B-5265
[1-5]

RESEARCH ARTICLE Indian Journal of Animal Research

Clinical and Hematological Effect of Constant Rate Infusion of Ketamine Alone and Ketamine-dexmedetomidine Combination on Isoflurane Anesthesia in Horses

Aswathy Gopinathan[1], Kiranjeet Singh[1], Shivaraju S.[1], Remya V.[1], Sangeetha P.[1], Divya Mohan[1]

10.18805/IJAR.B-5265

ABSTRACT

Background: Anaesthetic management of horses for a successful surgery is of utmost importance but a risky procedure than other companion animals. Peri-aneasthetic morbidity and mortality in horses could be alarming if proper combinations of drugs were not used. Balanced anaesthetic combinations are being explored by various authors to find safer combinations.Therefore current study was planned to evaluate the effect of CRI of ketamine alone and ketamine-dexmedetomidine combination for isoflurane anesthesia in horses.

Methods: Twenty four clinical cases of horses were randomly divided into three groups S, D and DK, having eight animals in each. Xylazine (1 mg/kg) and butorphanol (0.05 mg/kg) were given intravenously for premedication and ketamine (2 mg/kg) and midazolam (0.2 mg/kg) were used for induction of anesthesia. Normal saline (1000 ml/hour), ketamine alone (2 mg/kg/hr), ketamine (2 mg/kg/hr) and dexmedetomidine (2 µg/kg/hr) combination were given as CRI in groups S, K and KD, respectively. Thiopentone sodium (200 mg bolus, 5%) was given as fast intravenous to facilitate endotracheal intubation in some of the cases. Anesthesia was maintained with isoflurane in oxygen and anesthetic efficacy was evaluated based on clinical and haematological parameters.

Result: Overall quality of sedation, muscle relaxation, response to surgical stimuli, quality of intubation, anesthetic depth and quality of recovery was significantly ($p<0.05$) better in group KD. Down-time (min) and duration of anesthesia were non significantly less in group KD. CRI of ketamine and dexmedetomidine combination was having significant ($p<0.05$) thiopentone sodium and isoflurane sparing effect. Heart rateand RR, did not show any significant variation among groups but rectal temperature was significantly low in KD group than groups S and K. CRI of ketamine-Dexmedetomidine combination produced a better quality of anesthesia and significant thiopentone sodium and isoflurane sparing effect thus was found suitable for anesthesia of horses.

Key words: CRI, Dexmedetomidine, Horses, Ketamine.

INTRODUCTION

Anaesthetic management of horses during surgical procedures carried a greater risk of mortality than other companion animals (Hall and Clarke, 1991). Peri-aneasthetic morbidity and mortality which was higher in horses could be alarming (Wagner *et al.,* 2008). The anaesthetic effect of isoflurane was accompanied by a dose-related depression of the cardiovascular and respiratory function but with little analgesic effect. The use of ketamine (Muir and Sams, 1992) and various alpha-2-agonists (Schauvliege *et al.,* 2011) as constant rate infusions (CRIs) had been described in clinical and in experimental equine anaesthetic procedures. Preemptive ketamine infusion prior to premedication in horses enhanced quality of sedation and shortened the down-time in horses (Sharma *et al.,* 2019). The use of Alpha 2 agonists as continuous rate infusions abolished many side effects of these drugs than when used as bolus infusions (Marcilla *et al.,* 2012). Newer alpha 2 agonists like Dexmedetomidine had been suggested for continuous rate infusions in equine and it had been found to reduce the MAC value of isoflurane significantly (Schauvliege *et al.,* 2011). Balanced anaesthetic combinations were being explored by various authors to find safer combinations that can be used in conjunction with inhalant agents to reduce the side effects of inhalant agents and the drug sparing effects (Gopinathan *et al.,* 2021). Other characters like smooth induction, recovery, cardiovascular and pulmonary profile and stress parameters had to be evaluated for comprehensively assessing the safety of such drugs for application in surgeries.Present study explored

[1]Division of Surgery, ICAR-Indian Veterinary Research Institute, Izzatnagar, Bareilly-243 122, Uttar Pradesh, India.

Corresponding Author: Kiranjeet Singh, Division of Surgery, ICAR-Indian Veterinary Research Institute, Izzatnagar, Bareilly-243 122, Uttar Pradesh, India. Email: ksuppli@yahoo.co.in

How to cite this article: Gopinathan, A., Singh, K., Shivaraju, S., Remya, V., Sangeetha, P. and Mohan, D. (2024). Clinical and Hematological Effect of Constant Rate Infusion of Ketamine Alone and Ketamine-dexmedetomidine Combination on Isoflurane Anesthesia in Horses. Indian Journal of Animal Research. doi: 10.18805/IJAR.B-5265.

Submitted: 14-11-2023 **Accepted:** 21-02-2024 **Online:** 20-05-2024

safety of balanced anesthetic protocols with ketamine alone or in combination with dexmedetomidine, as constant rate infusion along with isoflurane anesthesia for surgeries in horses.

MATERIALS AND METHODS

Animals

Twenty four clinical cases of adult horses of either sex presented for hernia repair (5), soft tissue surgery (6), castration (9) and eye ball tumor (4) removal at institute referral veterinary polyclinics were included in the study. The average body weight of animals was 213.75 (170 kg to 310 kg) and were 2 to 7 year old. The cases in which surgical procedures were completed within 1 hours were included in the study. Due permission to for the study was taken from Institute Animal Ethics Committee (IVRI/SURG/12-15/012). Informed consent was taken from owner for surgery and collection of blood samples at required intervals.

Experimental design

The study was conducted on 24 apparently healthy adult horses and randomly divided into three groups designated as groups S, K and KD having eight animals in each. Animals in different groups were treated with CRI of drugs along with Isoflurane anaesthesia in oxygen as depicted in Table 1. All the animals were kept off food and off water for 12-14 hours prior to anesthesia. Jugular vein was prepared aseptically for placement of a catheter for drug administration and collection of blood. Before administration of preanesthetic drugs animals were restrained properly. Xylazine[1] (Xylaxin®, Indian Immunological Limited, Hyderabad, India) @ 1 mg/kg body weight) and Butorphanol[2] (Butodol-2®, Neon Laboratories Limited, Mumbai) @ 0.05 mg/kg body weight) were injected intravenouslyas preanesthetic drugs. Ten minutes after pre-anesthetics administration, anesthesia was induced with ketamine[3] (Ketamax-50®, Troikaa Pharmaceuticals Ltd. Uttarakhand, India) (2 mg/kg) and midazolam[4] (Mezolam®, Uttarakhand, India) (0.2 mg/kg) combination given intravenously. All the drugs were loaded in separate syringes before injection. Just after induction endotracheal tube was placed and CRI of the concerned group was started. Thiopentone sodium[5] (Thiosol*sodium, Neon Laboratories Limited, Mumbai (250 mg, 5%) bolus was administered whenever a deeper anaesthesia was required and anesthesia was maintained with Isoflurane (2%) in oxygen.

Clinical observations

The quality of sedation, ataxia, quality of intubations, muscle relaxation, anesthetic depth/analgesia, total dose of thiopentone/isoflurane required and Quality of recovery from anesthesia were recorded. Sedation was recorded after given preanesthetic as 0: No sedation, 1: Mild sedation with slightly lowered head, 2: Moderate sedation with the head lowered below manubrium, but respond to audible stimuli, 3: Intense sedation with the head lowered below manubrium, but no response to audible stimuli. Ataxia score was evaluated before and after premedication. It was graded on 0 to 3 scales as; 0- No ataxia, 1- Animal is stable but slightly swaying, 2-Animal is swaying and leaning against the stock, 3- Animal is leaning against the stock and swaying with its hind limbs crossed and its forelimbs buckling at the carpal joint. Down-time (min) was recorded as the time from the preanesthetic drug administration until the horse achieved recumbency. The quality of intubation was recorded as the ease and attempts to intubate. Muscle relaxation and anesthetic depthwere recorded 30 minutes after induction all the three groups. Relaxation of the trunk and limbs muscle was taken as a measure of muscle relaxation and evaluated by observing the muscle activity of trunk and limbs. The subjective observation was graded 0 to 3 scale as follows; 0: Muscle relaxation present in trunk and limbs, 1: Muscle twitching present in some regions of trunk and limbs, 2: Muscle twitching present over the majority portions of trunk and limbs, 3: Muscle rigidity present over the majority portions of trunk and limbs. Anesthetic depth was assessed by physical signs, including movement, the position of the eye, the degree of depression of the protective reflexes of the eye, the loss of the swallowing reflex, the rate and depth of breathing, and the horse's response to surgical stimulation. Anaesthetic depth was graded on 0 to 3 scale as follows; 0: No response to stimuli**,** 1: Nystagmus, a blood pressure response or a local muscle response, 2: Purposeful movement of limbs, head or neck**,** 3: Horse moved into sternal position or stood up.The total dose of thiopentone/isoflurane required during the entire surgical procedure in mg/kg and total ml and the duration of the anaesthesia for surgical procedure was also recorded. Quality of recovery was scored as 1: One attempt to stand, no ataxia, 2: One or two attempts to stand, some ataxia, 3: >2 attempts to stand, but quiet recovery, 4: >2 attempts to stand, excitation**,** 5: Severe excitation.The duration of the anesthesia (minutes) for surgical procedure was recorded in each case. Time from discontinuation of anaesthesia till first lifting of head was recorded *as* first head lift (minutes). Time taken by animal move to sternal recumbancy after discontinuation of anaesthesia was recorded *as* sternal recumbency (minutes). The time taken

Table 1: Anaesthetic drug combination used in animals of different groups.

Group	No . of animals	Treatment
Group S	8	Saline (1000 ml/hr)
Group K	8	Ketamine @ 2 mg/kg/hr
Group KD	8	Ketamine @ 2 mg/kg/hr and Dexmedetomidine @ 2 µg/kg/hr

by animal (minutes) from discontinuation of anaesthesia to stand was recorded as standing time.

Physiological parameters

Heart rate (beats/min), respiratory rate (breaths/min) and rectal temperature (°F) were recorded before administration of the drug(s) and at 0 (after induction), 15, 30, 45 and 60 min after administration of the drugs.

Hematological observations

Blood samples (5 ml) were collected from the jugular vein in disposable syringe before giving anesthesia (baseline) and at 0 (start of CRI), 15, 30, 45 and 60 min after injection of the drug(s). The blood samples were subjected to haemoglobin (g/dl), PCV, neutrophils, lymphocytes and monocyte (%) estimations.

Statistical analysis

Differences in different groups at different time intervals were compared by Repeated Measures ANOVA for parametrical data and Kruskal Wallis test for non parametric data. The data were analyzed by using SAS 9.3 software.

RESULTS AND DISCUSSION

The quality of sedation, ataxia, quality of intubations, muscle relaxation, anaesthetic depth, and quality of recovery from anaesthesia were recorded (Table 2). Muscle relaxation, anaesthetic depth and quality of recovery were significantly ($p<0.05$) better in group KD than others. There were no significant ($p<0.05$) differences in sedation and ataxia scores between the groups. The muscle relaxation and quality of intubation scores were non significantly ($p<0.05$) better in group KD than groups S and K. It is reported that addition of alpha 2 agonists in TIVA (Total Intravenous Anesthesia) improved sedation and muscle relaxation (Philip, 2013). The quality of intubation was good in groups S and K but excellent in group KD groups. The administration of alpha-2 agonists (Dexmedetomidine), greatly reduced the laryngeal and pharyngeal reflexes observed during ketamine administration in horses (Ko *et al*., 2000). Thus the presence of dexmedetomidine in KD group could be responsible for complete loss of laryngeal reflex. Pharyngeal, laryngeal reflexes, lacrimation and palpebral reflexes were more pronounced in horses of group K. Similar kind of findings were reported by Yamashita *et al*. (2007). Similar to the findings of Shivraju *et al*. (2022), shivering and muscle twitching were observed in groups S and K. This shivering may be due to persistent cutaneous vasodilatation in a cold environment or probably a reflection of the lack of analgesic in groups S and K. Addition of dexmedetomidine significantly ($p<0.05$) improved the muscle relaxation, anaesthetic depth and quality of recovery in group KD than groups S and K. The synergistic action among dexmedetomidine and ketamine, might have lead to this significant improvement of muscle relaxation, anaesthetic depth and quality of recovery in group KD (Ko *et al.,* 2000).

Mean ± SD values of Induction/down time, duration of anesthesia, time for head lift, sternal recumbency, standing time, total isoflurane requirement (ml), total thiopentone requirement (mg) and quality of recovery in different groups is presented in Table 3. Down-time (min) and duration of anesthesia were non significantly ($p<0.05$) less in group KD than groups S and K. Ketamine- dexmedetomidine combination significantly ($p<0.05$) reduced the isoflurane and thiopentone consumption and produced significantly ($p<0.05$) better quality of recovery. Animals of group KD took non significantly ($p<0.05$) longer time to first head lift time, sternal recumbency and standing times. This reduction in down time, dose requirement, improved quality of recovery, longer time to first head lift time, sternal recumbency and standing times was probably resulted from the synergistic action among alpha-2 agonist, and ketamine, resulting in deeper anaesthesia (Ko *et al.,* 2000).

Mean ± SE values of heart rate (beats/min), respiration rate (breaths /min), PCV (%), neutrophils (%), lymphocytes (%) and monocyte (%) in different groups at various time intervals are presented in Table 4. A non-significantly ($p<0.05$) decrease in heart rate and respiration rate was observed in all the groups from the induction time to the

Table 2: Mean ± SD values of scores sedation, ataxia, quality of induction, muscle relaxation, response to stimulus and quality of recovery in different groups.

Groups	Sedation	Ataxia	Quality of intubations	Muscle Relaxation	Anesthetic depth	Quality of recovery
S	2.00±0.447	2.00±0.894	2.00±0.837	2.00±1.095	3.00±0.894	3.00±1.14
K	3.00±1.1	2.00±0.45	2.00±0.707	2.00±1.034	3.00±0.548	2.00±0.548
KD	2.00±0.00	2.00±0.548	1.00±0.548	1.00±0.348[a]	2.00±0.247[a]	1.00±0.548[a]

Table 3: Mean ± SD values of induction/down time, duration of anesthesia, timefor head lift, sternal recumbency, standing time, total isoflurane requirement (ml), total thiopentone requirement (mg) and quality of recovery in different groups.

Groups	Induction /down time (min)	Duration of anesthesia (min)	Head lift time (min)	Sternal recumbency (min)	Standing time (min)	Isoflurane requirement (ml)	Thiopentone requirement (mg)	Quality of recovery
S	15.00±3.35	50.00±00	13.00±4.63	21.00±60	32.00±4.3	26.2±8.80[b]	700.00±124.2[b]	2±0.316[b]
K	13.40±2.29	48.00±4	9.00±2.703	19.00±3.91	28.00±4.006	19.00±2.87[b]	300.00±102.47[b]	1.8±0.49[b]
KD	11.00±2.87[a]	44.00±7.000	22.00±10.12[a]	24.00±9.16	38.00±9.002	14.00±2.44[a]	160.00±78.47[a]	1.20±0.400[a]

Table 4: Mean ± SE values of heart rate (beats/min), respiration rate (breaths /min), PCV (%), Neutrophils(%), lymphocytes(%) and monocyte (%) in different groups at various time intervals.

Parameter	Groups	Interval (min)					
		Pre	0	15	30	45	60
Heart rate	S	54.8±4.15	38.4±4.15	50.6±4.15	52.2±4.15	46.4±4.15	45.20±4.15
(beats/min)	K	52.4±4.15	33.8±4.15	44.8±4.15	46.2±4.15	45.2±4.15	50.20±4.15
	KD	52.2±4.15	34.6±4.15	43.6±4.15	45.8±4.15	44.6±4.15	43.00±4.15
Respiration rate	S	14.8±2.05	7.80±2.05	8.6±2.05	8.8±2.05	8.0±2.05	8.60±2.05
(breaths /min)	K	14.0±2.05	12.20±2.05	10.4±2.05	10.2±3.05	9.5±2.05	10.20±2.05
	KD	20.8±2.05	15.00±2.05	13.8±2.05	13.2±2.05	14.2± 2.0	15.40±2.05
Rectal temperature (°F)	S	100.36±0.2	99.8±0.29	99.88±0.29	98.96±0.2	99.4±0.2b	99.3±0.29 [b]
	K	99.76±0.29	100.94±0.2	100.16±0.2	99.9±0.2[b]	99.6±0.2[b]	99.4±0.2[b]
	KD	99.68±0.29	100.08±0.2	98.66±0.29	98.3±0.2[a]	97±4.29*[a]	97.6±0.2*[a]
Haemoglobin (g/dl)	S	12.34± 0.31	11.58±0.3	10.6±0.3*	9.8±0.31*	9.8±0.31*	10.22±0.3*
	K	12.24±0.31	11.64±0.31	11.14±0.3	11.18±0.3	11.20±0.31	11.74±0.3
	KD	12.42±0.3	11.88±0.31	11.4±0.3	10.78±0.3	11.22±0.31	11.68±0.3
PCV	S	33.42±0.7	33.4±0.7	33.5±0.7	32.6±0.7	32.20±0.7	32.3± 0.7
	K	34.68±0.7	33.4±0.7	31.83±0.7	32.4± 0.7	32.68±0.7	30.46±0.7
	KD	36.74±0.7	35.0± 0.7	34.45±0.7	33.4± 0.7	32.9±0.7	32.7± 0.7
Neutrophils	S	61.6±1.7	62.3±1.7	61.±1.73	58.7±1.7	56.9±1.73	57.26± 1.73
	K	65.4±1.7	64.8±1.73	64.2±1.73	64.9±1.73	63.48±1.73	62.54±1.73
	KD	64.2±1.7	63.3±1.73	62.±1.73	60.6±1.73	60.2±1.73	61.8±1.73
Lymphocytes	S	33.8±1.6	34.2±1.6	33.4±1.68	32.6±1.6	33.3±1.68	32.9±1.68
	K	31.8±1.68	31.5±1.68	29.1±1.68	29±1.68	29.2±1.6	29.50±1.68
	KD	30.8±1.6	30.8±1.6	30.7±1.68	31.2±1.6	29.6±1.6	29.8±1.68
Monocyte (%)	S	3.2 ± 0.2	2.8±0.2	2.1±0.2	2.2±0.2	2.8±0.2	2.9±0.2
	K	3.4 ± 0.2	2.7±0.2	2±0.2	2.24±0.2	2.24±0.2	2.4±0.2
	KD	3.3±0.2	2.6±0.2	2.1±0.2	2.06±0.2	2.42±0.2	2.8±0.2

*Differ significantly ($p<0.05$) from its respective baseline.

Values with different alphabets differ significantly ($P<0.05$) at corresponding intervals.

end of the observation period. This decrease in these parameters may be attributed to baroreceptor activation (Kerr *et al.,* 1996). The reduction may be caused by the activation of central and pre-synaptic sympathetic neuronal alpha-2 adrenoceptors in group KD by dexmedetomidine use (Moens, 2000). A decrease in heart rate in groups KD might be due to the overiding effect of dexmeditomidine over ketamine (Gopinathan *et al.,* 2021). A decrease in RR might also be attributed to co-administration of thiopental administration which often causes direct depression of the respiratory in the medulla. The incidence of postoperative bradycardia has been reported as high as 40% in healthy surgical patients who received dexmedetomidine (Aho *et al.,* 1993). In group KD hypothalamic centre suppression by dexmedetomidine might have lead to relaxation of intercostal muscles and decreased the respiration rate.In all groups, the rectal temperature decreased during anaesthesia till last observation. Similar type of observations in drop of rectal temperature during anesthesia was available in literature (Carmona *et al.,* 2007). Fall in rectal temperature was significant ($p<0.05$) in group KD from base line and from other groups between 30 to 60 minutes observations. Dexmedetomidine used in group KD is an alpha-2 adrenergic agonists caused depression of thermoregulation (Ponder and Clarke, 1980) and hypothalamic noradrenergic α-2 receptors to cause hypothermia (MacDonald *et al.,* 1988).

A gradual non significant decrease in hemoglobin and PCV values from base line was observed in all the groups and this decrease of hemoglobin was significant ($P<0.05$) in group S. This might be due to shifting of fluids from the extravascular compartment to the intravascular compartment to maintain the cardiac output in the animals (Wagner *et al.,* 1991) or due to haemodilution in response to fluid therapy during surgical procedures (Skarda, 1994). Neutrophils (%), lymphocytes (%) and monocyte (%) values fluctuated near base line value and did not show any specific pattern. Shivraju *et al*. (2022) also did not find any change in neutrophils (%), lymphocytes (%) and monocyte (%) values after administration of CRI of ketamine, dexmedetomidine and midazolam in horses.

CONCLUSION

From the results present study it could be concluded that CRI of ketamine-dexmedetomidine combination produced a better quality of anesthesia and significant thiopentone sodium and isoflurane sparing effect thus was found suitable for anesthesia of horses.

Conflict of interest

We all authors declare that there is no conflict of interest.

REFERENCES

Aho, M., Erkola, O., Kallio, A., Scheinin, H. and Korttila, K. (1993). Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. The Journal of Clinical Anesthesia. 5: 194–203.

Carmona, J.U., Giraldo, C.E., Aristizabal, W., García, A. and Vallejo, L.G. (2007). Evaluation of the effects of the sedation with azaperone/acepromazine and immobilization with guaiphenesin /thiopentone in mules. Veterinary Research Communication. 31: 125-132.

Gopinathan, A., Singh, K., Sarangom, S.B., Ramya, V., Sangeetha, P., Mohan, D. and Kumar, N. (2021). Studies to ealuate the safety of constant rate infusions of dexmedetomidine, Ketamine and lidocaine alone or in combination during isoflurane anesthesia in horses. Indian Journal of Animal Research. DOI: 10.18805/IJAR.B-4401.

Hall, L.W. and Clarke, K.W. (1991). General pharmacology of intravenous anaesthetic agents. Veterinary Anesthesia. 8: 90-97.

Kerr, C.L., McDonell, W.N. and Young, S.S. (1996). A comparison of romifidine and xylazine when used with diazepam/ketamine for short duration anesthesia in the horse. Canadian Veterinary Journal. 73: 601-609.

Ko, J.C., Lange, D.N., Mandsager, R.E., Payton, M.E., Bowen, C., Kamata, A. and Kuo, W.C. (2000). Effects of butorphanol and carprofen on the minimal alveolar concentration of isoflurane in dogs. Journal of the American Veterinary Medical Association. 217: 1025-1028.

Macdonald, E., Scheinin, H. and Scheinin, M. (1988): Behavioural and neurochemical effects of medetomidine, a novel veterinary sedative. European Journal of Pharmacology. 158: 119-127.

Marcilla, M. G., Schauvliege, S., Segaert, S., Duchateau, L. and Gasthuys, F. (2012). Influence of a constant rate infusion of dexmedetomidine on cardiopulmonary function and recovery quality in isoflurane anaesthetized horses. Veterinary Anaesthesia and Analgesia. 39(1): 49-58.

Moens, Y. (2000). The veterinary experience. Bailliere's Clinical Anesthesiology.14: 293-304.

Muir, W.W. and Sams, R. (1992). Effects of ketamine infusion on halothane minimal alveolar concentration in horses. American Journal of Veterinary Research. 53: 1802-1806.

Philip, L. (2013). Total intravenous anesthesia in horses. Veterinary Clinics of North America: Equine Practice. 29(1): 123-129.

Ponder, S. W. and Clarke, W. G. (1980). Prolonged depression of thermoregulation after xylazine administration to cats. Journal of Veterinary Pharmacology and Therapeutics. 3: 203-207.

Schauvliege, S., Gozalo-Marcilla, M., Verryken, K., Duchateau, L., Devisscher, L. and Gasthuys, F. (2011). Effects of a constant rate infusion of detomidine on cardiovascular function, isoflurane requirements and recovery quality in horses. Veterinary Anaesthesia and Analgesia. 38: 544-554.

Sharma, P., Gopinathan, A., Singh, K., Sarangom, S.B., Sowbhrenya, C., John, C. and Verma, M.R. (2019). A preliminary study on effectsof subanesthetic doses of preemptive ketamine given priorto premedication on total intravenous anesthesia for short-to medium-term surgicalprocedures in horses. Turkish Journal of Veterinary and Animal Sciences. 43: 456-468.

Shivaraju, S., Gopinathan, A., Singh, K. and Verma, M. R. (2022). Effect of Constant rate infusion of different anaesthetic adjuvants undergoing thiopentone sodium total intravenous anaesthesia in horses. Indian Journal of Animal Research. DOI: 10.18805/IJAR.B-4763.

Skarda, R.T. (1994). Caudal analgesia induced by epidural or subarachnoid administration of detomidine hydrochloride solution in mares. American Journal of Veterinary Research.55: 670-680.

Wagner, A.E., Mama, K.R., Steffey, E.P. and Hellyer, P.W. (2008). A comparison of equine recovery characteristics after isoflurane or isoflurane followed by a xylazine-ketamine infusion. Veterinary Anaesthesia and Analgesia. 35:154-160.

Wagner, A.E., Muir, W.W. and Hinchcliff, K.W. (1991). Cardiovascular effects of xylazine and detomidine in horses. American Journal of Veterinary Research. 52: 651-657.

Yamashita, K., Wijayathilaka, T.P., Kushiro, T., Umar, M.A., Taguchi,K. and Muir, W.W. (2007). Anesthetic and cardiopulmonary effects of total intravenous anesthesia using a midazolam, ketamine and medetomidine drug combination in horses. Journal of Veterinary Medical Science. 69: 7-13.