COMPARISON OF THE EFFECTS OF XYLAZINE BOLUS VERSUS MEDETOMIDINE CONSTANT RATE INFUSION IN HORSES ANESTHETISED WITH ISOFLURANE

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ABSTRACT

Inhalant anesthesia in horses carries a high rate of complications and mortality, despite its common use (1-4).

Medetomidine, a selective alpha$_2$ agonist, is approved in North America for use in dogs only (5). However, it is often used in horses as part of a balanced anesthetic protocol by using a constant rate infusion (CRI) of medetomidine and a reduced concentration of isoflurane (6). The premise behind this technique is that the lower concentration of isoflurane may result in less cardiovascular depression, while the addition of medetomidine provides supplemental analgesia and muscle relaxation, and smoothes recoveries (6, 7). Although a medetomidine CRI during isoflurane anesthesia has been evaluated in horses, no studies exist which compare a CRI of medetomidine to conventional xylazine bolus therapy using the same group of horses, breathing spontaneously in dorsal recumbency, without the influence of surgery.

This thesis has three principle sections. The first presents background information and a literature review relevant to the study as a whole. The second section describes the cardiopulmonary and anesthetic effects of medetomidine CRI compared to conventional therapy with xylazine. Finally, the third section describes the stress responses and recovery characteristics of medetomidine CRI compared to conventional therapy with xylazine.

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The horses that come through the AVC as patients inspired this work, in an effort to improve the safety of anesthesia for all horses. I am grateful to the horses used in this research.

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DEDICATION

To Charlie, always.

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1. GENERAL INTRODUCTION AND LITERATURE REVIEW

1.1. PROBLEMS ASSOCIATED WITH INHALANT ANESTHESIA IN ADULT HORSES

General anesthesia in mature horses is associated with greater morbidity and mortality compared to other species (4, 8, 9). Common complications of equine general anesthesia include hypotension, hypercapnia, hypoxemia, and arrhythmias (1-4). Both the physical conformation of the horse and this species' unique susceptibility to the adverse effects of inhalant anesthesia presumably contribute to the increased incidence of complications. Overall, equine general anesthesia carries a mortality rate of 0.68%-0.9% (1 death in 111 - 146 anesthetics) for non-colic related anesthetics (8). A multicentre epidemiological study found that cardiovascular collapse during or after inhalant anesthesia accounted for 33% of perioperative fatalities, while fractures and myopathies accounted for another 32%. Another study from a large referral centre in the United States reported a mortality rate of 0.12%, or 1 death in 855 anesthetics, but these cases were managed by board certified anesthesiologists and surgeons exclusively (10). This compares with a recent study which found a 0.15% (1 death in 662 anesthetics) mortality rate for dogs undergoing general anesthesia (11). In human patients, anesthesia – related mortality in the United States was recently reported to be 0.008% (1 death in 1 million anesthetics) (12).

When horses are placed in dorsal recumbency for general anesthesia, the mechanics of breathing are altered. The function of the diaphragm is decreased due to the weight of the abdominal viscera on the diaphragm, and because both inspiration and expiration

are active in the horse, anesthetic–induced muscle weakness further impairs respiration (13). Most anesthetised horses have some degree of ventilation/perfusion mismatch, whether in lateral or dorsal recumbency (2, 13-16). Dorsal recumbency induces greater impairment of oxygenation, however, as the weight of the abdominal and thoracic viscera reduce functional residual capacity and contribute to the increase in atelectasis (17). Ventilation is mechanically impaired by the effect of recumbency on the dependent lung, and inhalant anesthesia impairs gas exchange (13). Pulmonary perfusion decreases, due to decreased cardiac output associated with anesthetic drugs, regional changes in vascular resistance, and the inhibitory effect of anesthetics on hypoxic pulmonary vasoconstriction (18). A study comparing the relationship between ventilation and perfusion in the standing, unsedated horse to the halothane–anesthetised horse in either dorsal or left lateral recumbency found that both recumbent positions were associated with substantial mismatching between ventilation and perfusion (19). The impact was greatest in dorsal recumbency.

Hypoxemia (defined as partial pressure of oxygen (PaO_2) less than 60 mm Hg) is common during general anesthesia and recumbency in horses, even with a high inspired oxygen concentration, as a result of ventilation perfusion mismatching and/or venous admixture (2, 17). Hypoxemia may contribute to the stress response associated with anesthesia and surgery (20), and increases in glucose may be evident. As the equine oxygen haemoglobin dissociation curve is shifted to the left compared to other species, horses can maintain 90% saturation at a PaO_2 of 54 mm Hg (4). Controlled intermittent positive pressure ventilation (IPPV) generally improves arterial

oxygenation, but potentially at the expense of a further decrease in cardiac output (21). Controlled intermittent positive pressure ventilation can impair venous return to the heart, resulting in decreased stroke volume, cardiac output, and arterial pressure (22).

Moderate hypercapnia (defined as a partial pressure of carbon dioxide ($PaCO_2$) greater than 60 mm Hg) is also common in recumbent anesthetised horses, again due either to drug induced respiratory depression, or positioning, or both (2, 20). Inhalant anesthetics depress the respiratory centre, causing a dose–dependent decrease in both respiratory frequency and tidal volume (23). Horses anesthetised with halothane for two hours showed a steady increase in $PaCO_2$ above control values (24). Mild to moderate hypercapnia (50-65 mm Hg) may actually cause sympathetic stimulation and improvement of cardiac output and arterial blood pressure. In contrast, $PaCO_2$ values above 70 mm Hg result in significant respiratory acidosis leading to decreased cardiac contractility, and increased frequency of arrhythmias (2, 25). Mild hypercapnia has also been shown to offset the cardiovascular depression seen with IPPV in healthy horses undergoing elective surgical procedures (26).

Cardiovascular depression is a hallmark of general anesthesia in horses. Cardiac output, stroke volume, and left ventricular work all decrease in recumbent anesthetised ponies, with the most profound changes being seen in dorsal recumbency (21). Mean arterial pressure and pulmonary artery pressure are both significantly decreased with dorsal recumbency.

Hypotension (defined as mean arterial blood pressure less than 60 mm Hg) resulting in compromised tissue perfusion is common during general anesthesia in horses, and may be a factor in the development of post anesthetic myopathy (2, 4, 10). Horses are especially susceptible to the vasodilatory effects of inhalant anesthetics, and may remain hypotensive even at inadequate planes of anesthesia characterised by movement (2). Hypotension during inhalant anesthesia may also contribute to the stress response, due to its adverse effect on tissue perfusion (27).

In humans, anesthesia without surgery does not elicit a stress response (27). In contrast, anesthesia itself induces a stress response in the horse (24). Serum glucose values tend to increase during halothane anesthesia in ponies, but there is significant individual variation. Serum cortisol values also increase in association with halothane (24) or isoflurane (28) anesthesia in ponies, due to an incompletely understood pituitary adrenocortical response. Hypotension may be a contributing factor in the stress response to inhalant anesthesia (29). Surgical procedures increase cortisol values above those seen with anesthesia alone, and the increase is proportional to the invasiveness of the procedure (27). In contrast, total intravenous anesthesia using detomidine, ketamine, and guaifenesin in ponies and horses decreases cortisol values (29, 30), even when surgical procedures are performed (31). The decrease in cortisol may reflect the higher arterial pressures typically maintained during total intravenous anesthesia when compared to halothane anesthesia (29). It is unclear whether total

intravenous anesthesia prevents adrenocortical activation, or merely fails to stimulate it. In dogs, high doses of dexmedetomidine, the active enantiomer of the selective alpha$_2$ agonist medetomidine, cause a slight decrease in resting cortisol and in steroidogenesis (32). Pentobarbital anesthesia in ponies also prevents an increase in cortisol levels until the recovery period (33). Cortisol and catecholamine levels do not increase when glucose is administered as an infusion during halothane anesthesia in ponies (27). This may indicate that energy availability, and therefore metabolism, are important factors in the equine stress response. Acutely, stress promotes survival by activating the adrenocortical system, mobilizing glucose, and supporting the immune system (34). The effects of stress related to inhalant anesthesia on overall patient welfare and recovery quality are not known. Undesirable changes that may be caused by the stress response include lower glucose availability to tissues, decreased immune function, and prolonged tissue repair following surgical procedures. Stress and the resulting increase in norepinephrine release increases tissue oxygen consumption through increased heart rate and arterial blood pressure, and may lead to myocardial hypoxia.

1.2 MONITORING ANESTHESIA IN HORSES

Monitoring depth of anesthesia is a critical aspect of equine inhalant anesthesia. Horses that are maintained at an inadequate plane of anesthesia for the procedure being performed may experience pain or fear, or may move, causing injury to personnel, equipment, or themselves (35). Alternatively, horses that are maintained at

a plane of anesthesia that is excessive for the procedure often experience cardiopulmonary depression and its resultant complications. Most methods for evaluating depth of anesthesia in horses are qualitative and subjective. Lack of movement in response to surgical stimulation, enhanced muscle relaxation, ventromedial rotation of the eye, progressive loss of the palpebral reflex, and decreased respiratory rate and depth are all indicators of deepening anesthesia. In contrast, lacrimation, spontaneous palpebral reflexes, nystagmus, shivering, or movement all indicate insufficient depth during inhalant anesthesia. When medetomidine is used as a CRI adjunct to inhalant anesthesia, however, only nystagmus or movement are reliable indicators of insufficient anesthetic depth (36). The administration of medetomidine as a CRI during inhalant anesthesia has been shown to provide a more stable plane of anesthesia, requiring fewer additional drugs to maintain adequate depth of anesthesia during surgery (7).

The bispectral index (BIS) is a number ranging from 0 to 100, where 0 represents an isoelectric electroencephalogram (EEG) and 100 represents an awake, alert state (37-39). Artifact–free EEG signals are transformed into BIS numbers using Fournier and bispectral calculations based on an algorithm (38). The algorithm relates the phase angle coupling (agreement) of sine waves, the power spectrum (delta, 1-4 Hertz versus beta, 13-30 Hertz), and the proportion of isoelectric EEG. As anesthetic depth increases, there is greater phase coupling and a shift in the power spectrum to lower frequencies, and BIS values decrease. BIS is not routinely used to evaluate depth of anesthesia in horses, as it has not conclusively been shown to be an accurate indicator

of level of consciousness in horses anesthetised with isoflurane (39) or propofol (40). BIS has been shown to be a useful predictor of awakening in horses anesthetised with propofol (40). In humans, the BIS reflects central nervous system (CNS) depression, with a BIS value of 40-50 representing a surgical plane of anesthesia (37, 40).

Electromyogram (EMG) activity is also monitored by the BIS, by subdermal needles serving as electrodes. EMG signals are between 30-300 Hertz, which can potentially overlap the BIS power spectra (41). Significant EMG activity can falsely elevate BIS readings through this band overlap; it has been recommended that unexpectedly high BIS values be interpreted in light of simultaneous EMG readings.

1.3 RECOVERY FROM INHALANT ANESTHESIA IN HORSES

The anesthetic recovery phase is a particularly dangerous time for horses, with approximately 25% of anesthesia–related mortality occurring from fractures during this period (8). Hypoxemia in the recovery period is also a serious problem (42). Other common causes of poor outcome in the recovery phase include myopathy, neuropathy, upper airway obstruction, or pulmonary edema (4, 43, 44). Horses by nature are 'fight or flight' creatures, which predisposes them to attempts to flee during the excitement phase, which is invariably accompanied by ataxia (45, 46). As a result, many methods have been used in an attempt to reduce the incidence of catastrophic events during recovery. Assisted recoveries are one approach and may include the use of head and tail ropes, soft padding, slings, air cushions, or water systems. Each of these techniques, however, has its own unique set of intrinsic problems (4, 43, 47, 48).

Sedation in the early recovery period has also been assessed as a method of improving the outcome of inhalant anesthesia by promoting a longer, smoother recovery (4, 43, 45, 47, 49). Alpha$_2$ agonists are most commonly employed for this purpose; xylazine (0.1 mg/kg IV), detomidine (2 µg/kg IV), and romifidine (8 µg/kg IV) have all been used (45). Recently, the effect of 30 minutes of injectable anesthesia (xylazine 0.15 mg/kg IV bolus followed by 20 µg/kg/min, and ketamine 0.3 mg/kg IV bolus followed by 60 µg/kg/min) following 90 minutes of isoflurane anesthesia was examined and while the recoveries were longer, they were not of better quality (50). There is considerable individual variation in equine recoveries, and repeated anesthetic episodes in the same individual tend to show an improvement in recovery scores (51).

1.4 INHALANT ANESTHESIA IN HORSES

Inhalant anesthetic agents are widely used for anesthetic management in horses because they allow relatively rapid adjustments in depth, offer the possibility to control ventilation and supplement oxygen, and are eliminated rapidly from the body (52). All inhalant anesthetic agents require specialized equipment to administer them and scavenge the waste anesthetic gases (23, 52). The inhalant anesthetics all produce dose-dependent depression of the cardiovascular and respiratory systems. Halothane was introduced in 1957, but is no longer available in North America, having been replaced by isoflurane and sevoflurane (23). Both isoflurane and sevoflurane maintain cardiac output and arterial blood pressure better than halothane (53). Minimum alveolar concentration (MAC) values for halothane and isoflurane are 0.88 ±0.03 and

1.31 ±0.07 volumes %, respectively (54). Isoflurane, approved for horses since the 1980's, causes less cardiovascular depression than halothane, maintains better muscle perfusion, and allows anesthetic depth to be adjusted more quickly (23, 49, 55). In a study comparing halothane and isoflurane in horses positioned in dorsal recumbency undergoing surgical procedures, isoflurane causes more severe respiratory depression than halothane and routine mechanical ventilation is recommended (55, 56). A progressive increase in $PaCO_2$ was reported in horses anesthetised with isoflurane and positioned in lateral recumbency over a five hour period (56). In general, recoveries from inhalant anesthetics are worse with longer procedures (9). The poor recoveries associated with isoflurane anesthesia initiated the search for ways to improve equine recoveries with adjunctive anesthetic drugs (45, 49, 57).

Sevoflurane has been available in the United States since 1995; the cost of the drug has limited its use outside university settings (23). The MAC of sevoflurane in horses is 2.84 ± 0.16 volumes % (16). Its cardiorespiratory effects are similar to those of isoflurane, but its lower solubility allows for even more rapid changes in anesthetic depth (53). A study comparing 90 minutes of isoflurane or sevoflurane anesthesia in laterally recumbent horses showed similar cardiopulmonary effects between the two drugs, but sevoflurane provided faster recoveries, with improved recovery scores when compared to isoflurane (53). A more recent study comparing isoflurane to sevoflurane following romifidine–ketamine–diazepam induction for distal limb MRI showed no difference in recovery times or scores between the two groups, although temperament prior to drug administration was correlated with recovery score (58).

1.5 INTRAVENOUS ANESTHESIA IN HORSES

Total intravenous anesthesia has been investigated as a potentially safer alternative to inhalant anesthesia in horses, but is usually reserved for short duration cases or field anesthesia conditions. These protocols are associated with less cardiopulmonary depression and better analgesia and recovery characteristics than the inhalants, but drug accumulation can be a problem with prolonged infusions (6). Most techniques use a combination of an alpha$_2$ agonist, a dissociative anesthetic, and a centrally acting muscle relaxant (1, 59). The combination of xylazine, ketamine, and guaifenesin has been used for short duration anesthesia (30–90 minutes) since 1978 (59). These drugs can cause respiratory depression and bradycardia and monitoring remains just as important as with inhalant anesthesia (1). Romifidine (100µg/kg IV bolus) and ketamine (2.0 mg/kg IV bolus then 0.1 mg/kg/min for 30 minutes) has been compared to xylazine (1.0 mg/kg IV bolus then 0.05 mg/kg/min for 30 minutes) and ketamine (2.0 mg/kg IV bolus then 0.1 mg/kg/min for 30 minutes) (60). Both protocols were found to cause increased central venous pressure and decreased cardiac index (50 – 55% of baseline). Arterial blood pressure was maintained and second degree heart block was also noted. The authors found both of these combinations to be suitable for general anesthesia from a cardiopulmonary standpoint. Propofol in combination with ketamine and medetomidine has also been evaluated; following induction, medetomidine (1.25 µg/kg/hr IV) and ketamine (1.0 mg/kg/hr IV) were administered with a propofol (0.14

mg/kg/min) continuous infusion (61). All horses showed respiratory depression, hypercapnia, and hypoxemia, and required mechanical ventilation. Acceptable mean arterial blood pressures were maintained and recoveries were good. However, if ketamine is infused for extended periods, ketamine and its active metabolite norketamine will accumulate, which may contribute to poor recoveries (62). Other studies have evaluated medetomidine–propofol inductions in ponies, and medetomidine–ketamine–diazepam inductions in ponies and horses, followed by infusions of propofol (0.07 – 0.15 mg/kg/min) and medetomidine (3.5 μg/kg/hr) (36, 63-65). These animals had minimal respiratory depression but hypoxemia was seen in some. Cardiac output was reduced by 30-50%, which is comparable to that seen with short duration of injectable anesthesia. The authors recommended that ponies and horses be intubated and supplemented with > 90% oxygen, and that access to mechanical ventilation is also available. The ponies had good recoveries after a four hour infusion, as did the horses after a two hour infusion with surgery.

1.6 PARTIAL INTRAVENOUS ANESTHESIA IN HORSES

More recently, the concept of partial intravenous anesthesia (PIVA) has been investigated. This involves a combination of inhalant and intravenous anesthetic agents, allowing a lower concentration of inhalant anesthetic to be used to achieve the same depth of anesthesia (6). The premise of this method is that the lowered concentration of inhalant agent is associated with less cardiopulmonary depression, while the addition of injectable drugs allows better analgesia and improved recoveries.

It is accepted that the injectable agents do cause some cardiorespiratory depression and will accumulate over time (6, 66, 67). Most techniques of PIVA use a continuous, low infusion rate to achieve a reduction in MAC. However, one study evaluated the effects of two doses of xylazine hydrochloride each given as a single bolus, on the MAC of isoflurane in laterally recumbent horses (68). This study found that a bolus of 0.5 mg/kg IV of xylazine decreased isoflurane MAC by 25% at 42 minutes post injection, while 1.0 mg/kg decreased MAC by 34% at 67 minutes. The authors cautioned that although PaO_2 and $PaCO_2$ values did not change with xylazine administration, xylazine contributed to additional cardiovascular depression when added to inhalant anesthesia. It was also found that blood glucose concentration increased significantly, while urine production increased insignificantly following xylazine administration. Previous studies have shown that 1.1 mg/kg of xylazine, alone or in combination with ketamine at 2.2 mg/kg induces hyperglycemia lasting 180 minutes associated with decreased serum insulin lasting for 15-45 minutes in Thoroughbred horses (69, 70).

Medetomidine has also been evaluated for its anesthetic-sparing effects during isoflurane anesthesia in horses (7, 26, 71). Horses anesthetised with isoflurane were given medetomidine at a constant rate of 3.5 μg/kg/hr, and had lower isoflurane requirements (20%) and heart rates, with no change in respiratory rates (71). A study compared infusions of lidocaine to medetomidine in horses anesthetised with isoflurane, undergoing surgical procedures (7). Lidocaine was administered as a 2 mg/kg IV bolus followed by 50 μg/kg/min infusion and compared to medetomidine administered at 3.5 μg/kg/hr for the duration of the surgery. The horses subsequently

recovered unassisted. It was found that horses given lidocaine had higher heart rates and cardiac indexes, while horses given medetomidine had higher mean arterial blood pressures. No difference was seen between groups regarding PaO_2 and $PaCO_2$ values. The lidocaine horses were more reactive to the surgical procedures than were the medetomidine horses. In addition, the recovery scores were better in the horses that received medetomidine. Recovery was scored using a simple descriptive scale from one to five, with one representing an excellent recovery, and five representing a very poor recovery.

PIVA has also been evaluated during sevoflurane anesthesia (72). Horses were anesthetised for four hours using a CRI of guaifenesin (100g/L), ketamine (4g/L), and medetomidine (5mg/L) (GKM) plus sevoflurane compared to sevoflurane alone. Cardiovascular measurements in the GKM group were maintained at 70% of baseline values, and all horses had good recoveries. The authors concluded that medetomidine may have no cardiovascular effects at the low dose used in the study. Another study evaluated guaifenesin (24.5 mg/kg/hr), ketamine (0.98 mg/kg/hr), and medetomidine (1.22 µg/kg/hr) in combination with sevoflurane compared to sevoflurane alone in horses undergoing surgery in either lateral or dorsal recumbency (73). It was subjectively determined that the horses receiving the infusion had improved cardiovascular function and made fewer attempts to stand. The infusion produced higher blood pressures than did sevoflurane alone, and reduced the required sevoflurane concentration by 38%. Midazolam (0.02 mg/kg/hr) has been used in place of guaifenesin in combination with ketamine (1.0 mg/kg/hr) and medetomidine (1.25

μg/kg/hr), plus sevoflurane for four hours of anesthesia in lateral or dorsal recumbency (74). These horses had well maintained blood pressure and cardiac output (65-80% of baseline values). The horses had generally good recoveries, but some ataxia was observed and it was recommended that assistance be available.

1.7 ADRENERGIC RECEPTORS

The adrenergic receptor family is broadly grouped into alpha adrenergic receptors and beta adrenergic receptors. Each group is further divided into subtypes.

The $alpha_1$ adrenergic receptor subtypes $alpha_{1A}$, $alpha_{1B}$, and $alpha_{1C}$ have been identified (75). Their distribution varies among species, and within tissues. $Alpha_1$ receptors act via a G protein (G_p) to activate phospholipase C, which hydrolyses phosphoinositol and results in calcium release, causing vasoconstriction. $Alpha_2$ receptors act via G_i or G_o proteins and second messengers to cause sedation and analgesia. $Alpha_2$ agonist receptors are widely distributed throughout the body.

Beta adrenergic receptors are found in the myocardium and coronary vasculature (predominately $beta_1$), and in smooth muscle of vascular, bronchial, gastrointestinal, and genitourinary tissues (predominately $beta_2$) (75). $Beta_3$ receptors are thought to be involved in regulation of metabolism. These receptors are activated by the catecholamines norepinephrine and epinephrine, and act via a G protein (G_s) to stimulate the formation of adenylate cyclise and activate calcium channels. The end result of beta adrenergic activation is an increase in heart rate and cardiac contractility,

as well as relaxation of vascular, bronchial, gastrointestinal, and genitourinary smooth muscle.

1.8 ALPHA$_2$ ADRENERGIC RECEPTORS

Alpha$_2$ agonists are a group of drugs that are commonly used as sedatives, analgesics, and adjunctive anesthetic agents in horses. Alpha$_2$ adrenergic responses are mediated by a transmembrane signalling system comprised of a receptor protein, a guanine nucleotide–binding protein (G protein), and an effector mechanism (76, 77). Alpha$_2$ adrenergic receptors are located in many tissues throughout the body, including the cerebral cortex, locus ceruleus, spinal cord, sympathetic neurons, autonomic ganglia, pancreatic beta cells, nerve terminals, vascular smooth muscle, platelets, blood vessels, liver, and kidneys (5, 78). Binding of norepinephrine or epinephrine to the alpha$_2$ receptor's extracellular domain results in activation of an intracellular domain that is coupled to a G protein (78, 79). The G protein then activates various signalling cascades linked to effector proteins or ion channels (80). Specifically, alpha$_2$ receptors are linked to the inhibitory G protein (G_i) which is coupled to a variety of second messengers such as adenylyl cyclase, phosholipase C, and phospholipase A_2(78, 79). The effects on the second messengers are varied; adenylyl cyclase activity is decreased, while activity of phospholipase C and A_2 are increased. Potassium channel activity is increased, causing cell membrane hyperpolarisation, a decreased rate of firing of cells within the central nervous system, and subsequent sedation and analgesia (77, 78). Additionally, there is accelerated sodium/potassium exchange, mobilisation of arachadonic acid, and

increased intracellular calcium availability. Alpha$_2$ receptors are also linked to the G_o protein which inhibits voltage-gated calcium channels. This results in decreased release of neurotransmitters.

There are three cloned subtypes of alpha$_2$ receptors: alpha$_{2A}$, alpha$_{2B}$, and alpha$_{2C}$ (78). Of these, the alpha$_{2A}$ subtype is located in the central nervous system and is responsible for the analgesic (antinociceptive), sedative, anxiolytic, anesthetic-sparing, bradycardic, and hypotensive (mediated by decreased sympathetic outflow from the brain), effects of the alpha$_2$ agonists (5, 77, 78). The alpha$_{2B}$ receptor mediates the initial increase in vascular resistance which causes the reflex bradycardia associated with alpha$_2$ agonists (5, 77). The alpha$_{2C}$ receptor, located in the hippocampus and dorsal and ventral striatum, inhibits catecholamine release from the adrenal medulla, modulates dopamine transmission, and is responsible for the hypothermic effects (77, 78). Alpha$_2$ adrenoceptors are located both presynaptically and postsynaptically (78). Presynaptic alpha$_2$ receptors are important in regulating the release of neurotransmitters from sympathetic nerve endings, and may be involved in the inhibition of neurotransmitters other than norepinephrine in the central and peripheral nervous systems. Postsynaptic alpha$_2$ receptors are located in vascular and other smooth muscle cells where they mediate constriction, and are also found in adipocytes and secretory epithelial cells of the intestine, kidney, and endocrine organs. In addition, extrajunctional (that is, remote from norepinephrine-releasing nerve terminals) alpha$_2$ receptors are located on vascular smooth muscle cells, as well as

platelets and leukocytes; these receptors may be activated by circulating catecholamines such as epinephrine.

Alpha$_2$ agonists act at the level of the dorsal horn of the spinal cord and the brainstem (5, 77). Alpha$_2$ heteroceptors are receptors on non–noradrenergic neurons within the dorsal horn of the spinal cord. Alpha$_2$ heteroceptors are found both pre– and postsynaptically, and mediate the analgesic effects of alpha$_2$ agonists via decreased release of neurotransmitters and neuropeptides, and inhibition of ascending nociceptive transmission. Alpha$_2$ autoreceptors are alpha$_2$ receptors on noradrenergic neurons found supraspinally, specifically in the locus ceruleus. Alpha$_2$ autoreceptors directly mediate the sedative effects of alpha$_2$ agonists, and indirectly contribute to the analgesic effects of alpha$_2$ agonists by further activating heteroceptors.

1.9 ALPHA$_2$ ADRENERGIC DRUGS

Alpha$_2$ agonists are a group of drugs that are widely used in veterinary medicine. They are commonly given to horses prior to induction of general anesthesia (81). As a group, these drugs produce a clinically useful spectrum of effects including sedation, muscle relaxation, and analgesia, and are often administered to smooth the induction and recovery phases of general anesthesia (82). These agents also potentiate the actions of other sedatives and analgesics, thereby allowing a reduction in the doses of other anesthetic agents. They also offer the additional benefit of being completely reversible with specific antagonists (5, 81, 83).

After intravenous administration in horses, these drugs all cause an initial period of hypertension and bradycardia, followed by a longer period of hypotension, and decreased cardiac output (82). The initial hypertension associated with alpha$_2$ agonists is caused by vasoconstriction mediated by activation of peripheral extrajunctional alpha$_2$ receptors (5). The later phase of hypotension is due to decreased CNS sympathetic output caused by activation of central and peripheral alpha$_2$ receptors. The bradycardia seen after the administration of these drugs occurs due to inhibition of CNS sympathetic tone, inhibition of the release of norepinephrine from sympathetic nerve terminals, increased vagal tone resulting from increased systemic vascular resistance, and increase in acetylcholine release from cardiac parasympathetic nerves (5, 67). These effects are generally dependent on dose and route of administration (82).

Isoflurane anesthesia causes significant vasodilation and decreased arterial blood pressure at clinically relevant concentrations (5). In contrast, administration of alpha$_2$ agonists with isoflurane increases vascular tone and reduces isoflurane-mediated vasodilation and hypotension. All alpha$_2$ agonists have similar cardiopulmonary effects, with the main difference being duration of effect (82). In general, the sedative and analgesic effects are dose dependent with a ceiling effect, beyond which increasing dose simply increases duration of action of effect. Although the cardiovascular effects of alpha$_2$ agonists are generally well tolerated, the alpha$_2$ agonists are usually avoided in animals with significant pre-existing cardiovascular disease or shock (84).

Alpha$_2$ agonists cause an increase in urine production, with a concomitant decrease in urine osmolality in dogs (85) and horses (86, 87). The mechanism behind the production of large amounts of dilute urine is not known, but the most likely explanation is interference with the action of vasopressin in the renal collecting duct (88), as has been reported after alpha$_2$ agonist administration in rats (5). Another possible mechanism is inhibition of vasopressin release; however, healthy humans given a single bolus of dexmedetomidine show no change in measured vasopressin values (89). Xylazine (1.0 and 1.5 mg/kg, IV) given intravenously to horses causes the production of large volumes of dilute urine (86). Romifidine and detomidine also cause diuresis in horses, of similar degree and duration to that seen with xylazine (90).

1.10 XYLAZINE

Xylazine (2-(2,6 dimethylphenylamino)-4H-5,6 dihydro-1,3 thiazine hydrochloride) (91) is an alpha$_2$ agonist drug that was developed in 1962 as a human anti-hypertensive drug, but was found to cause CNS depression. Thus, it was reintroduced to veterinary medicine as a sedative, analgesic, and muscle relaxant (84, 92, 93). It acts via alpha$_2$ receptors to cause dose-dependent CNS depression (94). Its alpha$_2$:alpha$_1$ receptor selectivity ratio is 160:1 (93).

Xylazine provides somatic analgesia in horses, with the effect being maximal within 15 minutes, and waning by one hour (95). Xylazine causes bradycardia (76, 96) and a brief period of hypertension, followed by a longer period of hypotension when administered as an intravenous bolus (76). The bradycardia is due to increased vagal tone as a result

of hypertension (97). Second degree atrioventricular (AV) block and sinoatrial (SA) block are also commonly seen, even when xylazine is administered intramuscularly (98). However, no significant pressor response is seen after intramuscular administration of xylazine, because its lower blood levels cause less postsynaptic alpha$_2$ receptor stimulation (76).

Respiratory rate decreases after xylazine administration in horses, as well as cats and dogs (5). However, tidal volume increases and alveolar ventilation and PaO_2 are unchanged. Xylazine decreases pulmonary resistance in horses with recurrent obstructive airway disease and may be beneficial in these patients. In contrast, PaO_2 decreases in sheep given xylazine, due in part to a species-related inflammatory response of intravascular macrophages, and in part to mismatching between ventilation and perfusion (5).

In horses, xylazine reduces isoflurane MAC by 25% to 34% when administered as a bolus of 0.5 mg/kg or 1.0 mg/kg, respectively (68). When given intravenously to mares at 1.0 mg/kg and 1.5 mg/kg, xylazine increases urine production, decreases urine osmolality, and causes hyperglycemia in a transient and dose-dependent manner. This effect is greatest during the first hour, and lasts for two to three hours (86). This effect was not found when the mares were given 0.5 mg/kg xylazine intravenously. Another study found that pony mares also had a significant increase in urine production with a concomitant decrease in urine specific gravity for 30-60 minutes following intravenous administration of xylazine at 1.1 mg/kg (87). These pony mares also showed obvious

signs of sedation for 50 minutes following the administration of xylazine, and had significant increases (37%) in blood glucose at 30 minutes. In horses deprived of food and water for 24 hours prior to the administration of 0.5 or 1 mg/kg intravenous xylazine, urine production was still increased significantly for one hour after administration (99). Xylazine given intravenously at 1.1 mg/kg to conscious horses caused a brief increase in systemic blood pressure due to vasoconstriction and a decrease in heart rate and cardiac output which gradually returned arterial blood pressure to near baseline levels (100). In this study, xylazine was also shown to provide visceral analgesia for 97 minutes. Analgesia for both superficial and visceral pain was also found when xylazine 2.2 mg/kg was given intramuscularly to ponies (101). Conscious horses given intravenous xylazine at 0.3, 0.5, or 1.1 mg/kg showed a decrease in respiratory rate; a greater decrease was seen in horses with the highest initial rate (102). All horses showed some periods of apnea, ranging in duration from seven to 70 seconds. Tidal volume also decreased in these horses, but to a smaller degree than respiratory rate. Hypoxemia (PaO_2 decreased by 7.3-34.9 mm Hg) was seen within five minutes at all xylazine doses, with the shortest duration being seen at the lowest dose. It was concluded that hypoventilation contributed to hypoxemia but was not the only factor involved. Another study found that xylazine given intravenously at a dose of 0.5 mg/kg to ponies did not change tidal volume or respiratory rate (103). This study examined normal ponies and ponies with previously diagnosed recurrent obstructive airway disease. It was found that xylazine decreased pulmonary resistance and increased dynamic compliance, but only when ponies were experiencing an acute

episode of airway obstruction. No changes were seen in normal ponies or in affected ponies during remission, and no changes were seen in PaO_2 or $PaCO_2$.

Xylazine is also used in small animal anesthesia. A review article published in 1992 stated that xylazine should be used only as an adjunctive anesthetic in small animal practice, at intravenous doses ranging from 0.1 mg/kg to 0.5 mg/kg or intramuscular doses of 0.4 to 0.9 mg/kg; this is much lower than the previously described dose of 1.1 mg/kg (104). These authors also recommended a slow (over one minute) intravenous bolus to lessen the initial hypertension and reflex bradycardia.

In a study where four healthy adult horses were given intravenous xylazine at 0.6 mg/kg, the half-time of distribution was found to be 6 minutes, the volume of distribution was 2.5 L/kg, and the systemic half-life was 57 minutes (91). Total body clearance was 21 ml/kg/min. It was hypothesised that the rapid elimination of xylazine in horses is due to metabolism, not excretion. Half-lives and volumes of distribution in the cattle, sheep, and dogs were similar to the values found in horses.

1.11 MEDETOMIDINE

Medetomidine hydrochloride (4(5)-[1-2,3-dimethylphenyl) ethyl] imidazole) (76) is an $alpha_2$ agonist that is not approved for use in horses in North America. It is a potent, selective, and specific $alpha_2$ receptor agonist (105,106), with an $alpha_2$:$alpha_1$ receptor selectivity of 1620:1 (67, 93).

Medetomidine is provided as a racemic mixture of dexmedetomidine, and its optical enantiomer, levomedetomidine. Studies have shown that dexmedetomidine is the enantiomer which possesses the pharmacological activity (67, 107, 108). Male Wistar rats given dexmedetomidine 30 μg/kg to 1 mg/kg subcutaneously showed signs of sedation and hypothermia, whereas the rats given levomedetomidine from 10μg/kg to 1 mg/kg did not (108). This same study showed that rats given dexmedetomidine and the alpha$_2$ adrenoceptor antagonist atipamazole (1 mg/kg) at the same time had no signs of sedation or hypothermia. Recently, dexmedetomidine has become commercially available to veterinarians. Neither xylazine nor medetomidine show any specificity for the subtypes of the alpha$_2$ receptors (5, 109, 110). Medetomidine has been shown to provide analgesia in the horse, but with more pronounced ataxia than detomidine; it was hypothesised that this additional ataxia was due to more rapid central nervous system penetration of medetomidine due to its methyl group addition (111). Horses in this study also showed profound sedation when given medetomidine at 3.75, 7.5, or 10 μg/kg intravenous boluses.

Medetomidine given intravenously at 5μg/kg to horses resulted in a significant bradycardia and hypertension within two minutes, followed by a significant decrease in blood pressure over the 30 minute monitoring period (112). This study hypothesised that the bradycardia was peripherally mediated while the subsequent hypotension was centrally mediated, although this was not definitively proven. A study compared intravenous xylazine (1 mg/kg) to medetomidine (5 μg/kg and 10 μg/kg) in the same five ponies and one horse (113). All three regimens produced sedation, ataxia, lowering

of the head, and drooping of the lips and eyelids. No difference was seen in time to onset of sedation, but ataxia was more profound and lasted longer when medetomidine was given at 10 μg/kg. No difference was seen among the treatments with respect to degree or persistence of bradycardia. The authors concluded that medetomidine produced dose-dependent sedation that was similar to that caused by xylazine, but that medetomidine (10 μg/kg) was associated with more profound and longer lasting ataxia than xylazine.

In dogs, intramuscular medetomidine given at 30 μg/kg is equivalent to 2.2 mg/kg xylazine in terms of sedation and analgesia (104). A study compared the intravenous administration of either xylazine (0.4 mg/kg) or medetomidine (4 μg/kg) in conscious horses (114). Both groups of horses had similar cardiopulmonary responses, and the authors concluded that these doses provided equivalent sedation although the sedative effects were longer lasting in the horses given medetomidine. Cardiac output was significantly decreased in horses given intravenous xylazine (1 mg/kg) and medetomidine (3, 5, 7.5, and 10 μg/kg) (115). The authors found an initial period of hypertension followed by a period of slight hypotension in horses given xylazine and the three lower doses of medetomidine. Equipotent intravenous doses were determined to be 7.5 μg/kg medetomidine and 1 mg/kg xylazine for sedation. Another study in horses found equipotent intramuscular doses to be 2 mg/kg xylazine and 10 μg/kg medetomidine for sedation (116). These authors also found that horses given medetomidine prior to induction of general anesthesia had smoother transitions to

inhalant anesthesia than did horses given xylazine, and it was hypothesised that this was due to the degree of analgesia provided by medetomidine.

Conscious equids (eight ponies and one horse) were given a 5 μg/kg intravenous bolus of medetomidine, followed by an infusion of 3.5 μg/kg/hr for 115 minutes (81). Heart rate and cardiac output decreased, but they returned to baseline values within 40 minutes, and mean arterial pressure was well maintained. Most animals had reduced respiratory rates during the infusion, accompanied by a small increase in $PaCO_2$. The authors concluded that a 3.5 μg/kg/hr infusion of medetomidine in conscious horses and ponies is associated with minimal cardiopulmonary depression. Medetomidine is useful as a CRI, because the drug has a short half-life in horses and is cleared rapidly (117).

Medetomidine decreases the stress response associated with surgery in dogs. A bolus of medetomidine (15 μg, IV) given to dogs prior to ovariohysterectomy prevented increases in epinephrine and norepinephrine, and delayed the increase in adrenocorticotropic hormone (ACTH) and cortisol, when compared to dogs not given medetomidine (118). When administered as an intramuscular bolus to conscious dogs, medetomidine decreases norepinephrine and epinephrine levels and does not change cortisol values (119).

Medetomidine given to horses and ponies at 3.5 μg/kg/hr has been shown to decrease the MAC of isoflurane by 20% (71) and the MAC of desflurane by 28% (120). Women had a reduction in MAC of isoflurane by up to 90% when given dexmedetomidine as a

CRI of 170 ng/kg/min (10 μg/kg/hr) in addition to nitrous oxide in oxygen and fentanyl boluses (121). Medetomidine was also found to decrease the MAC of halothane in dogs by more than 90% when administered at 10 μg/kg intravenously (107).

In dogs anesthetised at 1 MAC isoflurane (1.3%), it has been shown that the response to hypercapnia is better preserved in dogs given medetomidine (20 μg/kg infused over 30 minutes) than in dogs anesthetised with isoflurane alone (122).

In a study where five ponies were given intravenous medetomidine at 7 μg/kg, it was found that the volume of distribution was 1.1 (± 0.17) L/kg, the distribution half-life was 7.6 (± 0.91) minutes, and the elimination half-life was 51.3 (± 13.09) minutes (123). These are very similar to values for horses given xylazine 0.6 mg/kg intravenously (91). Total body clearance was 4.0 (± 0.60) L/kg/hr; it was hypothesised that this very high value was due to extra hepatic sites of metabolism (123). All ponies developed bradycardia with first and second degree AV block or sinus arrhythmia following bolus administration, but returned to normal by seven minutes post injection. This study also determined that an infusion of medetomidine at 3.5 μg/kg/hr for two hours provided a constant level of sedation and induced steady state plasma medetomidine concentrations of 1-1.5 ng/ml.

1.12 RESEARCH OBJECTIVES

Inhalant anesthesia in adult horses is associated with a greater morbidity and mortality compared to other species, due to potential complications during the anesthetic and

recovery periods. Investigation into techniques that improve safety during both of these periods is an important area of research.

The goal of this research was to compare conventional bolus use of xylazine to a constant rate infusion of medetomidine in horses anesthetised with isoflurane, without the confounding effects of surgery and mechanical ventilation, or the variability inherent in clinical trials. The specific objectives of this research were:

1. To determine the cardiopulmonary effects of a medetomidine CRI when compared to xylazine bolus therapy in isoflurane-anesthetised horses.
2. To determine the effects on depth of anesthesia of a medetomidine CRI when compared to xylazine bolus therapy in isoflurane-anesthetised horses.
3. To determine the stress response effects of a medetomidine CRI when compared to xylazine bolus therapy in isoflurane-anesthetised horses.
4. To determine the recovery characteristic effects of a medetomidine CRI when compared to xylazine bolus therapy in isoflurane-anesthetised horses.

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2. COMPARISON OF THE EFFECTS OF XYLAZINE BOLUS VERSUS MEDETOMIDINE CONSTANT RATE INFUSION ON CARDIOPULMONARY FUNCTION AND DEPTH OF ANESTHESIA IN HORSES ANESTHETISED WITH ISOFLURANE

2.1 ABSTRACT

The effects of xylazine bolus versus medetomidine constant rate infusion (MCRI) on cardiopulmonary function and depth of anesthesia in dorsally recumbent spontaneously breathing isoflurane-anesthetised horses were compared. In a prospective, randomised crossover manner, ten healthy adult Standardbred horses were studied. Horses were premedicated with xylazine or medetomidine intravenously. Anesthesia was induced with diazepam and ketamine and maintained with isoflurane for 150 minutes. In the xylazine (XYL) treatment, end-tidal isoflurane (ETISO) was maintained at 1.7% and xylazine was administered at the end of anesthesia. In the MCRI treatment, ETISO was maintained at 1.4% and medetomidine was infused throughout anesthesia. Data were analysed using an analysis of variance for repeated measures and multiple comparison tests ($p<0.05$). Heart rate was lower but mean arterial pressure was greater from 20- 40 minutes with MCRI treatment. Respiratory rate and rectal temperature were greater with MCRI treatment. Bispectral index was lower with MCRI treatment from 80-150 minutes, and electromyogram data was lower with MCRI treatment from 30-150 minutes. In isoflurane-anesthetised horses, premedication and administration of medetomidine as a CRI resulted in decreased heart rate, improved arterial pressure from 20 through 40 minutes after

induction of anesthesia, and better preserved body temperature when compared to xylazine bolus. Greater depth of anesthesia and muscle relaxation was seen, despite the lower isoflurane concentration.

2.2 INTRODUCTION

Cardiovascular depression, hypoxemia, and hypoventilation are common problems associated with inhalant anesthesia in horses. Cardiac output, stroke volume, and left ventricular work all decrease during anesthesia and dorsal recumbency in horses (1). Positioning and anesthetic drugs contribute to impaired oxygen exchange (2), increased mismatch between ventilation and perfusion (V/Q) (3-6) and atelectasis (7). Hypoventilation is common if horses are not mechanically ventilated, due in part to positioning, and in part to the decrease in minute ventilation caused by inhalant anesthetics (6, 8, 9). Mild to moderate hypercapnia (defined as partial pressure of carbon dioxide ($PaCO_2$) > 50-65 mm Hg) may improve cardiac output through sympathetic stimulation. However, severe hypercapnia and respiratory acidosis decrease cardiac contractility and increase the frequency of arrhythmias (6, 10).

Alpha$_2$ agonists are commonly used in conjunction with inhalant anesthesia in horses. Historically, xylazine has been used for premedication and is often administered again prior to recovery, to smooth these transition times.

Medetomidine, a more selective alpha$_2$ agonist, has recently been investigated in association with inhalant anesthesia in horses (11). The short half-life of medetomidine in horses (51 minutes) (12) as well as its selectivity and potency (13), make it suitable

for administration as a CRI to reduce the concentration of isoflurane required to maintain anesthesia in horses (11, 14). Medetomidine CRI at a rate of 0.0035 mg/kg/hr decreases the MAC of isoflurane by 20% (14). The addition of medetomidine CRI to isoflurane anesthesia may result in improved cardiopulmonary stability, optimal analgesia and muscle relaxation, and decreased chance of patient movement in response to surgical stimulation (11, 15). The sedative effects of medetomidine at 0.004 mg/kg are comparable to those of xylazine at 0.4 mg/kg (16).

Traditionally, depth of anesthesia in horses has been evaluated using eye signs such as spontaneous palpebral reflex and nystagmus, and patient movement. It has been shown, however, that administration of medetomidine CRI permits more brisk eye reflexes to be preserved while horses are maintained at a 20-30% lower inhalant anesthetic concentration, and only nystagmus or movement are reliable indicators of insufficient depth of anesthesia when medetomidine CRI is used (11, 14, 17).

Bispectral index (BIS) is a number ranging from 0 (isoelectric electroencephalograph, EEG) to 100 (awake, alert EEG) (18, 19). While BIS has not been validated in the horse, there has been considerable recent investigation into its use. Thus far, it has not been seen as a reliable indicator of background anesthetic depth, but it has been useful in predicting awakening (20, 21). In humans, BIS reflects central nervous system depression, with a BIS value of 40-50 representing a surgical plane of anesthesia. Electromyogram (EMG) activity is also monitored by the BIS, by subdermal needles serving as electrodes. EMG signals are between 30-300 Hertz, which can potentially

overlap the BIS power spectra (22). Significant EMG activity can falsely elevate BIS readings through this band overlap.

This prospective, crossover study compares the effects of administration of a single xylazine bolus at the end of inhalant anesthesia to medetomidine CRI administration throughout anesthesia, without the confounding effects of surgery or the variability inherent in clinical trials. To the authors' knowledge, this is the first study to compare medetomidine CRI to the more conventional practice of administering xylazine prior to recovery in isoflurane-anesthetised horses. We hypothesize that medetomidine CRI would be associated with better cardiovascular performance, improved ventilation, and a more stable plane of anesthesia when compared to xylazine bolus administration.

2.3 MATERIALS AND METHODS

2.3.1 Animals

This study was approved by the University Animal Care Committee, and was conducted in compliance with the published standards of animal care. Ten Standardbred horses (five mares, four geldings, and one stallion) were studied. Horses ranged in age from 3 to 7 years (Mean 3.8 years ± 1.3 years) and weighed 400 to 560 kg (Mean 450.3 ± 47.1 kg). Prior to inclusion in the study, horses were determined to be healthy on the basis of a physical examination, complete blood count, serum biochemistry, and arterial blood gas analysis. Food but not water was withheld for 12 hours prior to anesthesia.

2.3.2 Experimental Design

Horses were randomly assigned to one of two treatment protocols at admission. Each horse received both protocols, with a minimum of 10 days between trials. On the morning of each treatment, baseline heart rate (HR) was recorded. A 14-gauge catheter (Becton Dickinson and Co., NJ) was placed in the left jugular vein. Horses were premedicated with either xylazine hydrochloride (Bayer HealthCare, Bayer, Inc., Toronto, Canada) 0.7 mg/kg intravenously (IV), or medetomidine hydrochloride (Orion Pharma, Espoo, Finland) 0.007 mg/kg IV. Ten minutes later, anesthesia was induced with diazepam (Sandoz, Princeton, NJ) 0.05 mg/kg IV and ketamine hydrochloride (Bimeda-MTC Animal Health Inc.) 2.5 mg/kg IV. Horses were orotracheally intubated with a 26 mm internal diameter cuffed endotracheal tube (Smiths Medical, Waukesha, WI) and positioned in dorsal recumbency on a padded surgery table. Horses were connected to a large animal anesthetic circuit (Surgivet Anesco LDS 3000 Anaesthesia Machine) which provided isoflurane (USP Pharmaceutical Partners of Canada, Inc.) in oxygen. Connection to the breathing circuit was called time zero. Horses breathed spontaneously throughout each treatment. Oxygen flow was 10 L/minute for the first 10 minutes, and 6 L/minute thereafter (23). The isoflurane vaporizer was set to maintain an end-tidal concentration of 1.7% (1.2 minimum alveolar concentration (MAC) isoflurane) during XYL treatment, and 1.4% (1.0 MAC isoflurane) during MCRI treatment. During MCRI treatment horses were given medetomidine at a rate of 0.005 mg/kg/hr, using a syringe pump (Smiths Medical MD Inc., St. Paul, MN). The infusion was started 10 minutes after induction, and stopped when isoflurane was

discontinued. Horses were given an isotonic crystalloid solution (lactated Ringer's injection USP 5000ml, Mississauga, ON) at a rate of 10 ml/kg/hr throughout each treatment. Horses that moved during the maintenance phase of anesthesia were given ketamine (0.5 mg/kg, IV). Anesthesia was maintained for 150 minutes. At the end of XYL treatment, horses were given xylazine (0.2 mg/kg, IV) immediately before disconnection from the anesthetic machine. During recovery, oxygen was supplemented at 15 L/minute by insufflation into the endotracheal tube until extubation, then nasally until the horse rolled into sternal recumbency. Endotracheal tubes were removed after horses regained their swallowing reflex. Horses were allowed to recover without assistance.

2.3.3 Monitoring

A 1.1 x 48 mm 20-gauge catheter (Becton Dickinson and Co., NJ) was placed in the facial artery after the horse was connected to the anesthetic machine. A disposable pressure transducer (Edwards Lifesciences PX272 Pressure Monitoring Kit with TruWave Disposable Pressure transducer) was zeroed at the level of the point of the shoulder, for measurement of invasive blood pressure. Arterial blood gas samples were collected anerobically using a vented syringe (Vital Signs Colorado, Inc., Englewood, CO). Heart rate was measured by thoracic auscultation for one minute, and respiratory rate (RR) was manually counted for one minute. Continuous monitoring of electrocardiogram (ECG) and invasive blood pressure was done using a calibrated patient monitor (GE Medical Systems, Milwaukee, WI). Continuous monitoring of

inspired and expired isoflurane and end-tidal carbon dioxide was done using a calibrated airway gas monitor (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). Subdermal electrodes were placed for BIS monitoring (Aspect Medical Systems, Inc., Leiden, The Netherlands) in each horse, using a previously described method (20, 21).

All physiologic parameters, except rectal temperature, were continuously monitored, and recorded every ten minutes throughout each treatment. Rectal temperature was measured (AMG Medical Inc., Montreal, QC) and recorded every 10 minutes. Ten minutes after discontinuation of inhalant anesthesia, HR, RR, and arterial blood pressure were measured and recorded in the recovery stall.

2.3.4 Blood Gas Analysis

Blood was collected for immediate analysis of arterial blood gas parameters (ITC, Edison, NJ) at times 30, 60, 90, and 150, and 10 minutes after discontinuation of inhalant anesthesia while the horse was recovering in lateral recumbency.

2.3.5 Statistical Analysis

Data analysis was performed using a commercially available software package (Sigma Stat 3.0, SPSS® Science software, Chicago, IL). Continuous cardiopulmonary data are reported as means ± standard deviation (SD). Binomial data for eye reflexes, movement, and ketamine administration are reported as percents. Continuous data were analysed using a two-way repeated measures analysis of variance (ANOVA).

When a significant treatment–time interaction was found, Holm-Sidak multiple comparison tests were used to compare differences between treatments over time. Significant p-values for treatment–time interactions are reported for continuous data. Binomial data were compared using McNemar's test. Ketamine administration was compared using a paired t-test. A post hoc analysis compared BIS values during treatments with and without horse movement using a two-way repeated measures ANOVA with Holm-Sidak multiple comparison tests. Significance for all tests was set at a p-value of ≤ 0.05.

2.4 RESULTS

Cardiovascular data were measured at 10 minute intervals throughout each treatment, and are summarised in Table 1. Mean baseline HR values did not differ between treatments. Heart rate was significantly lower ($p< 0.001$) with MCRI treatment compared with XYL treatment from 40 minutes through 150 minutes. Arterial pressure decreased immediately after induction of anesthesia with both treatments; however, this decrease was less profound with MCRI treatment. Values for systolic arterial pressure (SAP) and mean arterial pressure (MAP) were significantly ($p<0.001$ for both) greater with MCRI treatment from 20 minutes through 40 minutes. Values for diastolic arterial pressure (DAP) were significantly ($p<0.001$) greater with MCRI treatment from induction through 30 minutes. Arterial pressures increased with both treatments from 60 minutes through 10 minutes after disconnection from the breathing circuit (10POST); however this increase was less profound with MCRI treatment. Values for

SAP and MAP were significantly ($p<0.001$) lower with MCRI treatment from 70 minutes through 150 minutes, and 10POST. Values for DAP were significantly ($p<0.001$) lower with MCRI treatment from 80 minutes through 150 minutes, and 10POST.

Respiratory rate and rectal temperature were measured at 10 minute intervals, and are summarised in Table 2. Respiratory rate did not change over time with XYL treatment, while it increased with MCRI treatment from 60 minutes through 140 minutes. Respiratory rate was significantly ($p<0.001$) greater with MCRI treatment at 60, 70, 100, and 140 minutes. Rectal temperature decreased over time in both treatments, and was significantly ($p<0.001$) greater with MCRI treatment from 90 minutes through 150 minutes. Arterial pH, partial pressure of oxygen (PaO_2), and $PaCO_2$ were not significantly different between treatments (Table 2).

Bispectral index, EMG data, and eye reflex data were recorded at 10 minute intervals and are summarised in Table 3. Values for BIS were significantly ($p=0.002$) lower with MCRI treatment from 80 minutes through 150 minutes. Values for EMG were significantly ($p<0.001$) lower with MCRI treatment from 30 through150 minutes.

There was no significant difference between treatments for spontaneous palpebral reflex from zero to 30 minutes, although horses tended to exhibit more spontaneous palpebral reflex responses with MCRI treatment (Table 3). From 30 through 150 minutes, significantly ($p=0.001$) more horses exhibited a spontaneous palpebral reflex with MCRI treatment. Tearing, nystagmus, movement, and supplemental ketamine administration did not differ between treatments. Horses tended to show more tearing

with XYL treatment during the first 30 minutes of anesthesia, and with MCRI treatment from 40 minutes on. Nystagmus tended to be seen more often with XYL treatment. With MCRI treatment, two horses moved, and the number of supplemental ketamine doses given to each horse ranged from zero to five. With XYL treatment, six horses moved, and the number of supplemental ketamine doses given to each horse ranged from zero to five.

A post hoc analysis showed that BIS values during treatments where horses moved were significantly ($p=0.003$) greater than during treatments where horses did not move at every time point from 10 through 150 minutes except 90 minutes (Table 4).

2.5 DISCUSSION

Reflex bradycardia is an expected response to IV administration of alpha$_2$ agonists, due to the initial phase of hypertension produced by these agents. Heart rate was lower with MCRI treatment compared with XYL treatment, but this decrease respresented only a 10% change from baseline in these horses. While all alpha$_2$ agonists produce bradycardia, the lower heart rates seen with MCRI treatment is likely a result of the greater total cumulative dose of medetomidine compared with xylazine.

After intravenous administration, alpha$_2$ agonists cause an initial period of hypertension and bradycardia, followed by a longer period of hypotension and reduced cardiac output (24). These changes are due to inhibition of central nervous system sympathetic tone and norepinephrine release, increased vagal tone, and increased acetylcholine release from cardiac parasympathetic nerves (25). Arterial pressure was

better maintained with MCRI treatment in the period shortly after induction compared with XYL treatment. This is an important finding, as hypotension early in anesthesia may be a contributing factor in post anesthetic morbidity and mortality (6, 26, 27). Mean MAP values with MCRI treatment were not less than 72 mmHg at any time point, while those with XYL treatment were below the clinically accepted value of 70 mmHg (28) from 20 minutes to 50 minutes after induction of anesthesia.

Mature horses are particularly vulnerable to respiratory depression during inhalant anesthesia (4, 5, 26, 29). There is considerable variation in the respiratory response to administration of alpha$_2$ agonists in anesthetised horses (24). Respiratory rate was greater with MCRI treatment compared with XYL treatment late in anesthesia. It may be that the lower concentration of isoflurane with MCRI treatment allowed horses to respond to the increased dead space ventilation that accompanies anesthesia, while horses were unable to respond with XYL treatment.

Partial pressure of carbon dioxide was moderately high with both treatments. This was an expected finding in spontaneously breathing, dorsally recumbent horses, and contributes to sympathetic stimulation and an improvement in cardiac output (6, 10) and blood pressure (5).

All horses had low values for PaO_2 with both treatments, which is an expected finding in spontaneously breathing, dorsally recumbent horses (2). To ensure normal lung function in each horse, a physical examination was performed and an arterial blood sample was obtained prior to inclusion in the study. All horses had PaO_2 values above

88.8 mm Hg while breathing room air (30). The PaO_2 values during anesthesia suggest that despite their relatively small body size, these horses all developed atelectic areas of lung during the early maintenance phase of anesthesia, resulting in poor oxygenation. Horses and ponies develop atelectic areas in dependent lung regions within 20 minutes of being positioned in dorsal recumbency, and impairment in gas exchange is proportional to the atelectasis (2).

Core body temperature steadily decreases over time in anesthetised adult horses (31). Temperature was measured rectally in this study, which accurately reflects core temperature in anesthetised adult horses (32). Rectal temperature was better maintained with MCRI treatment compared with XYL treatment; this may reflect less vasodilation with MCRI treatment due to the lower isoflurane concentration.

Although it remains to be validated in horses, this study found BIS to be a predictor of background anesthetic depth and awakening. Mean BIS values were lower with MCRI treatment, with significant differences seen late in anesthesia. A post hoc analysis showed that mean BIS values were greater during treatments with movement compared with treatments with no movement. The higher BIS values correlate well with traditional signs of inadequate depth such as movement. Perhaps with the changing levels of stimulation found in clinical surgical cases, BIS would not be as valuable a predictor, but in horses not subjected to surgical stimulation BIS provided reliable information regarding depth of anesthesia. EMG values were lower with MCRI

treatment. This increase in muscle relaxation is an expected result, and is consistent with the data from chronically instrumented cats given dexmedetomidine (33).

A spontaneous palpebral reflex, generally an indicator of a light plane of anesthesia, was exhibited significantly more times with MCRI treatment during the maintenance phase of anesthesia. While a spontaneous palpebral index is a reliable indicator of a light plane of anesthesia with inhalant anesthesia, when medetomidine is administered as a CRI during inhalant anesthesia only nystagmus or movement are reliable indicators of insufficient anesthetic depth (17). No significant difference was seen between treatments for nystagmus or ketamine administration, indicating that the horses were at a similar plane of anesthesia during both treatments.

We intended to maintain the ETISO at 1.3% (0.9 MAC isoflurane) during MCRI treatment, but the mean ETISO for these treatments was 1.4% (1.0 MAC isoflurane). This resulted in an increased depth of anesthesia with MCRI treatment, and may be a confounding factor in the study presented here. We also used a methane – sensitive airway gas analyser. At the oxygen flow rates used in this study, ETISO concentrations are approximately 0.3% lower than those reported during the maintenance phase of anesthesia (23). However, this measurement error is the same for both trials, and does not affect the analysis of the data.

In horses anesthetised with isoflurane, premedication with and administration of medetomidine as a CRI resulted in better maintenance of arterial pressure in the period immediately following induction of anesthesia compared to xylazine bolus

administration. Despite more active eye signs, horses had lower BIS and EMG values with MCRI treatment. Further work in carefully controlled clinical trials is needed to fully evaluate medetomidine CRI during inhalant anesthesia in equine patients undergoing surgery.

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Table 1. Summary of cardiovascular parameters in horses given xylazine or medetomidine and anesthetised with isoflurane

Variable	Treatment				Time				
		20	**30**	**40**	**50**	**60**	**90**	**150**	**10POST**
HR	Xylazine[a]	38(4)	39(5)	41(3)	42(4)	41(4)	38(5)	42(5)	36(7)
	Medetomidine[a]	34(4)	35(4)	35(6)*	35(5)*	32(4)*	32(4)*	32(5)*	35(6)
SAP	Xylazine	83(9)	78(12)	83(14)	92(17)	104(14)	116(10)	122(14)	141(20)
	Medetomidine	93(12)*	92(11)*	94(12)*	96(12)	98(13)	100(11)*	101(8)*	127(12)*
DAP	Xylazine	49(8)	46(10)	52(14)	62(17)	71(16)	84(10)	94(12)	114(15)
	Medetomidine	61(9)*	59(10)*	59(10)	59(12)	64(15)	76(11)*	78(10)*	104(8)*
MAP	Xylazine	62(9)	58(11)	64(14)	74(17)	84(15)	97(10)	106(11)	123(16)
	Medetomidine	74(11)*	74(11)*	72(11)*	72(14)	76(15)	87(10)*	87(9)*	113(8)*

Variables expressed as Mean (SD)
HR = heart rate, expressed in beats per minute
[a] Mean (SD) baseline HR: XYL trial = 33(5), MCRI trial = 33(7)
SAP = systolic arterial pressure, DAP = diastolic arterial pressure, MAP = mean arterial pressure, expressed in mm Hg
Time expressed in minutes after connection to breathing circuit
10POST = 10 minutes after disconnection from breathing circuit
* Significantly ($p \leq 0.05$) different from xylazine

Table 2. Summary of respiratory parameters in horses given xylazine or medetomidine and anesthetised with isoflurane

Variable	Treatment				Time				
		20	30	40	50	60	90	150	10POST
RR	Xylazine	5(2)	6(3)	5(2)	6(3)	5(2)	5(2)	6(3)	10(3)
	Medetomidine	6(3)	6(4)	6(2)	7(5)	8(7)*	8(5)	8(4)	12(3)
$ETCO_2$	Xylazine	49(5)	50(5)	51(4)	50(4)	50(4)	47(5)	44(7)	
	Medetomidine	56(7)*	54(4)	53(5)	53(5)	52(7)	52(7)*	50(8)*	
pH	Xylazine		7.324(0.037)			7.332(0.041)	7.324(0.050)	7.341(0.039)	7.425(0.056)
	Medetomidine		7.320(0.054)			7.332(0.030)	7.324(0.044)	7.344(0.038)	7.441(0.040)
$PaCO_2$	Xylazine		65.8(8)			67.8(8.7)	67.8(11.5)	65.6(9)	52.1(11.5)
	Medetomidine		68.9(12.3)			68.1(7.7)	71.5(10.8)	70.1(10.5)	53.2(6.4)
PaO_2	Xylazine		126.3(53.8)			108.6(40.4)	75.5(19.7)	62.6(14.9)	53.2(11.2)
	Medetomidine		127.1(59.5)			116.9(41.8)	80.2(19.8)	61.8(13.8)	54.3(8.1)
TEMP(°C)	Xylazine	37.3(0.3)	36.9(0.2)	36.7(0.4)	36.7(0.4)	36.3(0.5)	36(0.6)	35.6(0.7)	
	Medetomidine	37.5(0.3)	37.1(0.5)	36.9(0.5)	36.9(0.4)	36.7(0.6)	36.7(0.5)*	36.4(0.6)*	

Variables expressed as Mean (SD)
RR = respiratory rate, expressed in breaths per minute
$ETCO_2$ = end-tidal carbon dioxide; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen
$ETCO_2$, $PaCO_2$, PaO_2 expressed in mm Hg
TEMP = rectal temperature
Time expressed in minutes after connection to breathing circuit
* Significantly ($p \leq 0.05$) different from xylazine

Table 3. Summary of depth of anesthesia in horses given xylazine or medetomidine and anesthetised with isoflurane

Variable	Treatment				Time			
		20	**30**	**40**	**50**	**60**	**90**	**150**
BIS	Xylazine	54(7)	52(11)	53(12)	53(10)	54(9)	53(6)	55(7)
	Medetomidine	48(6)	49(8)	49(9)	49(11)	49(11)	45(9)*	45(11)*
EMG	Xylazine	36(2)	37(2)	40(7)	40(3)	40(3)	39(3)	39(4)
	Medetomidine	34(2)	34(3)*	33(3)*	33(2)*	33(2)*	32(2)*	31(3)*
SPR	Xylazine	30	10	20	10	10	0	0
	Medetomidine	40	30*	20*	20*	30*	10*	10*
Tearing	Xylazine	20	10	0	0	0	0	0
	Medetomidine	10	0	10	0	10	10	0
Nystagmus	Xylazine	0	0	0	0	0	10	20
	Medetomidine	0	0	0	0	0	0	10
Movement	Xylazine	20	10	20	10	10	10	0
	Medetomidine	10	0	10	0	0	0	0

BIS = bispectral index
EMG = electromyogram
BIS, EMG expressed as Mean (SD)
SPR = spontaneous palpebral reflex
SPR, tearing, nystagmus, movement expressed as % horses exhibiting sign
Time expressed in minutes after connection to breathing circuit
* Significantly ($p \leq 0.05$) different from xylazine

Table 4. Bispectral index values during trials with and without movement

Time	BIS, Movement	BIS, No Movement
20	53(6)*	45(4)
30	57(9)*	46(7)
40	59(8)*	46(6)
50	58(10)*	47(8)
60	59(8)*	47(9)
90	53(6)	47(10)
150	56(8)*	46(10)

BIS = bispectral index, expressed as Mean (SD)

Time expressed in minutes after connection to breathing circuit

* Significantly ($p \leq 0.05$) different from trials with no movement

3. COMPARISON OF THE EFFECTS OF XYLAZINE BOLUS VERSUS MEDETOMIDINE CONSTANT RATE INFUSION ON THE STRESS RESPONSE, URINE PRODUCTION, AND RECOVERY CHARACTERISTICS IN HORSES ANESTHETISED WITH ISOFLURANE

3.1 ABSTRACT

The effects of xylazine bolus versus medetomidine constant rate infusion (MCRI) on cortisol and glucose concentrations, urine production, and recovery characteristics in dorsally recumbent spontaneously breathing isoflurane-anesthetised horses were compared. In a prospective, randomised crossover manner, ten healthy adult Standardbred horses were studied. Horses were premedicated with xylazine or medetomidine intravenously (IV). Anesthesia was induced with diazepam and ketamine and maintained with isoflurane for 150 minutes. In the xylazine (XYL) treatment, end-tidal isoflurane (ETISO) was maintained at 1.7% and xylazine was administered at the end of anesthesia. In the MCRI treatment, ETISO was maintained at 1.4% and medetomidine was infused throughout anesthesia. Serum cortisol and glucose were measured before, during, and after anesthesia. Urine specific gravity and volume were measured during anesthesia. Unassisted recoveries were digitally recorded for later evaluation by blinded observers. Data were analysed using a paired t-test, a paired signed rank test, or analysis of variance (ANOVA) for repeated measures and multiple comparison tests ($p \leq 0.05$). Cortisol was lower and glucose was higher with MCRI compared to XYL treatment. Time to sternal recumbency was longer with MCRI treatment but no difference was seen for times to extubation, first movement, or

standing. Objective and visual analog recovery scores were significantly better with MCRI compared to XYL treatment. In horses anesthetised with isoflurane, premedication and administration of medetomidine as a CRI resulted in decreased cortisol levels, increased glucose levels, and superior recovery characteristics when compared to conventional therapy with xylazine.

3.2 INTRODUCTION

The stress response activates the sympathetic nervous system and the adrenocortical system, resulting in increased levels of the catecholamines epinephrine and norepinephrine, as well as serum cortisol and glucose (1). Cortisol increases tissue metabolism while decreasing glucose use by cells, and the hyperglycemic effect is further exacerbated by decreased insulin levels. While the stress response may promote survival in the short term, stress in the context of a veterinary hospital setting is maladaptive. In equine patients, more so than other animals, the stress response during anesthesia and recovery may constitute a significant source of morbidity.

Inhalant anesthesia, even without surgery, has been shown to induce a stress response in the horse, characterized by increased serum cortisol (2). Surgical procedures increase cortisol values above those seen with anesthesia alone, and the increase is proportional to the invasiveness of the procedure (3). In contrast, total intravenous anesthesia in horses does not lead to an increase in serum cortisol even when surgical procedures are performed (4, 5). Alpha$_2$ agonists are a routine component of

intravenous anesthetic protocols, and this group of drugs decreases the stress response through their inhibition of sympathoadrenal output (6).

Alpha$_2$ agonists also cause an increase in urine volume and a decrease in urine specific gravity, through interference with the action of vasopressin on the renal tubules and collecting ducts (7, 8). Clinically, increased urine volume may impact the quality of anesthetic recovery as horses may attempt to stand too early in the recovery period due to discomfort from bladder distension.

The anesthetic recovery phase is a particularly dangerous time for horses, with approximately 25% of anesthesia–related mortality occurring from fractures during this period (9). Horses by nature are 'fight or flight' creatures. This predisposes them to attempts to flee during the excitement phase, which is invariably accompanied by ataxia and muscle weakness (10, 11). As a result, many methods have been used in an attempt to reduce the incidence of catastrophic events during recovery. Assisted recoveries are one approach and may include the use of head and tail ropes, soft padding, slings, air cushions, or water systems.

Sedation in the early recovery period has also been assessed as a method of improving the outcome of inhalant anesthesia by promoting a longer, smoother recovery (3, 10, 12-14). Alpha$_2$ agonists are the drugs most commonly employed for this purpose. Historically, xylazine has been used for premedication prior to inhalant anesthesia and is often given as a bolus injection prior to recovery.

Medetomidine, a more selective alpha$_2$ agonist, has recently been investigated in association with inhalant anesthesia in horses (15). The short half-life of medetomidine in horses (51 minutes) (16), as well as its selectivity and potency (17), make it suitable for administration as a CRI to reduce the concentration of isoflurane required to maintain anesthesia in horses (15, 18). Medetomidine CRI at a rate of 0.0035 mg/kg/hr has been shown to decrease the minimum alveolar concentration (MAC) of isoflurane by 20% (18). The addition of MCRI to isoflurane anesthesia may result in improved cardiopulmonary stability, optimal analgesia and muscle relaxation, and improved recoveries (15, 19). The sedative effects of medetomidine at 0.004 mg/kg are comparable to xylazine at 0.4 mg/kg (20).

Equine anesthetic recoveries are difficult to evaluate objectively. Multiple systems to score recoveries have been proposed, and a universally accepted and validated recovery scoring system does not exist (21). Behavioral recovery scores (BRS) that include timed end points, as well as behavioral and strength assessments have been used in an attempt to standardise recovery scores using a comprehensive approach (14). Visual analogue scores (VAS) are simpler to use, involving a descriptive analog scale to subjectively evaluate overall recovery (21, 22). Both of these systems can lead to disparate results between observers, depending on experience and interpretation (23). Mean attempt interval (MAI) is a novel index for assessing equine anesthetic recoveries and was used for the first time in the current study. This parameter was calculated by dividing the time between extubation and standing (in minutes) by the number of attempts to stand. Thus, the slow smooth recoveries were distinguished

from the fast scrambling recoveries or those recoveries that were prolonged due to weakness. Time from extubation to standing was chosen because it represents a hard time point, making the MAI more objective. Other time points such as time of disconnection from the breathing circuit may be more variable, and therefore less standardised between horses.

This prospective crossover study compares the effects of administration of a single xylazine bolus at the end of inhalant anesthesia to medetomidine CRI administration throughout anesthesia, without the confounding effects of surgery or the variability inherent in clinical trials. To the authors' knowledge, this is the first study to compare medetomidine CRI to the more conventional practice of administering xylazine prior to recovery in isoflurane–anesthetised horses. We hypothesize that medetomidine CRI would be associated with lower cortisol levels, higher glucose levels, increased urine production, and superior recoveries when compared to xylazine bolus administration.

3.3 MATERIALS AND METHODS

3.3.1 Animals

This study was approved by the University Animal Care Committee, and was conducted in compliance with the published standards of animal care. Ten Standardbred horses (five mares, four geldings, and one stallion) were studied. Horses ranged in age from 3 to 7 years (Mean 3.8 years ± 1.3 years) and weighed 400 to 560 kg (Mean 450.3 kg ± 47.1 kg). Prior to inclusion in the study, horses were determined to be healthy on the

basis of a physical exam, complete blood count, serum biochemistry, and arterial blood gas analysis. Food but not water was withheld for 12 hours prior to anesthesia.

3.3.2 Experimental Design

Horses were randomly assigned to one of two treatment protocols at admission. Each horse received both protocols, with a minimum of 10 days between treatments. On the morning of each treatment, horses had blood drawn for analysis of serum glucose and cortisol. A 14 gauge catheter (Becton Dickinson and Co., NJ) was aseptically placed in the left jugular vein. Horses were premedicated with either xylazine hydrochloride 0.7 mg/kg IV (Bayer HealthCare, Bayer, Inc., Toronto, Canada), or medetomidine hydrochloride 0.007 mg/kg IV (Orion Pharma Espoo, Finland). Anesthesia was induced with diazepam USP 0.05 mg/kg IV (Sandoz, Princeton, NJ) and ketamine hydrochloride USP 2.5 mg/kg IV (Bimeda – MTC Animal Health Inc.). Horses were orotracheally intubated with a 26 mm internal diameter cuffed endotracheal tube (Smiths Medical, Waukesha, WI) and positioned in dorsal recumbency on a padded surgery table. Horses were connected to a large animal anesthetic circuit (Surgivet Anesco LDS 3000 Anesthesia Machine) which provided isoflurane (USP Pharmaceutical Partners of Canada Inc.) in oxygen. Connection to the breathing circuit was called time zero. Horses breathed spontaneously throughout each treatment. Oxygen flow was 10 L/minute for the first 10 minutes, and 6 L/minute thereafter, for each treatment. The isoflurane vaporiser was set to maintain an end-tidal concentration of 1.7% (1.2 MAC isoflurane) in the XYL treatment, and 1.4% (1.0 MAC isoflurane) in the MCRI treatment.

Horses in the MCRI treatment were given medetomidine at a rate of 0.005 mg/kg/hr, using a syringe pump (Medfusion 3500, Smiths Medical MD Inc., St. Paul, MN). The infusion was started at time 10 (10 minutes after induction of anesthesia), and stopped at the time isoflurane was discontinued. Horses were given an isotonic crystalloid solution (lactated Ringer's injection USP 5000ml, Mississauga, ON) at a rate of 10 ml/kg/hr throughout each treatment. A urinary catheter (20 FG x 54", CDMV, Ste. Hyacinthe, QC) was placed at the beginning of anesthesia, and the urinary bladder was emptied. Urine was collected in a graduated cylinder (Nalgene 2000ml) for measurement of urine volume and specific gravity throughout anesthesia. The urinary catheter was removed immediately prior to transport to the recovery stall. Horses that moved during the maintenance phase of anesthesia were given ketamine (0.5 mg/kg, IV). Anesthesia was maintained for 150 minutes. At the end of the XYL treatment, horses were administered xylazine (0.2 mg/kg, IV) immediately before disconnection from the anesthetic machine. Horses were recovered in the same 3.4 m x 3.6 m dimly lit recovery stall. During recovery, oxygen was supplemented at 15 L/minute by insufflation into the endotracheal tube until extubation, then nasally until horses rolled into sternal recumbency. Endotracheal tubes were removed after horses regained their swallowing reflex. Horses were allowed to recover without assistance. Recoveries were monitored using a high resolution low light camera (Sanyo VCC-6584 colour digital) and recorded digitally (Sony DVD recorder RDR-HX780).

3.3.3 Data Collection

Blood was drawn early in the morning of each treatment for analysis of serum glucose (Roche Cobas C501, hexokinase method) and cortisol (Siemens Immulite, chemiluminescence immunoassay). Blood was collected for measurement of serum glucose and cortisol at 30, 60, 90, and 150 minutes, and also ten minutes after disconnection from inhalant anesthesia and 30 minutes after the horses stood in the recovery stall. The urinary bladder was emptied at the time of urinary catheter placement, and urine volume and specific gravity were measured at 30, 60, 90, and 150 minutes. Urine volume was measured using a graduated cylinder (Nalgene 2000ml). Urine specific gravity was measured using a temperature compensated hand-held refractometer (Reichert Inc, Depew, NY). Recoveries were continuously monitored, and later evaluated by two blinded observers experienced in equine recoveries. Three recovery scoring systems were used. With MAI, a larger number indicates a slower recovery with fewer attempts to stand and defines a superior recovery. Using VAS, 0 was defined as the worst recovery possible and 10 the best recovery possible. With BRS, a total score of 11 represents the best recovery possible while a score of 100 represents the worst recovery possible. Times from the end of anesthesia (disconnection from the breathing circuit) to first movement, extubation, sternal, and standing were also recorded.

3.3.4 Statistical analysis

Data analysis was performed using commercially available software packages (Sigma Stat 3.0 SPSS® Science software, Chicago, IL; Minitab, Inc., State College, PA). Serum cortisol and glucose and urine volume and specific gravity were analysed using a two-way repeated measures analysis of variance. When a significant treatment–time interaction was found, Holm-Sidak multiple comparison tests were used to compare differences between treatments over time. Significant p-values for treatment–time interactions are reported. Early morning baseline serum cortisol and glucose values were compared using a paired t-test. Recovery times, MAI, and VAS were also analysed using a paired t-test. The BRS results were analysed using a Wilcoxon paired signed rank test. Recovery scores from both observers were averaged before the data was analysed. Significance for all tests was set at a p-value of ≤ 0.05.

3.4 RESULTS

Serum cortisol levels significantly increased over time with both treatments; however, this increase was less profound with MCRI treatment. Cortisol levels were significantly ($p<0.001$) lower at times 60, 90, 150, 10 minutes post anesthesia, and 30 minutes after horses stood in MCRI treatment compared to XYL treatment (Table 5). The trial order also had a significant effect on baseline cortisol levels. When data from both treatments were pooled, cortisol was significantly ($p<0.001$) lower at baseline in the second trial compared to the first (Table 6).

Serum glucose values were significantly (p=0.009) higher with MCRI treatment at 150 minutes, and 10 minutes post anesthesia compared to XYL treatment (Table 5). The trial order did not have a significant effect on baseline glucose levels.

While urine volume tended to be higher and urine specific gravity tended to be lower with MCRI treatment compared to XYL treatment, there was considerable variation among horses and this difference was not statistically significant (Table 7).

Mean time to sternal recumbency was significantly (p=0.019) longer with MCRI treatment compared to XYL treatment (Table 8). Times to extubation, first movement, and standing, and number of attempts to attain sternal and standing were not statistically different between treatments (data shown in Tables 8 and 9). While both observers reported higher mean attempts to stand with XYL treatment compared to MCRI treatment, this difference was not significant (Table 9).

The MAI and VAS were significantly (p=0.025 and p=0.047, respectively) better with MCRI treatment compared to XYL treatment (Table 10). While the BRS tended to be better with MCRI treatment compared to XYL treatment, this was not significant. Recovery quality was better with MCRI treatment in 8 of 10, 7 of 10, and 6 of 10 horses when assessed using MAI, VAS, and BRS, respectively. The trial order did not have a significant effect on recovery quality.

3.5 DISCUSSION

Alpha$_2$ agonists are known to inhibit the release of cortisol, a classic marker of the stress response. While the mechanism of this effect is not completely understood, it may be due to a specific alpha$_2$ receptor response, an indirect effect of the sedation and analgesia mediated by alpha$_2$ agonists, or other receptor responses (24, 25). In the current study, serum cortisol levels were lower with MCRI treatment compared with XYL treatment, indicating that MCRI treatment blunted the stress response associated with inhalant anesthesia compared with XYL treatment. As the total cumulative dose of medetomidine was greater than xylazine, it is not surprising that the impact on cortisol was greater.

Baseline serum cortisol levels were greater for Trial 1 (i.e. first) compared to Trial 2 (i.e. second). This suggests that admission to the Veterinary Teaching Hospital (VTH) was associated with a significant stress response that diminished over the ten day hospitalisation period. Though all horses were admitted to the VTH for a minimum of 18 hours prior to their first trial, this finding indicates that 18 hours was not sufficient for complete acclimatisation.

The increases in serum glucose concentrations observed with both XYL and MCRI treatments were presumably a result of alpha$_2$ receptor-mediated inhibition of insulin release from pancreatic beta cells (26-28). While xylazine has been shown to have a greater potential to increase glucose compared with medetomidine after a single bolus injection (24), glucose concentrations were greater with MCRI treatment compared

with XYL treatment in our study. This suggests that the effect on serum glucose is dose-dependent and the higher concentrations observed with MCRI treatment reflected the greater cumulative dose of drug given throughout anesthesia.

Alpha$_2$ agonists result in the production of large amounts of dilute urine (8, 29), through their interference with the action of vasopressin in the renal collecting duct (7). While not significant, urine volume tended to be higher and urine specific gravity tended to be lower with MCRI treatment compared to XYL treatment. Once again, this is not surprising in light of the greater cumulative dose of medetomidine compared with xylazine.

The effects of MCRI and XYL treatment on the duration of recovery can be evaluated by analysing the times to critical end-points (i.e. extubation, first movement, sternal, and standing). Time to sternal recumbency was significantly greater with MCRI treatment compared with XYL treatment, despite the fact that horses were maintained at a lower ETISO concentration with MCRI treatment compared with XYL treatment (1.4% versus 1.7%). While times to other critical end-points (extubation, first movement, and standing) were not statistically significant between treatments, all tended to be greater with MCRI treatment.

Equine recoveries are difficult to evaluate due to the large number of factors involved and the subjective nature of the evaluations. For these reasons, a universally accepted and validated recovery scoring system does not currently exist. The authors have proposed a novel index for evaluating the quality of equine anesthetic recoveries called

Mean Attempt Interval (MAI). This parameter defines an optimal recovery as one that is slow with minimal attempts to stand. The MAI permits differentiation of an optimal recovery from one that is fast but characterised by scrambling or prolonged due to weakness. Observer agreement was better when MAI was used to assess recovery quality compared to when VAS and BRS were used. This may be due, in part, to the more objective nature of the MAI. In the current study, recovery quality was significantly better with MCRI treatment compared with XYL treatment when assessed using MAI and VAS. However, the BRS was unable to detect a significant difference. Horses subjected to more than one recovery may experience a learning phenomenon (11, 30); this potential confounder was limited by the randomisation of trial order. In the current study, trial order was not found to have a significant effect on the quality of recovery with any of the scoring systems used.

In horses anesthetised with isoflurane, premedication with and administration of medetomidine as a CRI resulted in decreased cortisol levels and improved MAI and VAS recovery scores compared to conventional therapy with xylazine. Further work in carefully controlled clinical trials is needed to fully evaluate medetomidine CRI during inhalant anesthesia in equine patients undergoing surgery.

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Table 5. Cortisol and glucose levels in horses given xylazine or medetomidine and anesthetised with isoflurane

Variable	Treatment				Time			
		Baseline	**30**	**60**	**90**	**150**	**10POST**	**30POST**
Cortisol	Xylazine	123.4 (38.1)	105.6 (22.4)	129.2 (63.9)	233.3 (72.9)	288.9 (51.8)	292 (60.5)	267 (39.2)
	Medetomidine	116.9 (20.7)	95.6 (25.3)	71.6 (11.3)*	115.7(46.7)*	169.3 (37.7)*	164.7(46.1)*	170.4 (44.3)*
Glucose	Xylazine	4.7 (0.3)	6.5 (0.7)	5.8 (0.6)	5.5 (0.9)	5.4 (1.6)	5.9 (1.7)	6.7 (1.2)
	Medetomidine	4.8 (0.4)	6.6 (1.2)	6.4 (1.7)	6.7 (1.9)	7.0 (1.7)*	7.3 (1.6)*	7.5 (0.4)

Variables expressed as Mean (SD)
Cortisol expressed in nmol/L, cortisol normal values 70-180 nmol/L
Glucose expressed in mmol/L, glucose normal values 3.6-5.6 mmol/L
Baseline = AM preanesthetic values
Time expressed in minutes after connection to breathing circuit
10POST = 10 minutes after disconnection from breathing circuit
30POST = 30 minutes after horses successfully stood
*Significantly ($p \leq 0.05$) different from xylazine

Table 6. Baseline cortisol and trial order

Treatment	1st Trial	2nd Trial	P value
Overall	142.9 (22.8)	97 (15)*	<0.001
Xylazine	156.6 (21.1)	90.1 (7.3)	NR
Medetomidine	129.2 (16.0)	104.6 (18.0)	NR

Cortisol (in nmol/L) expressed as Mean (SD)

Overall = mean cortisol value, regardless of treatment

NR = not reported

*Significantly different from 1st trial

Table 7. **Urine volume and specific gravity in horses given xylazine or medetomidine and anesthetised with isoflurane**

Variable	Treatment		Time		
		30	**60**	**90**	**150**
Urine volume	Xylazine	160 (172)	383 (426)	97 (122)	265 (293)
	Medetomidine	302 (203)	1580 (954)	1370 (1239)	1315 (1824)
Urine specific gravity	Xylazine	1.021 (0.013)	1.018 (0.014)	1.017 (0.011)	1.020 (0.011)
	Medetomidine	1.015 (0.013)	1.007 (0.003)	1.006 (0.002)	1.007 (0.003)

Variables expressed as Mean (SD)
Urine volume expressed in ml
Urine specific gravity expressed in g/dl
Time expressed in minutes after connection to breathing circuit

Table 8. **Critical recovery events in horses given xylazine or medetomidine and anesthetised with isoflurane**

Variable	Treatment	Time	P value
Time to Extubation	Xylazine	9 (2)	0.083
	Medetomidine	11 (3)	
Time to 1st Movement	Xylazine	13 (7)	0.110
	Medetomidine	19 (8)	
Time to Sternal	Xylazine	20 (5)	0.019
	Medetomidine	28(11)*	
Time to Standing	Xylazine	25 (10)	0.051
	Medetomidine	33 (12)	

Data expressed as Mean (SD)
Time measured in minutes after disconnection from breathing circuit
*Significantly different from xylazine

Table 9. Attempts to sternal and standing in horses given xylazine or medetomidine and anesthetised with *isoflurane*

Variable	Treatment	Observer 1		Observer 2	
		score	P value	score	P value
Attempts to Sternal	Xylazine	1 (1)	1	1 (1)	1
	Medetomidine	1 (1)		1 (1)	
Attempts to stand	Xylazine	3 (1)	0.168	2 (1)	0.138
	Medetomidine	2 (1)		1 (1)	

Attempts to sternal, standing expressed as number of horses, Mean (SD)

Table 10. Recovery scores in horse given xylazine or medetomidine and anesthetised with isoflurane

Variable	Treatment	Score	P value
MAI	Xylazine	8.6 (5.1)	0.025
	Medetomidine	15.4 (7.0)*	
VAS	Xylazine	7 (2)	0.047
	Medetomidine	8 (1)*	
BRS	Xylazine	33 (28,40)	0.084
	Medetomidine	25 (22,28)	

MAI = mean attempt interval (time in minutes between extubation and standing ÷ number of attempts to stand)

VAS = visual analog score (0= worst, 10 = best recovery)

BRS = behavioural recovery score (11 = best recovery, 100 = worst recovery)

MAI, VAS expressed as Mean (SD)

BRS expressed as Median (25, 75%)

*Significantly ($p \leq 0.05$) different from xylazine

4. GENERAL DISCUSSION

Worldwide, horses are anesthetised with inhalant anesthetics on a daily basis. Despite this, the morbidity and mortality associated with inhalant anesthesia in mature horses is significantly higher than with other species (1, 2, 3). Horses are particularly susceptible to the adverse effects of inhalant anesthesia, and this presumably contributes to the increased incidence of perioperative complications (1, 4-6). Cardiovascular depression, hypoxemia, and hypoventilation are common complications of equine general anesthesia. Anesthesia and dorsal recumbency decrease cardiac output (7), impair oxygen exchange (8), and cause atelectasis (9) in horses. Inhalant anesthesia induces a stress response in horses (10) characterised by increases in serum cortisol and glucose, and this may contribute to poor outcomes. Recovery from inhalant anesthesia is a particularly dangerous time for horses, being associated with significant morbidity and mortality (2). For these reasons, recent attention has focussed on techniques to improve the safety of both the anesthetic and recovery periods for horses.

Alpha$_2$agonists in general, and medetomidine in particular, have been used as adjunctive drugs during inhalant anesthesia (11). Benefits of this class of drug include their sedative, analgesic, muscle relaxant, and anesthetic-sparing properties (12). Medetomidine is a potent and selective (13) alpha$_2$ agonist with a short half-life in the horse (14); these properties make it suitable for administration as a CRI to reduce the concentration of inhalant required to maintain anesthesia (15, 16). To date, no studies

have been conducted that compare medetomidine CRI to the more conventional practice of administering a bolus of xylazine prior to recovery in isoflurane-anesthetised horses.

The research reported here has clarified some of the questions regarding the effects of *medetomidine constant rate infusion (CRI) during isoflurane anesthesia in mature* horses. The research reported in chapter two examined the effect of medetomidine CRI on cardiopulmonary function and depth of anesthesia. The study found that medetomidine CRI results in better maintenance of arterial pressure in the period immediately after induction. As hypotension early in anesthesia may be a contributing factor in post-anesthetic myopathy (1, 5, 17), this result is significant. Heart rate decreases significantly, but is not associated with other arrhythmias. The study reported in chapter two also found that bispectral index (BIS) was lower with medetomidine CRI, despite these horses being maintained at a lower end-tidal isoflurane concentration. Bispectral index is an indicator of central nervous system depression in humans (18, 19), but remains to be validated in the horse. The current research found BIS to be an accurate predictor of background anesthetic depth and awakening. Electromyogram activity also decreases with the improved muscle relaxation provided by medetomidine CRI.

The research reported in chapter three examined the effect of medetomidine CRI on the stress response and recoveries. The study found that medetomidine CRI resulted in lower cortisol levels, and this reflects a blunting of the stress response associated with

inhalant anesthesia in horses. As the stress response may adversely affect recoveries and outcome (20), this is a valuable finding. Glucose is higher with medetomidine CRI, but this is attributed to the greater total cumulative dose of medetomidine versus xylazine, and does not reflect a stress response in this situation. Recoveries are also superior with medetomidine CRI, being slower with fewer attempts to stand. As 25% of anesthetic-related deaths in horses are during the recovery period (2), this result is significant.

A novel recovery scoring method was introduced in chapter three. Mean attempt interval (MAI) was calculated by dividing the time between extubation and standing by the number of attempts to stand. Thus, slow smooth recoveries were distinguished from fast scrambling recoveries or those recoveries that were prolonged due to weakness. This parameter is far more objective than other methods used to score equine recoveries. To date, no universally accepted and validated scoring system for equine recoveries exists (21), and the MAI may become a standard scoring methodology for equine recoveries.

The research reported here shows clear benefits to the use of medetomidine CRI in isoflurane-anesthetised horses. The next logical step in the pursuit of this subject is the use of medetomidine CRI in carefully controlled clinical trials. The clinical utility of BIS during inhalant anesthesia and medetomidine CRI in surgical equine cases has not yet been investigated. The effect of mechanical ventilation on cardiopulmonary function has been established in horses (7), but this has not been evaluated with medetomidine

CRI compared to the more conventional use of xylazine bolus. Further work validating the use of MAI to score equine recoveries is also warranted.

Although this area of research is still far from complete, medetomidine CRI has been shown to be beneficial during the maintenance and recovery phases of general anesthesia in horses. Medetomidine CRI resulted in improved cardiopulmonary function, more stable depth of anesthesia, decreased stress response, and improved recoveries during isoflurane anesthesia in horses.

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APPENDIX A

1. Cardiovascular parameters in horses given xylazine or medetomidine and anesthetised with isoflurane (complete data set)

Variable	Treatment	0	10	20	30	40
HR(bpm)	Xylazine	32(5)	33(6)	38(4)	39(5)	41(13)
	Medetomidine	30(03)	34 (6)	34(5)*	35(6)	35(6)*
SAP(mmHg)	Xylazine		99(15)	83(8)	78(12)	83(14)
	Medetomidine		104(8)	93(12)*	92(11)*	94(12)*
DAP(mmHg)	Xylazine		61(12)	49(8)	46(9)	52(14)
	Medetomidine		68(9)*	61(9)*	59(10)*	59(10)
MAP(mmHg)	Xylazine		75(11)	62(9)	58(11)	64(14)
	Medetomidine		80(9)	74(11)*	73(9)*	72(11)*

Variable	Treatment	50	60	70	80	90
HR(bpm)	Xylazine	42(4)	41(4)	40(6)	42(5)	38(5)
	Medetomidine	35(5)*	35(4)*	35(5)*	33(5)*	32(4)*
SAP(mmHg)	Xylazine	92(17)	104(14)	111(12)	114(9)	116(10)
	Medetomidine	96(12)	98(13)	101(15)*	101(12)*	100(11)*
DAP(mmHg)	Xylazine	63(17)	71(16)	78(16)	83(11)	84(10)
	Medetomidine	59(12)	64(15)	72(17)	74(10)*	76(11)*
MAP(mmHg)	Xylazine	74(17)	84(15)	91(14)	96(10)	97(10)
	Medetomidine	72(14)	76(15)	82(15)*	85(10)*	87(10)*

Variable	Treatment	100	110	120	130	140
HR(bpm)	Xylazine	39(5)	41(4)	41(5)	40(6)	42(5)
	Medetomidine	32(4)*	32(4)*	33(5)*	33(4)*	33(5)*
SAP(mmHg)	Xylazine	120(10)	121(9)	119(13)	122(14)	124(14)
	Medetomidine	103(8)*	104(10)*	104(9)*	103(10)*	101(12)*
DAP(mmHg)	Xylazine	89(11)	92(12)	90(10)	92(11)	96(13)
	Medetomidine	77(9)*	80(12)*	82(10)*	77(11)*	78(11)*
MAP(mmHg)	Xylazine	102(11)	105(10)	103(10)	105(11)	108(12)
	Medetomidine	87(8)*	89(10)*	89(10)*	87(9)*	87(11)*

Variable	Treatment	150	10POST	30POST
HR(bpm)	Xylazine	42(5)	36(7)	44(6)
	Medetomidine	33(5)*	35(6)	41(10)
SAP(mmHg)	Xylazine	122(14)	141(20)	
	Medetomidine	101(8)*	127(12)*	
DAP(mmHg)	Xylazine	94(12)	114(15)	
	Medetomidine	78(10)*	103(8)*	
MAP(mmHg)	Xylazine	105(11)	123(16)	
	Medetomidine	87(9)*	112(7)*	

Data expressed as Mean (SD)
0-150 is time in minutes after connection to breathing circuit
10POST represents 10 minutes after disconnection from the breathing circuit 30POST represents 30 minutes after horse successfully stood after anesthesia
*Indicates a significant ($p \leq 0.05$) difference from xylazine

APPENDIX B

2. Respiratory parameters in horses given xylazine or medetomidine and anesthetised with isoflurane (complete data set)

Variable	Treatment	Baseline	0	10	20	30
RR(bpm)	Xylazine	14(5)	5(3)	7(4)	5(2)	6(3)
	Medetomidine	15(4)	6(7)	5(4)	6(3)	6(4)
TEMP(^{o}C)	Xylazine		37.3(0.3)	37.4(0.2)	37.2(0.2)	36.9(0.2)
	Medetomidine		37.4(0.4)	37.3(0.3)	37.2(0.5)	37.1(0.5)
PH	Xylazine					7.324(0.037)
	Medetomidine					7.320(0.054)
$Pa0_2$(mmHg)	Xylazine					126.3(53.8)
	Medetomidine					127.1(59.5)
$PaCo_2$(mmHg)	Xylazine					65.8(8.0)
	Medetomidine					68.9(12.3)
HCO_3(mM)	Xylazine					33.6(1.7)
	Medetomidine					34.8(2.1)
BE(mM)	Xylazine					5.2(1.3)
	Medetomidine					6.0(1.7)
SaO_2(%)	Xylazine					96.6(3.3)
	Medetomidine					96.9(2.3)

Variable	Treatment	40	50	60	70	80
RR(bpm)	Xylazine	5(2)	6(3)	5(2)	6(3)	5(2)
	Medetomidine	6(2)	7(5)	8(7)*	9(5)*	8(5)
TEMP(^{o}C)	Xylazine	36.7(0.3)	36.7(0.4)	36.5(0.4)	36.3(0.5)	36.3(0.5)
	Medetomidine	36.9(0.5)	36.9(0.4)	36.8(0.5)	36.7(0.6)	36.7(0.5)
PH	Xylazine			7.322(0.041)		
	Medetomidine			7.332(0.030)		
$Pa0_2$(mmHg)	Xylazine			108.6(40.4)		
	Medetomidine			126.9(59)		
$PaCo_2$(mmHg)	Xylazine			67.8(8.7)		
	Medetomidine			68.1(7.7)		
HCO_3(mM)	Xylazine			34.5(1.8)		
	Medetomidine			35.6(2.3)		
BE(mM)	Xylazine			5.9(1.4)		
	Medetomidine			6.9(1.7)		
SaO_2(%)	Xylazine			96.2(2.6)		
	Medetomidine			96.8(2.4)		

Variable	Treatment	90	100	110	120	130
RR(bpm)	Xylazine	5(2)	6(2)	6(3)	6(3)	6(3)
	Medetomidine	8(5)	9(6)*	8(5)	8(5)	8(5)
TEMP(^{0}C)	Xylazine	36.0(0.6)	36.0(0.6)	35.9(0.7)	35.9(0.7)	35.7(0.8)
	Medetomidine	36.7(0.5)*	36.6(0.6)*	36.5(0.5)*	36.4(0.6)*	36.4(0.6)*
PH	Xylazine	7.324(0.050)				
	Medetomidine	7.324(0.044)				
$Pa0_2$(mmHg)	Xylazine	75.5(19.7)				
	Medetomidine	80.2(19.8)				
$PaCo_2$(mmHg)	Xylazine	67.9(11.5)				
	Medetomidine	71.5(10.8)				
HCO_3(mM)	Xylazine	34.5(1.8)				
	Medetomidine	36.5(2.5)				
BE(mM)	Xylazine	5.9(0.9)				
	Medetomidine	7.5(1.8)				
SaO_2(%)	Xylazine	91.8(6.1)				
	Medetomidine	93.0(4.8)				

Variable	Treatment	140	150	10POST	30POST
RR(bpm)	Xylazine	6(3)	6(3)	9(3)	13(4)
	Medetomidine	9(5)*	8(4)	12(3)	11(3)
TEMP(^{o}C)	Xylazine	35.6(0.7)	35.6(0.7)	36.2(0.6)	
	Medetomidine	36.4(0.6)*	36.4(0.6)*	36.4(0.5)*	
PH	Xylazine		7.341(0.039)	7.425(0.056)	
	Medetomidine		7.339(0.043)	7.441(0.040)	
$Pa0_2$(mmHg)	Xylazine		61.6(14.6)	52.4(11.6)	
	Medetomidine		62.6(13.3)	54.3(8.1)	
$PaCo_2$(mmHg)	Xylazine		65.6(9.0)	52.1(11.5)	
	Medetomidine		71.5(10.8)	53.2(6.4)	
HCO_3(mM)	Xylazine		34.9(2.0)	33.1(2.4)	
	Medetomidine		37.5(2.8)	35.4(2.0)	
BE(mM)	Xylazine		6.6(1.4)	7.1(0.9)	
	Medetomidine		8.6(2.0)	9.4(1.6)	
SaO_2(%)	Xylazine		87.7(6.1)	86.7(6.2)	
	Medetomidine		87.8(7.2)	88.4(4.2)	

Data expressed as Mean (SD)
0-150 is time in minutes after connection to breathing circuit
10POST represents 10 minutes after disconnection from breathing circuit
30POST represents 30 minutes after horse successfully stood after anesthesia
* Indicates a significant ($p \leq 0.05$) difference from xylazine

APPENDIX C

3. Depth of anesthesia in horses given xylazine or medetomidine and anesthetised with isoflurane (complete data set)

Variable	Treatment	0	10	20	30	40	50
BIS	**Xylazine**		53(7)	49(6)	52(11)	53(12)	53(10)
	Medetomidine		48(6)	47(6)	49(8)	49(9)	49(11)
EMG	Xylazine		36(2)	35(2)	37(2)	40(7)	40(3)
	Medetomidine		34(2)	34(3)	34(3)*	33(3)*	33(2)
SPR	Xylazine	0	0	0	0	0	10
	Medetomidine	40	40	40	40*	20*	20*
Tearing	Xylazine	30	20	10	10	0	0
	Medetomidine	10	10	0	0	10	0
Nystagmus	Xylazine	0	0	0	0	0	0
	Medetomidine	10	0	0	0	0	0

Variable	Treatment	60	70	80	90	100	110
BIS	Xylazine	54(9)	54(9)	53(7)	53(6)	57(7)	56(6)
	Medetomidine	49(11)	46(10)	46(8)*	45(9)*	44(8)*	45(11)*
EMG	Xylazine	40(3)	40(4)	40(3)	39(3)	40(3)	39(3)
	Medetomidine	33(2)*	33(3)*	32(2)*	32(2)*	32(2)*	32(2)*
SPR	Xylazine	10	10	0	0	10	10
	Medetomidine	30*	20*	20*	10*	20*	20*
Tearing	Xylazine	0	0	0	0	0	10
	Medetomidine	10	20	10	10	0	0
Nystagmus	Xylazine	0	0	0	10	0	20
	Medetomidine	0	10	0	0	0	0

Variable	Treatment	120	130	140	150
BIS	Xylazine	55(8)	58(8)	56(6)	55(7)
	Medetomidine	44(8)*	45(10)*	45(11	45(11)*
EMG	Xylazine	40(3)	40(3)	39(4)	39(4)
	Medetomidine	32(3)*	32(3)*	32(2)*	32(3)*
SPR	Xylazine	0	0	0	0
	Medetomidine	30*	0*	10*	0*
Tearing	Xylazine	0	0	0	0
	Medetomidine	0	10	10	0
Nystagmus	Xylazine	10	0	10	30
	Medetomidine	0	10	0	0

0-150 is time in minutes from connection to breathing circuit
BIS = bispectral index
EMG = electromyogram data
SPR = spontaneous palpebral reflex
BIS, EMG expressed as Mean (SD)
SPR, tearing, nystagmus expressed as percent horses exhibiting sign
*Indicates a significant ($p \leq 0.05$) difference from xylazine