavior with anxious horses having lower MNT throughout the study when compared to more relaxed horses. Baseline algometry values ranged from 1.7-23.7 N force. There was a rapid increase in MNT in both ketamine treated groups (P-value = 0.001). A statistically significant increase in MNT from baseline was not observed until minute 10 in the control group, with some control horses showing no, or a negative change in MNT.

### Cardiac Telemetry

Statistically significant differences were seen in heart rate of individual animals (P-value = 0.0019). There was also a statistically significant difference in heart rate between groups at each time point in minutes (P-value = 0.0004) with horses in the ketamine treated groups maintaining a higher heart rate for longer. An initial increase in heart rate from minute 1 to 3 was seen in all

ketamine treated horses compared to control horses. A transient atrioventricular block was observed in 30% (8/24) horses in the study, equally distributed throughout groups.

**Sedation**

There was a time-dependent, statistically significant, dose dependent increase in sedation from baseline noted immediately after administration in ketamine treated groups resulting in a prolonged sedation score in ketamine treated horses compared to controls (P-value = .0015). More horses in the ketamine treated groups reached a more profound sedation plane sooner than the control horses (Figure 4). There was no significant difference in sedation scores between any group after minute 10 (P-value=0.31).

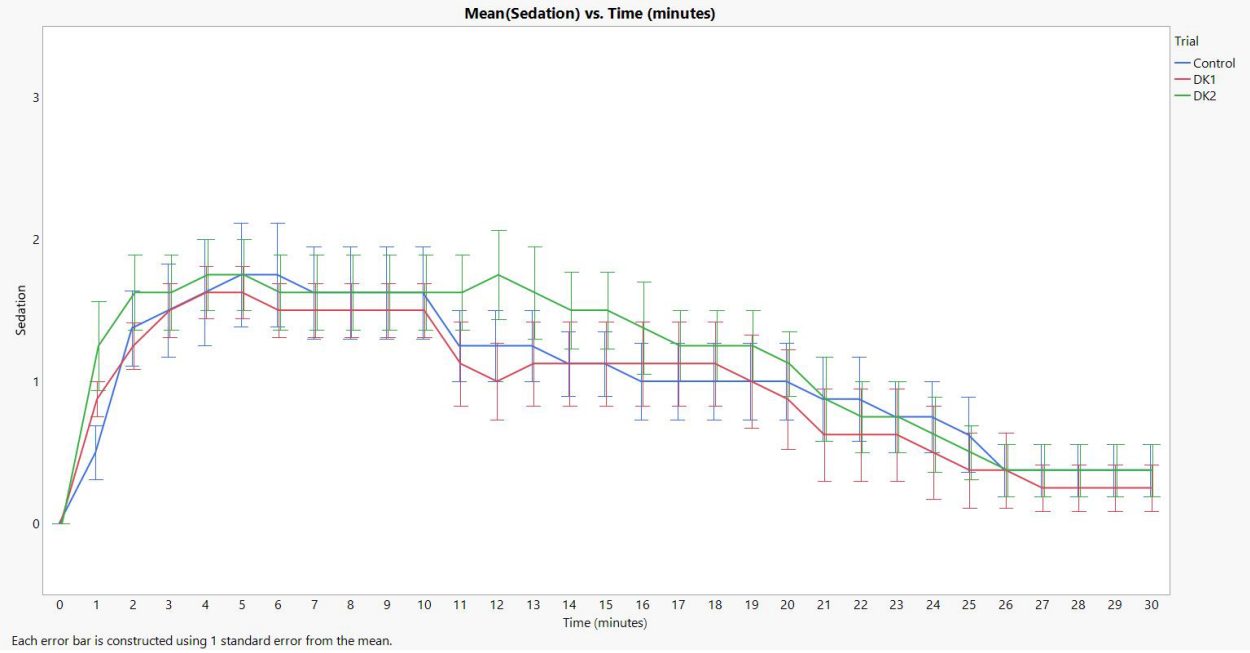


Figure 4 Graph showing the mean sedation scores of horses throughout each trial

There was a statistically significant increase in surgical condition of individual animals and individual treatment groups (P-value=.0015) as well as time (P-value =<.0001). Horses in ketamine treated groups reached a more favorable surgical condition sooner than control horses and tapered more slowly. Control groups had a more predictable plateau between minutes 10 and

20 (Figure 5). There was a dose dependent increase in presence of appropriate surgical condition in the ketamine treated groups.

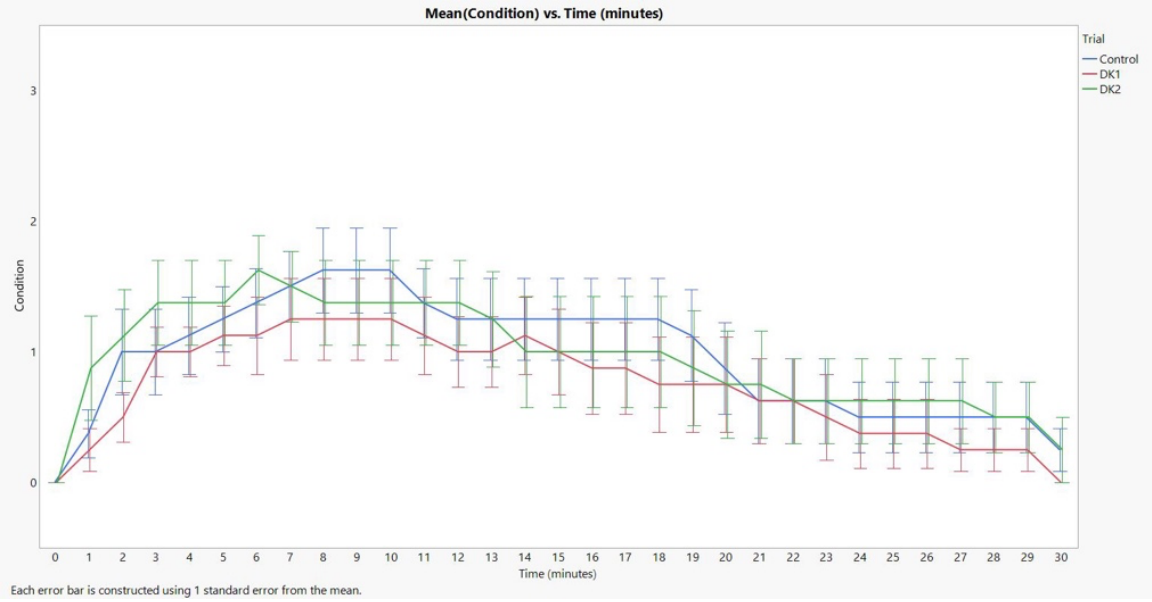


Figure 5 Graph showing the mean surgical condition scores of horses throughout each trial.

**Ataxia**

Ataxia scores were statistically significant between all groups and individual animals (P-value = 0.0001). A significant, predictable, immediate increase in ataxia within 1 minute was seen in either ketamine treated groups. A more gradual increase in ataxia was seen in the control group, to a lesser extent than the ketamine treated groups (Figure 6). No statistical significance in ataxia scores were seen by minute 8 (P-value = 0.0947).

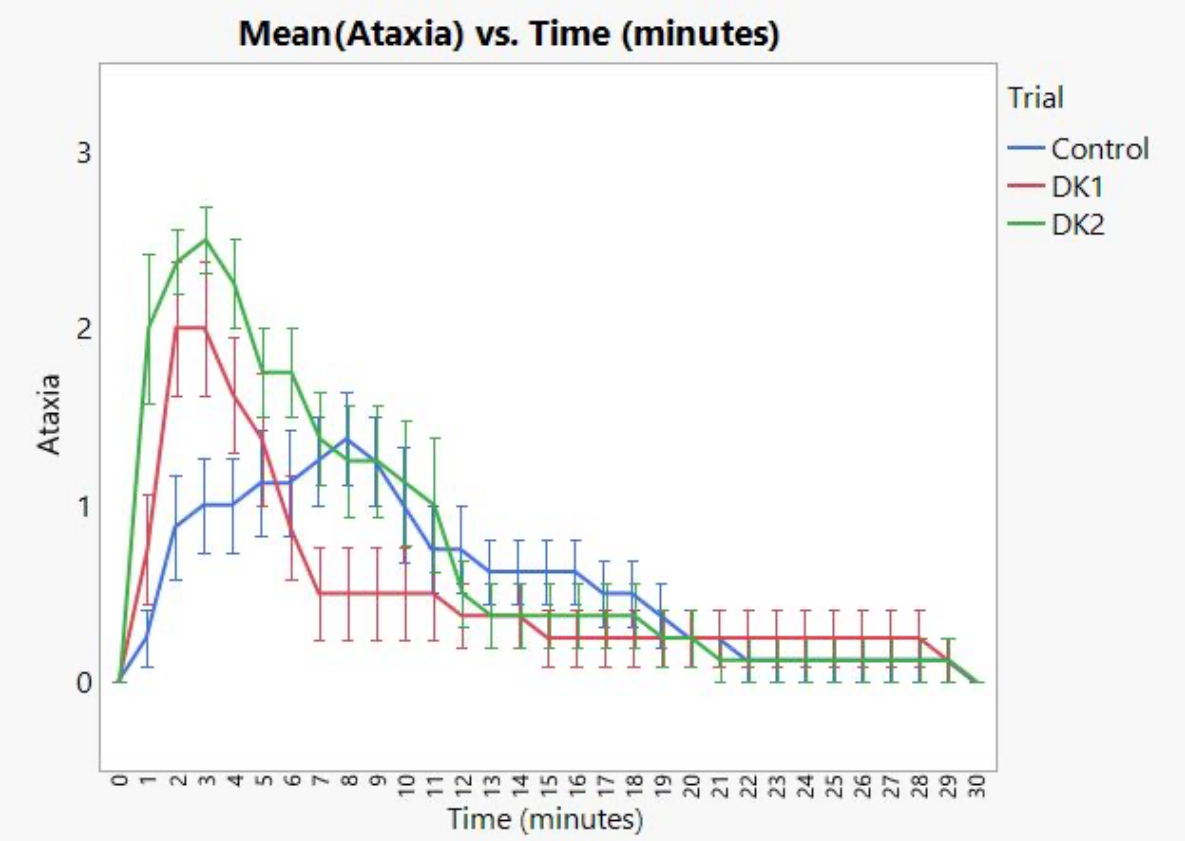


Figure 6 Graph showing ataxia scores of horses throughout each trial.

# Discussion

This study demonstrated the sedative and analgesic effects of adding low dose ketamine to detomidine. The addition of ketamine significantly increased algometry scores, ataxia, surgical condition, and ataxia in treated horses. These effects were seen initially after sedation in ketamine treated groups. There was a statistically significant differences in individual animal algometry readings with differences correlating to individual animal's pre-sedation behavior. Animals with higher vital parameters and more anxious or aggressive behavior had a lesser increase MNT throughout the study when compared to more relaxed horses. A statistically significant differences were seen in heart rate of individual animals between groups at each time point initially with horses in the ketamine treated groups maintaining a higher heart rate for longer. A time-dependent, statistically significant, dose dependent increase in sedation and surgical condition from baseline was noted immediately after administration in ketamine treated groups resulting in prolonged sedation and condition scores in ketamine treated horses compared to controls. However, there was no significant difference in sedation or surgical condition scores between any group after minute 10 of each trial.

Ataxia scores were statistically significant between all groups and individual animals. This dose-dependent, predictable, immediate increase in ataxia within 1 minute was seen in both ketamine treated groups. There was no statistical significance in ataxia scores seen by minute 8. Some horses in the DK2 group experienced severe ataxia and muscle rigidity. This demonstrated the dose dependent effects of ketamine in the standing horse. This ataxia resulted in recumbency in one horse in the DK2 group. There was extreme variability in response to treatment protocol between individual animals at higher doses of ketamine (0.4mg/kg). Therefore, higher doses of ketamine may not be favorable as recumbency is possible. Even at lower doses of ketamine (0.2mg.kg) a significant change in sedation, surgical condition, and MNT were seen and could support the use of lower doses of ketamine.

Ketamine, a phencyclidine derivative, originally known as CI-581, was synthesized in the early 1960s as an anesthetic agent with unique properties including minimal negative effects on the

cardiorespiratory system (Gorlin, Rosenfeld, and Ramakrishna 2016). Due to these properties, it gained popularity as a prehospital pain control aid on the battlefields of Vietnam where it became known as the “buddy drug”. There, soldiers would carry ketamine to administer to injured soldiers, thus offering pain relief without the respiratory depression associated with the use of an opioid such as morphine.

Ketamine has been shown to have both sedative and analgesic properties when administered to horses as well. These effects are seen at anesthetic, and subanesthetic doses, as well as when administered as a constant rate infusion (CRI). Ketamine is a commonly available veterinary anesthetic drug with clinical application in standing and anesthetized horses; however limited evidence is available on its application in the standing horse as a single bolus dose. The dose of ketamine used to facilitate sedation in this study (0.2-0.4mg/kg) is much lower than typical anesthetic doses of ketamine that range from 2-4mg/kg (Coetzee et al. 2010). The behavior of ketamine administered to the standing horse has been minimally investigated as a single bolus alone or in combination with an alpha-2 adrenoreceptor agonists (Fielding et al. 2006). Sub-anesthetic combination of xylazine and ketamine given intravenously or intramuscularly has been reported to provide mild sedation without recumbency in cattle (Coetzee et al. 2010). Administration of ketamine alone depressed the nociceptive withdrawal reflex of ponies even at very low plasma concentrations (Peterbauer et al. 2008).

There have been only minor adverse effects reported with the use of injectable ketamine in the adult horse. These include muscle rigidity, mild, transient tachycardia followed by bradycardia, mild transient hypotension followed by hypertension, and mild excitation after prolonged (>2 hour) constant rate infusion. These side effects are not expected with the low doses of ketamine used in standing horses (Gorlin, Rosenfeld, and Ramakrishna 2016; Fielding et al. 2006; Peterbauer et al. 2008; Meenan 2010). At anesthetic doses, ketamine has a variety of cardiovascular effects, including increases in cardiac index, mean aortic pressure, pulmonary arterial pressure, systolic and diastolic arterial pressure, and heart rate. Ketamine does not appear to influence gastrointestinal motility and has only minimal and transient effects on ventilation with an apparent decrease in airway resistance in dogs and humans. (Fielding et al. 2006).

Ketamine possesses value as an analgesic drug for use in equine patients that are systemically compromised from cardiovascular, respiratory, or gastrointestinal diseases.

Ketamine has a rapid distribution with peak plasma concentrations being reached within sixty seconds following intravenous bolus administration, thus excitatory effects are rapid but short lived(Waterman, Robertson, and Lane 1987). These changes, including dysperception and ataxia were proven to be transient at one minute, and absent by five minutes post administration(Peterbauer et al. 2008). The primary metabolite of ketamine, norketamine, can be detected in the plasma of horses as early as two minutes after injection of the parent drug. Recovery from ketamine anesthesia and sedation in the horse is due to its rapid redistribution of the drug from the central compartment. This explains the abrupt recovery from ketamine anesthesia often observed in the horse (Waterman, Robertson, and Lane 1987) as well as the rapid and predictable return to baseline seen in the current study.

Combining ketamine with an alpha-2 agonist results in what is referred to as an "additive effect." This is the combination of one or more drugs to reduce the amount of each drug and the incidence of adverse effects of any one or all of those drugs that would be needed if administered alone. There is an increased duration of effect of ketamine when it is administered in combination with other agents. Initially, a protocol using sub-anesthetic intravenous ketamine in combination with an alpha-2 agonist (dexmedetomidine) was developed at Walter Reed Army Medical center for refractory pain from CRPS. This is now considered a hallmark in the treatment of many refractory pain and psychological disorders in humans and small animals(Meenan 2010). The co-administration of an alpha-2 agonist or opioid can counteract the muscle rigidity and excitation seen after administration of ketamine alone. These drugs also offer valuable sedative and analgesic properties and have been found to have a synergistic effect with ketamine, prolonging these effects (Müller et al. 2017).

Alpha-2 agonists are the most commonly used and readily available sedative in horses (Fielding et al. 2006). When sedation of an animal experiencing pain is desired, these drugs are often combined with a different drug class such as an opioid. Opioid administration in horses is utilized sparingly. This is due to the local gastrointestinal effects seen after solo or co-

administration of opioids in horses. These drugs are implicated in hypomotility syndrome affecting multiple gastrointestinal organs and have been reported to lead to prolonged or increased incident of colic in horses. Repeated administration of opioids has been shown to decrease frequency of defecation, decrease weight of fecal output, decrease borborygmus, decrease fecal moisture, and increase overall gastrointestinal transit time, as well as result in site specific cecal dysfunction in some studies(Boscan et al. 2006; Gough et al. 2022; Müller et al. 2017). While more recent literature states that only extended morphine administration is associated with a significant increased risk in postanesthetic colic in the horse (Haralambus et al. 2024). Therefore, the administration of a drug other than an opioid, such as ketamine, in combination with an alpha-2 agonist has significant clinical merit. Low dose ketamine might have equivalent or higher efficacy and safety when compared to opioids for managing acute pain (Ying and Zuo 2023).

Xylazine, a readily available alpha-2 agonist used in equine patients, has been investigated as a co-administered drug with ketamine in a standing stun in both ponies and cattle (Coetzee et al. 2010; Peterbauer et al. 2008). This combination was shown to prolong the effects of both drugs and resulted in superior sedation and pain mitigation. The sedative effects of xylazine are less than that of detomidine in effect and duration. There is also a more profound, dose dependent ataxia, with similar cardiovascular depression as seen in detomidine (Nout-Lomas et al. 2017). Therefore, the use of detomidine in combination with sub-anesthetic ketamine was chosen for the current study.

Pressure algometry is a tool used to detect responses to applied mechanical stimuli within tissues. To quantify applied pressure, pressure algometry is used to gradually apply pressure over specified landmarks until an avoidance response is noted, which is termed the MNT. As nociceptive thresholds and the response to noxious stimuli are individually based, pressure algometry may be more useful for the quantification of intra-subject responses, rather than a method for assessing nociceptive differences between horses (Haussler 2020). This was demonstrated in this study as individual horses had varying MNT measurements. Due to the individual variability mechanical nociceptive thresholds should be combined with other clinical and available indicators. Nociceptive thresholds should be recorded with minimal restraint in a quiet area in a routine and systematic manner to limit any external factors from influencing the

response. In an effort to avoid variability during the MNT testing, horses in the current study were housed with herd members, in a climate controlled building, and were tested only after an acclimation period to avoid conditioned fear or pain responses (Haussler 2020).

The Ghent Sedation Algorithm (GSA) adapted for adjustment of alpha-2 administration rates was chosen to monitor sedation depth in this study. The GSA was developed at Ghent University, taking the degree of ataxia, the apparent depth of sedation and the surgical conditions into account, with numerical rating scores (NRS) scores from 0 to 3 (table 1) for the three parameters. These scores are based on the most often used criteria to evaluate sedation. Using the three NRS, a decision can be made to increase or decrease the administration rate of sedatives according to a detailed algorithm. The GSA allows constant adjustment of sedation depth and quality, and may be useful under both clinical and experimental conditions using alpha-2 agonists and other sedatives in horses (Schauvliege et al. 2019).

Limitations of the study are the small sample size and the use of non-clinically affected horses. Therefore, there may not be a direct comparison to the response of painful or agitated horses. There was a wide variability in behavior, age, and condition of animals used in the study, this may have resulted in more variable responses to sedation. Finally, the study was conducted over several months' time span. Local weather, temporal, and hormonal variations of animals may have contributed to the variability in responses of horses throughout the study period.

# Conclusion

In conclusion ketamine is readily available, cost effective, and has a predictable effect when administered at sub-anesthetic doses to the standing horse in combination with detomidine. We demonstrated that the co-administration of these drugs resulted in an additive effect by prolonging both standing sedation and MNT. The addition of sub-anesthetic doses of ketamine to detomidine has potential application for achieving rapid onset of standing sedation in painful or distressed animals. Some animals administered higher doses of ketamine (0.4mg/kg) did become profoundly ataxic. A dose of ketamine at 0.2mg/kg in addition to detomidine at 0.01mg/kg given intravenously as a bolus did not have any observable deleterious effects in this study.

The use of this protocol for wound repair, standing surgical procedures, painful manipulations, or as an adjunctive pain management in severe colic can be considered. Due to the increase in ataxia seen with the addition of ketamine, this may not be a viable option for horses with neurological defects, unstable fractures, or other causes of weakness.

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# Glossary of Terms

MNT: Mechanical nociceptive threshold

CRPS: Chronic regional pain syndrome

CRI: Constant rate infusion

GSA: Ghent Sedation Algorithm

NRS: Numerical rating scores