The Journal of Animal & Plant Sciences, 24(6): 2014, Page: 1695-1700
ISSN: 1018-7081

ANAESTHETIC EFFECTS OF MEDETOMIDINE HCl WITH PROPOFOL, KETAMINE AND CHLORAL HYDRATE IN EQUINES

H. Akbar, M. A. Khan, M. S. Khan, M. A. Khan[*], S. G. Bokhari, A. Nasir and A. A. Anjum[**]

Department of CMS, [*]Department of Epidemiology and Public Health, [**]Department of Microbiology, University of Veterinary and Animal Sciences, Lahore
Corresponding author's E mail: Hamid.akbar@uvas.edu.pk

ABSTRACT

Efficacy of medetomidine HCl anesthesia was evaluated in 48 horses, divided randomly into six groups (n=8). Initially, propofol, ketamine and chloral hydrate were evaluated individually as sole anesthetic drugs in groups A C and E, respectively. Later on the efficacy of medetomidine HCl as pre-anesthetic was assessed by using it in combination with other drugs. In group B, medetomidine HCl was used at 15µg/Kg BW and anesthesia was induced with propofol. Similarly, in group D, the combination of medetomidine HCl and ketamine was used, whereas in group F, medetomidine HCl was combined with chloral hydrate for production of anesthesia. The anesthesia thus produced in each animal was evaluated in order to find out the best anesthetic combination in horses. Statistical analysis of the parameters including induction, sedation, analgesia, recumbency and recovery was carried out at significance level of ($P<0.05$). Results of medetomidine used in combination with propofol, ketamine and chloral hydrate (groups B, D and F) were efficient than alone. Amongst the six groups, the most rapid induction (1.87±0.83) and sedation scores (1.87±0.83) were recorded with ketamine. Propofol manifested the lowest analgesia and recumbency scores of (1.50±0.53) and (1.87±0.64) with average time 10-20 minutes. The combination of medetomidine and chloral hydrate (group F) depicted the longest duration of sedation (4.75±0.70), recumbency (5.25±0.70), sedation (3.25±0.70), analgesia (4.75±0.70) and recovery (4.50±1.2).

Key words: Anesthesia, Induction, Recumbancy, Sedation, Analgesia and Recovery.

INTRODUCTION

The anesthetic agents being used in Pakistan at present are not safe in terms of induction, maintenance, duration and recovery often resulting in serious anesthetic emergencies and deaths due to failure of anesthesia. Equine anesthesia is associated with high morbidity and mortality (Johnston *et al*., 1995). Medetomidine HCl has gained the attention of many animal practitioners as a sedative-analgesic in recent years (Segal *et al*., 1988; Kastner *et al*., 2001a). It belongs to alpha 2 adrenoceptor group and is an ideal sedative and analgesic drug, discovered in 1980 (Kamerling *et al*., 1991) and is more potent than widely used alpha-2-agonist xylazine (Virtanen *et al*., 1988).

Propofol is a non-cumulative intravenous anesthetic agent, having rapid onset and recovery, producing smooth induction and requires intermittent injections for maintenance of anesthesia (Muir *et al*., 2007). The use of propofol alone is impractical in horses because it provides little analgesia (Mama *et al*., 1995). Propofol is often used in combination with other analgesics and sedatives in equines because of its poor analgesic properties and high cost (Langley and Keel, 1988).

Ketamine has known analgesic property in horses and lessens the autonomic response to noxious stimuli (Wright, 1982). It possesses analgesic properties even at sub-anesthetic doses (Correll *et al*., 2004) and reduces the requirement of volatile anesthetics (Muir and Sams, 1992). Ketamine is not recommended as a sole anesthetic agent because recovery is not smooth and muscle turgidity occurs (Muir *et al*., 1998). Moreover, muscle relaxation is not adequate as produced by xylazine (Wagner *et al*., 1991). Therefore, ketamine is commonly combined with alpha 2 agonist having good muscle relaxation properties (Green *et al*., 1996). Medetomidine HCl is being used with ketamine to induce anesthesia for diagnostic and minor to moderate surgical procedures in different animal species (Raekallio *et al*., 1994; Hellebrekers *et al*., 1997; Hoffman *et al*., 2002).

Chloral hydrate is widely used as sole agent to induce anesthesia in equines. It does not meet the requirements of an ideal anesthetic and offers poor analgesia and muscle relaxation. It is a dire needs issue now-a-days to work out an efficacious drug combination which can fulfill all the requirements of a safe and reliable anesthetic for horses. Initially, Propofol, Ketamine and Chloral hydrate were evaluated alone as sole anesthetics and then in combination with Medetomidine HCl.

MATERIALS AND METHODS

Forty-eight healthy horses of either sex aged between 6-10 years weighing 250-350 kg were housed in

stables at Surgery Section, University of Veterinary & Animal Sciences, Lahore. The animals were acclimatized for a week prior to start experiments. Mean while, a thorough physical examination and necessary blood analysis was carried out to ascertain the health status of the animals and to rule out any abnormality of vital organs.

Experimental plan: In group A horses, a bolus dose of propofol was administered alone at 2.2mg/kg BW intravenously for induction of anesthesia. In group B, Medetomidine HCl (Domitor Pfizer, Pvt. Ltd.) was used intravenously at 15µg/Kg BW (Bryant *et al*., 1991) as pre-anesthetic and five minutes later anesthesia was induced with propofol (Gobbifol, Gobi-Nova Argentina). In group C, Ketamine HCl (Ketasol), 2mg/kg BW intravenously was used alone as induction agent. In group D, again medetomidine HCl was used as preanesthetic and five minutes later ketamine HCl was used intravenously for induction of anesthesia. In group E, chloral hydrate (Symans Pharmaceuticals, Pvt. Ltd.) at 100mg/kg BW intravenously was used solely as anesthetic agent, while in group F, medetomidine HCl was used as prenesthetic and five minutes later anesthesia was induced with chloral hydrate.

Induction: Induction in horses was assessed by following protocol. Time taken by drug to induce anesthesia was allotted scores. Score 1 was allotted to animals gaining induction in 10-20 seconds, score 2 for 30-40 seconds, score 3 for 50-60 seconds, score 4 for induction in 70-80 seconds and score 5 for 90-100 seconds (Matthews *et al*., 1999).

Recumbency: Recumbency protocol was adopted from studies of Mama *et al*., (1995). Recumbency was evaluated on the basis of duration, horses remain recumbent and the scores were allotted on basis of length of recumbency time. Score 1 was allotted to animals remaining recumbent for 1-10 minutes, score 2 for 10-20 minutes, score 3 for 20-30 minutes, score 4 for 30-40 minutes and score 5 for animals remaining recumbent for 40-50 minutes.

Sedation: Degree of sedation was assessed by presence or absence of following five reflexes: head down, saliva drooling, jaw tone, palpebral reflex and gait incoordination. The body reflexes were observed post administration of drug and noted. Total five reflexes were monitored and scoring was done from (1-5) on the basis of number of reflexes lost.

Analgesia: Analgesic effect was evaluated by checking presence or absence of five reflexes and scoring was done from (1-5) on the basis of number of reflexes lost. The reflexes for analgesia evaluation included ear twitch, anal reflex, toe pinch reflex, tail response and pedal reflexes. Mosquito forceps and needle pricks were used to see whether these reflexes were present or not.

Recovery: Recovery period was the time taken by the horses post administration of injection to complete recovery from anesthetic effects as already studied by Clark *et al*., (2008). For recovery evaluation, score 1 was allotted to animals recovering in 20-30 minutes, score 2 for 30-40 minutes, score 3 for 40-50 minutes, score 4 for 50-60 minutes and score 5 for animals showing good recovery in 60-70 minutes.

In group B, C, D, E and F the effect of drugs was evaluated following same procedures and protocols as for group A.

Statistical analysis: The data were analyzed statistically by one way ANOVA and Duncans multiple range tests using SPSS version 13.0 at $P < 0.05$ significance level.

RESULTS

Rapid induction of anesthesia was produced by group C with lowest value of scores (1.50±0.53). Statistically, the value was significantly lower than groups E, D, B and F (2.37±0.51), (4.12±0.83), (4.25±1.03) and (4.75±0.70), respectively. Induction with combination of medetomidine HCl and chloral hydrate was recorded to be the longest (4.75±0.70). Statistically combination groups showed significant difference ($p<0.05$) with groups in which drugs were used alone.

Duration of recumbency in anesthetized horses was recorded to be the longest in group F (5.25±.70) using combination of medetomidine HCl and chloral hydrate. The combinations of medetomidine HCl/ propofol and medetomidine HCl/ketamine produced moderate duration of recumbency (4.25±0.70). Statistically, the values in combination groups were significantly longer than groups in which the drugs were used alone.

The combination of medetomdine HCl and chloral hydrate (group F), produced the most ideal sedation characterized by effects of sedation up to 35 minutes (3.25±0.70), *P<0.050*. Sedation produced by other combinations (groups B and D) were of a moderate degree with average score (2.12±0.64) and (2.12±0.83) indicating an average time of 20-30 minutes. Ketamine, propofol and chloral hydrate alone (groups A, C and E) depicted lesser degree of sedation than combination groups. Average scores in groups were (1.87±0.83), (1.50±0.53) and (1.50±0.53), respectively.

The combination of medetomdine HCl and chloral hydrate (group F) proved to be the most ideal analgesic under experimental conditions. Analgesia was rapid and longest in duration, with an average score of (4.75±0.70) depicting an average time of 48 minutes (*P<0.050*). Analgesia produced by other combinations (groups B and D) was of moderate degree with average

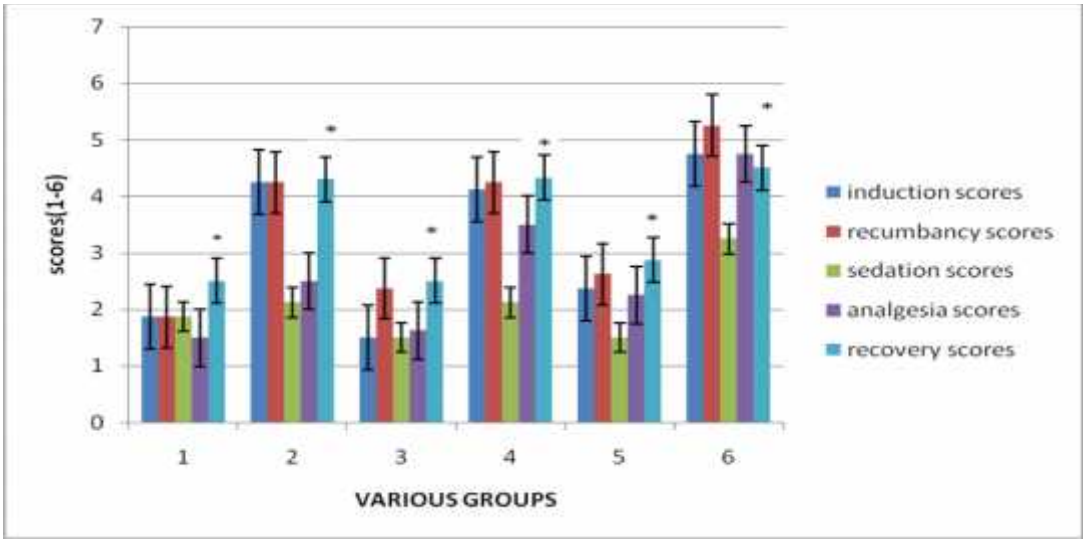
scores (2.50±0.53) and (3.50±0.53) indicating time of 33 minutes. Ketamine, propofol and chloral hydrate (groups A, C and E) depicted lesser degree of analgesia than combinations. Average scores in these groups were (1.50±0.53), (1.62±0.51) and (2.25±0.70) respectively and differed significantly with combination groups.

Recovery in anesthetized animals was quickest in groups A (propofol) and C (ketamine). Average score was (2.50±0.53), depicting average time of 27 Minutes. Recovery score recorded in group E (chloral hydrate) was (2.87±1.1) indicating average time of 29 minutes. Contrarily recovery in groups anesthetized with combination drugs was of moderate duration, with an average time of 45, 44 and 46 minutes in groups B, D and F, respectively. Medetomidine and chloral hydrate combination (group F) took the longest time to recover with average score (4.50±0.53) depicting an average time of 46 minutes. Statistically combination groups showed significant difference with groups in which drugs were used alone. Results of induction, recumbency, sedation, analgesia and recovery are presented in table (1) and bar diagram as figure (1). The best combination showing best results in all parameters studied and showing minimal unwanted effects proved to be group F (medetomidine HCl and chloral hydrate combination) followed by group B (medetomidine HCl and propofol combination. The combination groups were better in efficacy and duration of anesthetic effects where as the groups in which medetomidine HCl was used alone did not show better results in terms of induction, recumbancy, sedation, analgesia and recovery.

Table 1. Effects of medetomidine HCl as pre-anesthetic on propofol, ketamine HCl and chloral hydrate induced anesthesia

S. No	Groups	Treatments	Parameters evaluated				
			Induction	Recumbency	Sedation	Analgesia	Recovery
1	A	Propofol	1.87±0.83^{a}	1.87±0.64^{a}	1.87±0.83^{a}	1.50±0.53^{a}	2.50±0.53^{a}
2	B	Medetomidine HCl/propofol	4.25±1.03^{c}	4.25±0.70^{c}	2.12±0.64^{a}	2.50±0.53^{b}	4.37±0.74^{b}
3	C	Ketamine HCl	1.50±0.53^{a}	2.37±0.51^{ab}	1.50±0.53^{a}	1.62±0.51^{a}	2.50±0.53^{a}
4	D	Medetomidine HCl/ketamineHCl	4.12±0.83^{c}	4.25±0.70^{c}	2.12±0.83^{a}	3.50±0.53^{c}	4.33±0.81^{b}
5	E	Chloral hydrate	2.37±0.51^{b}	2.62±0.51^{b}	1.50±0.53^{a}	2.25±0.70^{b}	2.87±1.1^{a}
6	F	Medetomidine HCl/chloral hydrate	4.75±0.70^{c}	5.25±0.70^{d}	3.25±0.70^{b}	4.75±0.70^{d}	4.50±1.2^{b}

Means carrying same superscripts differed non-significantly (p>0.05) and having different superscripts differed significantly (p<0.05).



1: Propofol, 2: Medetomidine+propofol, 3: Ketamine HCl, 4: Ketamine HCl+medetomidine HCl, 5: Chloral hydrate and 6: Chloral hydrate+medetomidine HCl,* <0.05.

Figure 1: Effects of medetomidine HCl as pre-anesthetic on propofol, ketamine HCl and chloral hydrate induced anesthesia.

DISCUSSION

The efficacy of medetomidine HCl in enhancing the anesthesia induced by propofol, ketamine HCl and chloral hydrate was evaluated. The best combination among six groups was worked out for producing anesthesia in equines.

In first experiment propofol was employed as sole anesthetic agent in experimental horses. Propofol has been reported to induce and maintain safe anesthesia with uneventful recovery when used as continuous infusion in horses (Flaherty *et al*., 1997; Umar *et al*., 2007). Induction of anesthesia with alpha 2 agonists followed by propofol combined with guaifenisen produces smooth and excitement free induction in horses. Induction with alone propofol was noticed to be rapid and smooth (Aguiar *et al*., 1993; Bettschart-Wolfensberger *et al.*, 2005). In present study the mean induction time of anesthesia with propofol alone was 21.25 seconds post injection which was smooth and quick in all animals. This finding is in agreement with Mathews *et al*. (1989) with an induction time of 24 seconds. In contrast, Taylor and Mama *et al.* (1995) declared medetomidine HCl as unsatisfactory for induction and maintenance of anesthesia. Statistically, the horses of group A (propofol) showed non-significant ($p>0.05$) difference in induction with horses anesthetized with ketamine HCl (group C) but significant ($p<0.05$) with all other groups in the current study. The induction of anesthesia in horses administered with a combination of medetomidine HCl and propofol (group B) was achieved in 10 seconds and was smooth in pattern. This finding is similar with results of Betschart-Wolfensberger (2005). The recovery pattern in horses administered with medetomidine plus propofol (group B) was smooth and achieved in 45-55 minutes. In corroboration results had been documented by Bettschart-Wolfensberger (2003). The induction of anesthesia with medetomidine HCl plus propofol combination was smooth and in agreement with results of Betschart-Wolfensberger, (2005). Combination of medetomidine HCl and propofol was suitable for total intravenous anesthesia in ponies (Bettschart-Wolfensberger *et al*., 2001). Field *et al*. (1993) and El-Sayad (2006) found that chloral hydrate induced rapid induction with severe nervous manifestations like stiffness of head, neck and limbs, tremors and struggling.

In current study, Propofol was used in combination with medetomidine which is in line with the approach of Lengley and Keel (1998). Propofol in combination with ketamine in horses has been reported to provide sufficient anesthesia (Flaherty *et al*., 1997; Ohta *et al*., 2004; Umar *et al*., 2007). Propofol produces short duration of action and has cumulative effects and rapid recovery (Langley and Keel, 1998). Ketamine resulted in unwanted effects such as muscle tremors, shivering etc. Ketamine stimulates undesirable catatonic responses like stimulation of limbic system, disphoria, hallucinations, delirium and excitement (Benson and Thurmon, 1990). Duration of recumbency in chloral hydrate plus medetomidine HCl treated group was 45 minutes with loss of all body reflexes and is comparable to picture augmented by Silverman and Muir (1993) and El-Sayad (2006). Chloral hydrate is relatively a good hypnotic but a poor analgesic (Reid *et al*., 1993) and is in accord with results of present experiment. The amount of chloral hydrate needed to produce anesthesia sometimes approaches minimal lethal dose (Reid *et al*., 1993; El-Sayad, 2006).

Duration of recovery is a crucial phase of anesthesia in equines. The poor recovery may result in fractures of quarters (Johnston *et al*., 1995). Qualitative duration of recovery is positively correlated and duration of anesthesia is negatively associated with recovery (Young and Taylor, 1993). The recovery time with medetomidine HCl and propofol combination in present study was (5.25±0.70) with average 53 minutes time and is in line with the findings of (Bueno *et al*., 1999). Mean recovery time for standing in propofol anesthesia was reported to be 20.9 minutes post anesthesia with medetomidine infusion (0.06-0.1mg/kg/min and 0.0583ug/kg/min) by Bettschart- Wolfensberger, (2001). Medetomidine HCl enhances the anesthesia produced by propofol, ketamine and chloral hydrate. Present study will definitely open the new horizons to choose good anesthetics alone or in the form of cocktail to minimize the hazards of conventional drugs in horses.

REFERENCES

Aguiar, A.J.A., C.A. Hussniu, S.P.L. Luna, G.B. Castro, F. Massone and A.L. Alves (1993). Propofol compared with propofol / guaiphenesin after detomidine premedication for equine surgery. J. Vet. Anaesth. 20: 26-28.

Benson, G.J. and J.C. Thurmon (1990). Intravenous anesthesia. Vet. Clin. North Am. Equine Practice. 6: 513-528.

Bettschart-Wolfensberger, R. (2003). Medetomidine-ketamine anaesthesia induction followed by medetomidine-propofol in ponies: infusion rates and cardiopulmonary side effects. Equine Vet. J. 35: 308-313.

Bettschart-Wolfensberger, R., K.K. Karin, N.S. Kästner and A. Fürst (2005). Total intravenous anaesthesia in horses using medetomidine and propofol. Vet. Anas. Analg. 32(6): 348–354.

Bettschart-Wolfensberger, R., S.L. Freeman, N. Jaggin-Schmucker and K.W. Clarke (2001). Infusion of a combination of propofol and medetomidine for long-term anaesthesia in ponies. Am. J. Vet. Res. 62: 500-507.

Bryant. C.E., G.C. England and K.W. Clarke (1991). Comparison of the sedative effects of medetomidine and xylazine in horses. Vet. Rec. 129: 421-423.

Bueno, A.C., J. Cornick-Seahorn, T.L. Seahorn, G. Hosgood and R.M. Moore (1999). Cardiopulmonary and sedative effects of intravenous administration of low doses of medetomidine and xylazine to adult horses. Am. J. Vet. Res. 60: 1371−1376.

Clark, L., R. Clutton, K. Blissitt and M. Chase-Topping (2008). The effects of morphine on the recovery of horses from halothane anaesthesia. Vet. Anaesth. Analg. 35: 22-29.

Correll, G.E., J. Maleki, E.J. Gracely, J.J. Muir and R.E. Harbut (2004). Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Med. 5(3): 263–275.

El-Sayad, A.M.M. (2006). Using of propofol as a general anesthetic in equine in comparison with other anesthetics. M.Sc. Thesis. Tanta univ. Kafr El sheikh branch.

Field, K.J., W.J. White and C.M. Lang (1993). Anaesthetic effects of chloral hydrate pentobarbitone and urethane in adult male rats. Lab. Anim. 27(3): 258–269.

Flaherty, D., J. Reid, E. Welsh, A.M. Montiero, P. Lerche and A. Nolan (1997). A pharmacodynamic study of propofol or propofol and ketamine infusions in ponies undergoing surgery. Res. Vet. Sci. 62: 179-184.

Green, S.M., K.J. Clem and S.G. Rothrock (1996). Ketamine safety profile in the developing world: survey of practitioners. Acad. Emerg. Med. 3(6): 598-604.

Hellebrekers, L.J., J.F. Van, C.U. Hird, R. Rosenhagen, O.S. Vainio (1997). Clinical efficacy and safety of propofol or ketamine anaesthesia in dogs premedicated with medetomidine. Vet. Record. 142: 631-634.

Hoffman, J.N., S. Steinhagen, C. Kast, H.P. Scheuber, M. Jochum, C. Gippner-Steppert, D. Inthorn, F.W. Schildberg and D. Nolte (2002). Chronic left heart catheterisation for microvascular blood flow determination in the rabbit: A minimally invasive technique using specially designed port devices. J. Surg. Res. 102: 119-125.

Johnston, G.M., P.M. Taylor, M.A. Holmes and J.L.N. Wood (1995). Confidential enquiry into perioperative equine fatalities (CEPEF-1): preliminary results. Equine Vet. J. 27: 193-200.

Johnston, G.M., P.M. Taylor, M.A. Holmes and J.L.N. Wood (1995). Confidential enquiry into perioperative equine fatalities (CEPEF-1): preliminary results. Equine Vet. J. 27: 193-200.

Kamerling, S., M. Keowen, C. Bagwell and W. Jochle (1991). Pharmacological profile of medetomidine in the equine. Acta. Vet. Scand. 87: 161-162.

Kastner, S.B., M. Boller, A. Kutter, M.K. Akens and R. Bettschart-Wolfensberger (2001a). Clinical comparison of preanaesthetic intramuscular medetomidine and dexmedetomidine in domestic sheep. Dtsch. Tierarztl. Wochenschr. 108: 409-413.

Langley, M.S. and R.C. Keel (1988). Propofol: A review of its pharmacodynamics and pharmacokinetic properties and use as an intravenous anaesthetic. Drugs. 35: 334–372.

Langley, M.S. and R.C. Keel (1988). Propofol: A review of its pharmacodynamics and pharmacokinetic properties and use as an intravenous anaesthetic. Drugs. 35: 334-372.

Mama, K.R., E.P. Steffey and P.J. Pascoe (1995). Evaluation of propofol for general anesthesia in premedicated horses. Am. J. Vet. Res. 57: 512-516.

Matthews, N.S., S.M. Hartsfield, B. Hague, G.L. Carroll and C.E. Short (1999). Detomidine-propofol anesthesia for abdominal surgery in horses. Vet. Surg. 28(3): 196-201.

Muir, W.W. and J.E. Gadawski (1998). Respiratory depression and apnea induced by propofol in dogs. Am. J. Vet. Res. 38: 195-201.

Muir, W.W. and R. Sams (1992). Effects of ketamine infusion on halothane minimal alveolar concentration in horses. Am. J. Vet. Res. 53: 1802-1806.

Muir, W.W., J.A. Hubell, R.M. Bednarski and R.T. Sharda (2007). Hand Book of Veterinary Anesthesia: 4th Edn. Chap 3. Mosby. An Affiliate of Elsevier Inc. USA. Pp: 140-163.

Ohta, M., K. Oku, K. Mukai, K. Akiyama and Y. Mizuno (2004). Propofol-ketamine anesthesia for internal fixation of fractures in race horses. J. Vet. Med. Sci. 66(11): 1433-1436.

Raekallio, M., M. Hackzell and L. Eriksson (1994). Influence of medetomidine on acid-base balance and urine excretion in goats. Acta. Vet. Scand. 35: 283-288.

Reid, J., A.M. Nolan and E. Welsh (1993). Propofol as induction agent in the goat: a pharmacokinetic study. J. Vet. Pharmacol. Ther. 16(4): 488-493.

Segal, I.S., R.G. Vickery and J.K. Walton (1988). Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. Anesthesiol. 69: 818-23.

Silverman, J. and W.W. Muir (1993). A review of lab animal anesthesia with chloral hydrate and chloralose. Lab. Anim. Sci. 43(3): 210-216.

Silverman, J. and W.W. Muir (1993). A review of laboratory animal anesthesia with chloral hydrate and chloralose. Lab. Anim. Sci. 43: 210 –216.

Umar, M.A., K. Yamashita, T. Kushiro and W.W. Muir (2007). Evaluation of cardiovascular effects of total intravenous anesthesia with propofol or a combination of ketamine-medetomidine-propofol in horses. Am. J. Vet. Res. 68(2): 121-127.

Virtanen, R., J.M. Savola, V. Saano and L. Nyman (1988). Characterization of the selectivity, specificity and potency of medetomidine as an x2-adrenoceptor agonist. Eur. J. Pharmacol., 150, 9-14.

Wagner AE, Muir WW III and Hinchcliff KW (1991). Cardiovascular effects of xylazine and detomidine in horses. Am. J. Vet. Res. 52: 651–657.

Wright, M. (1982). Pharmacologic effects of ketamine and its use in veterinary medicine. J. Am. Vet. Med. Assoc. 180: 1462-1471.

Young, S.S. and P.M. Taylor (1993). Factors influencing the outcome of equine anaesthesia: A review of 1314 cases. Equine Vet. J. 25: 147–151.