"Comparative Studies On The Efficacy Of Propofol, Midazolam Alone And In Combination As Intravenous Anaesthetics In Swine"

THESIS

SUBMITTED TO THE

RAJENDRA AGRICULTURAL UNIVERSITY

(FACULTY OF POST-GRADUATE STUDIES)

PUSA (SAMASTIPUR), BIHAR

In partial fulfilment of the requirements

FOR THE DEGREE OF

MASTER OF VETERINARY SCIENCE IN

(VETERINARY SURGERY & RADIOLOGY)

By

NARENDRA KUMAR

Registration No. M/VSR/34/2004-2005

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By

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DEDICATED

TO

MY

RESPECTED

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CERTIFICATE- I

This is to certify that thesis entitled *"COMPARATIVE STUDIES ON THE EFFICACY OF PROPOFOL, MIDAZOLAM ALONE AND IN COMBINATION AS INTRAVENOUS ANAESTHETICS IN SWINE"* submitted in partial fulfilment of the requirements for the Degree of **Master of Veterinary Science (Veterinary Surgery and Radiology)** of the Faculty of post-graduate studies, Rajendra Agricultural University, Pusa, Samastipur, Bihar is the record of bonafied research work carried out by **Dr.Narendra KUMAR**, Registration No. M/VSR/34/2004-2005, under my supervision and guidance. No part of the thesis has been submitted for any other degree or diploma.

It is further certified that the assistance and help received during the course of this investigation and preparation of the thesis have been fully acknowledged.

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We, the undersigned members of the Advisory Committee of **Dr. Narendra Kumar**, Registration No. M/VSR/34/2004-2005, a candidate for the Degree of **Master of Veterinary Science** with major in **Veterinary Surgery and Radiology** have gone through the manuscript of the thesis and agree that the thesis entitled *"COMPARATIVE STUDIES ON THE EFFICACY OF PROPOFOL, MIDAZOLAM ALONE AND IN COMBINATION AS INTRAVENOUS ANAESTHETICS IN SWINE"* may be submitted by **Dr. Narendra Kumar** in partial fulfilment of the requirements for the degree.

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This is to certify that the thesis entitled *"COMPARATIVE STUDIES ON THE EFFICACY OF PROPOFOL, MIDAZOLAM ALONE AND IN COMBINATION AS INTRAVENOUS ANAESTHETICS IN SWINE"* submitted by **Dr. Narendra Kumar** Registration No. M/VSR/34/2004-2005, in partial fulfilment of the requirements for the Degree of **Master of Veterinary Science (Veterinary Surgery and Radiology)** of the Faculty of Post-Graduate studies, Rajendra Agricultural University, Pusa, Samastipur, Bihar was examined and approved on 20/04/07 2007.

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"All might not have been mentioned, but none is forgotten."

Place: *B.V.C., PATNA*

Date: 25/06/07

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CHAPTER - I

INTRODUCTION

INTRODUCTION

Pig is an omnivorous mammal belonging to **family-Suidae, sub-order Suiformes** and **Order Artiodactyla**. In the beginning of its history, which probably goes back some 7000 years, the pig was a forest dwelling animal descendent of wild European boar (*Sus scrofa*). The feature common to all pigs possess as a flat rounded snout on a flexible muzzle, also there is modification of the upper canine teeth into tusk. Some popularly recognised breeds of pigs are **Hampshire, Poland-China, Landrace, Berkshire, Chesterwhite, Duroc, Yorkshire, Tamworth, Hereford** etc.

Because of squealing, struggling and sometimes aggressive nature, pigs are difficult to handle which make the operator disposed to adopt tranquilizing, immobilizing and anaesthetizing agent often desirable or necessary. Satisfactory anaesthesia for the performance of painful surgical interferences on animal is essential from two standpoints: the first, Humanitarian, and second that of Technical Efficiency.

The important surgical manoeuveres in swine, which require anaesthesia for painless operations are caesarean section, castration, amputation of prolapsed uterus, claw amputation, scrotal hernia, umbilical hernia, orthopedic surgery, colostomy in pig to correct colon stricture, correction of cryptorchidism, clitorotomy for fattening, removal of scirrhous cord, hysterectomy etc. (Fussell, *et al.,* 1960; Tableman, 1960; Dyson, 1964; Mc Fadden, 1961; Bollwahn, 1964; Beswick, 1964; Wright, 1963; and Buz'ko *et al.*1961).

Surgery carried out on pigs using either local analgesia or general anaesthesia in farms. When general anaesthesia is employed under farm condition, simple method giving short-term anaesthesia is enough, as surgery is usually limited in complexity. However, the pigs are often used as an experimental animal in research project involving long and complicated surgery and in such circumstance sophisticated anaesthetic techniques, possibly even including cardiopulmonary by-pass may be required.

Today pigs are increasingly used in various research projects like, xenografting, bone marrow transplantation etc. Advanced heart and other surgeries of human are also done firstly on porcine model. These require further advanced combination of anaesthetic drugs that have list of good qualities like more control over depth of anaesthesia, least harm on the different metabolism of pigs, so it can produce good surgical analgesia for desired period and produce no complication during recovery.

In spite of all the achievements made by the scientist and anaesthetist, there is no single anaesthetic method or agent that produces an ideal anaesthesia under all circumstances. Although, numbers of agents are being used as anaesthetic agents, there is an explicit need for employing the efficacy of particular agent, which can be safely used to produce the desired effect.

In such circumstances the present research work has been conducted using new combination of anaesthetics on pigs. One is an anxiolytic Midazolam and another is hypnotic Propofol.

Propofol is an intravenous anaesthetic agent chemically unrelated to other anaesthetics such as barbiturates, alpha-2 agonists, phencyclidines. Many researches were done in the early 70s, to develop a new and safe injectable anaesthetic and it was discovered that some phenol derivatives

has hypnotic properties. Those researches resulted in the development of a new molecule, (*2, 6-di-isopropyl phenol*) popularly named as **Propofol.** It had a short duration of action in small experimental animals like horses (Nolan and Hall, 1985), dogs (Watkins *et al*; 1987), sheep (Waterman, 1988) and cats (Brearley et *al*; 1988).

Midazolam ***(8-chloro-6 (2-fluorophenol)-1-methyl-4H-imidazol)*** a potent, short acting, water-soluble benzodiazepine derivative is a promising intravenous (I/V) anaesthetic agent (Reves *et al.*, 1978). It is about twice as potent as diazepam and its half-life is considerably shorter than that of diazepam and thus it is less cumulative and recovery is more rapid (Reves *et al.*, 1985). These properties have led it, to be used as "Preanaesthetic". It can be given by intramuscular (I/M) route as it is not painful and does not produce thrombophlebitis like Diazepam.

In this endeavour, this research work was undertaken to explore the possibilities to evolve the general anaesthesia in swine as Midazolam, Propofol alone and in combination for various operative procedures by analyzing the effects on clinical, haematoloical, biochemical and anaesthesiological studies. Keeping in view of above-mentioned facts, the present study has been undertaken with following objective:

(a) To study the efficacy of propofol as intravenous (I/V) anaesthesia.
(b) To study the efficacy of midazolam as intravenous (I/V) anaesthesia.
(c) To study the efficacy of above two drugs in combination as intravenous (I/V) anaesthesia.
(d) Comparative study of all the above drugs.

The selection of anaesthetic method depends on the nature of the operation performed; its magnitute, site and duration. The duration of the operation influences the selection of the anaesthetic agent especially when adopting general anaesthesia. For major interferences under general anaesthesia, particularly when the operation is for long duration and it requiring animal to remain quiet for several hours after operation. Overall the anesthetics agent must be used judiciously in animals.

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CHAPTER - II

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Available literatures reveal scanty information regarding use of Propofol and Midazolam in combination as general anaesthetic in swine, but Nolan and Hall (1985) assessed the use of propofol, solubilised in a non-ionic emulsifying agent for the induction and maintenance of anaesthesia in experimental ponies. Pilot studies revealed that premedication with xylazine (0.5 mg/kg body weight) intravenously followed by propofol (2.0 mg/kg) intravenously provided a satisfactory smooth induction. Two infusion rates (0.15 and 0.2 mg/kg/minute) were compared for maintenance of anaesthesia. An infusion rate of 0.2 mg/kg/ minute produced adequate anaesthesia in those ponies. Cardiovascular changes included a decrease in arterial pressure and cardiac output during maintenance. Respiratory depression was manifested by a decrease in rate and an increase in arterial carbon dioxide tension. Post anaesthetic recovery was rapid and smooth after one hour.

Hall and Chambers (1987) Premedicated 40 dogs with acepromazine (0.05 mg/kg) and atropine (0.02 mg/kg) to determine the minimum infusion rate of propofol needed to maintain anaesthesia and to compare the quality of the anaesthesia with that produced by halothane/nitrous oxide/oxygen. In 30 dogs, anaesthesia was induced with propofol and maintained with a continuous infusion, while in other ten dogs anaesthesia was induced with thiopentone and maintained with the inhalation agents. An infusion rate of 0.4 mg/kg/minute of propofol produced surgical anaesthesia in dogs breathing oxygen or oxygen-enriched air.

Cardiovascular and respiratory effects were similar to those in dogs anaesthetized with halothane/nitrous oxide and, with both anaesthetic regimens, myocardial oxygen consumption appeared to increase with increasing duration of anaesthesia. A possible familial susceptibility resulting in a more prolonged recovery was revealed, and propofol infusion was associated with a 16% incidence of vomiting in the recovery period. It was concluded that in canine continuous infusion of propofol to maintain anaesthesia in healthy dogs was safe but less satisfactory than the use of halothane/nitrous oxide.

Watkins *et al.* (1987) studied an emulsion formulation of the intravenous anaesthetic propofol in dogs and marked smooth induction of anaesthesia which was possible to maintain anaesthesia by intermittent injection. The mean dose for induction of anaesthesia in unpremedicated dogs was 5.95 mg/kg body weight. When no premedication was administered anaesthesia was maintained by a total dose of approximately 0.806 mg/kg/minute. Premedication in between 0.02 to 0.04 mg/kg of acepromazine reduced the mean induction dose by about 30% and the maintenance dose by more than 50%. In 68 unpremedicated dogs given one dose, recovery was complete in a mean time of 18 minutes, and after maintenance of anaesthesia by intermittent injection in 65 dogs the mean recovery time was 22 minutes from administration of the last dose. Premedication with acepromazine did not produce statistically significant increase in those recovery times. The quiet, rapid and complete recovery proved to be most valuable in cases where the animal had to be returned to the owner's care with the minimum of delay.

Brearley *et al.* (1988) had done a trial in which Propofol was administered to 49 cats to induce anaesthesia. The mean dose required was 6.8 mg/kg and that was not affected by prior administration of

acepromazine maleate. In 27 cases, propofol was also used as the principal maintenance agent (mean dose rate 0.51 mg/kg/minute). Inductions were very smooth and problem-free. Intubation was easily achieved in 15 cats with the aid of local desensitisation by lidocaine spray or neuromuscular relaxation by suxamethonium. Heart rate did not vary significantly during induction or maintenance of anaesthesia but respiratory rates did fall significantly. Recovery from anaesthesia was remarkably smooth in all cases and there was no significant difference in recovery time between the cats in which halothane was the principal maintenance agent and cats, which received propofol alone. Side effects were seen during recovery in eight cats and included retching, sneezing and pawing of the face.

Waterman (1988) studied that Propofol, a short-acting intravenous anaesthetic which was given by slow intravenous injection into a cephalic vein to induce anaesthesia in 5 sheep, weighing between 30 and 50 kg. Following intubation, anaesthesia was maintained with 1% halothane vaporized in a 50/50 oxygen/nitrous oxide mixture. Induction and recovery was compared with that of another 5 sheep in which anaesthesia was induced by the administration of 5% halothane vapourised in a 50/50 oxygen/nitrous oxide mixture and anaesthesia was maintained as in the first group. Both groups of sheep were starved overnight but were not premedicated. The mean dose of propofol required to induce anaesthesia was 3.5 mg/kg (range 3.0-4.0 mg/kg) and induction was very good. Recovery time after approximately 32 minutes anaesthesia were almost identical for both the groups. The mean time (in minutes) to swallowing was 1.8 ± 0.8, to sternal recumbency 6.0 ± 2.0 and to standing 8.0 ± 3.6 in the propfol group compared with 2.0 ± 0.7, 3.6 ± 1.5 and 9.2± 3.8 for the halothane group respectively.

Tranquilly *et al.* (1990) evaluated a preliminary trial of the Midazolam- Xylazine mixtures in 12 dogs in different doses by different routes (IM and IV). Both drugs regimens induce rapid and profound sedation or anaesthesia with variation in duration of action. High dose of Xylazine (2.2mg/kg IM) had and arousal time of 95.4 $\pm$ 8.9 minutes and walking time of 155.4 $\pm$ 8.8 minutes which exceeded the I/V Xylazine (1.1mg/kg) values 3 times. Partial reversal of CNS depression was accomplished with antagonist of either drug.

Hellebrekers (1991) studied sulfentanyl and Midazolam anaesthesia in 24 dogs with gastric dilation and volvulus which were admitted for surgery. Mean body weight and average age of the dogs were 38 $\pm$ 2 kg and 7 $\pm$ 0.5 years respectively. A smooth and easy induction was obtained by I/V sulfentanyl / Midazolam, without previous premedication. All patients demonstrated great haemodynamic stability with only a sporadic occurrence of ventricular ectopic beats. During the recovery period no upward signs could be detected.

Court and Greenbalt (1991) studied the pharmacokinetics of Midazolam following I/V and I/M administration of 0.5mg Midazolam hydrochloride per kg b.wt. to 5 healthy mixed bred dogs. The deposition of Midazolam following I/V administration was characterized by very rapid elimination and mean elimination half life was 77 $\pm$ 18 minutes following I/M administration and absorption of 549 $\pm$ 121µg/ml was decreased within 15 minutes and systemic availability was over 90% in each dog.

Cullen and Reynoldson (1993) experienced the prolonged Propofol (6.55mg/kg) anaesthesia after Xylazine (0.8mg/kg IM) and Medetomidine (30µg/kg IM) premedication with the production of apnoea and hypoxaemia. Propofol alone reduced blood pressure and transient rise in heart rate, hypoxaemia was pronounced in Medetomedine / Propofol grou and Bradycardia was a

common feature in both Xylazine and Medetomidine group but hypertension was considerably recorded in Medetomidine group.

Greene *et al.* (1993) observed 12 % decrease in dose of thiamylal required for tracheal intubation after Midazolam compared to that after the placebo. They also suggested the Thiamylal dose was significantly decreased after Midazolam compared with placebo for dog weighing more than 15 Kg. but not for dogs weighing less than 15kg.

Rosenberg *et al.* (1997) used propofol alone on 100 patients. They compa red the complication rates and times to awakening and to discharge for propofol versus other drugs used for sedation in those patients. In review 277 total procedures were performed on 236 patients. Propofol was given alone in 127 cases and other medication (Midazolam, Fentanyl, Ketamin-alone or in combination) were given in 141 cases or a total of 268 cases. The complication rate for those 268 cases was 19% (51 complications).There were 24 complications in the Propofol group (9 airways and 15 haemodynamic) and 27 complications in other medication group (20 airways and 7 haemodynamic). Airways complication requiring repositioning of patient bag-valve-mask ventilation, higher oxygen flow rates, racemic Epinephrine or intubation occurred more frequently with the non-propofol medications. Haemodynamic complication resolved immediately for both groups with crystalloid infusion. In their experience, propofol had been a viable alternative to other commonly used sedatives during invasive procedures by providing a lower airways complication rate, shorter average time to awakening and discharge and potential cost saving for pediatric outpatient procedures.

Reimann *et al.* (2000) observed that the low dose Midazolam (2mg) and repeated injections of Propofol (median 100 mg) with maximum bolus of 50 mg produced a synergistic sedation, which was an effective and

economic alternative to Benzodiazepine based analgosedation. It was associated with a high degree of patient comfort from the point of view of the endoscopist. Rapid recovery was observed in combination anaesthesia.

Vulpe and Nastasa (2000) described different anaesthetic techniques for immobilizing small animals (dogs and cats) for radiological examination. The effects of the techniques on vital parameters was assessed and the following drug combinations were recommended in decreasing order of preference: i.v. medetomidine (2 μg/kg) + midazolam (0.5 mg/kg); i.v. fentanyl (0.02 mg/kg) + midazolam (0.3 mg/kg); i.v. morphine (2 mg/kg) + droperidol (3 mg/kg).

Nastasa *et al.* (2000) used to determine the effects and anaesthetic duration of 0.1% medetoidine (0.03 ml/kg), 20% ketamine (0.05 ml/kg) and 0.5% midazolam (0.125 ml/kg) combination in 17 race dogs. It was observed that after 4 minutes of administration there was installation of deep nervous depression. After 7 minutes, there was progressive diminution of tension. There was a reduced medial rotation of eyeball. After 40 minutes, the mucous membranes were pale and hypermediated with a capillary refilling time of 1 to 2 seconds. The complete recovery time was 80 minutes without secondary adverse effects.

They also conducted the study to determine the effects of 0.5% midazolam (0.14 ml/kg), 10% ketamine (0.1 ml/kg) and 2% xylazine (0.02 ml/kg) combination in 13 racing dogs. It was observed that immediately after administration, the animals experienced a hypnotic sleep with loss of voluntary control. After 20 minutes, there was a reduction in breathing and patellar reflex. 30 minutes after,there was paleness of mucosa with a capillary refilling time of 2 seconds. The recovery was complete within 20 minutes of animals awakening without secondary adverse effects.

Cura *et al.* (2000) observed the effects of 0.5% fentanyl (0.042 mg/kg) and 0.5% midazolam (1.5 mg/kg) combination in racing dogs (n=15). It was observed that as early as the time of administration the dogs experienced instillation of nervous depression with loss of voluntary movements and attenuation of tendinous, muscular reflexes and breathing. The eyeballs were in the centre with pupillary reflex. Mucous membranes were hypermediated and dry with a capillary refilling time of 2 seconds. After 40 minutes there was a slight decrease of vital signs. The dogs had a slow recovery period accompanied by behavioral disturbances in 20%. It was concluded that the anaesthetic combination could be recommended as preanaesthetics with minor risk to the animals.

Stegmann *et al.* (2001) conducted anaesthesia with Propofol (4mg /kg) after I/V premedication with or without Midazolam (0.1 mg/ kg), in a group of 8 dogs scheduled for ovariohysterectomy. Midazɔl m administration induced acute behavioural changes and increase reflex suppression after Propofol induction. Compared to the control group, the dose required to obtain loss of the pedal reflex was significantly reduced by 37% and the end-tidal isoflurane concentration during maintenance, reduced by 23%.

Stegmann and Bester (2001) done a randomized, placebo-controlled clinical trial where anaesthesia was induced with propofol (4 mg/kg) after intravenous premedication with or without midazolam (0.1 mg/kg), in a group of 8 dogs scheduled for ovariohysterectomy. Midazolam administration induced acute behavioural changes and increased reflex suppression after propofol induction. Compared to the control group, the dose required to obtain loss of the pedal reflex was significantly reduced by 37% and the end-tidal isoflurane concentration during maintenance, reduced by 23%.

Gulanber *et al.* (2001) applied midazolam-ketamine anaesthesia in 15 dogs. Heart rate, respiratory rate and rectal temperature were taken during preanaesthetic and anaesthetic periods. Blood samples were taken for complete blood count and blood biochemical values during preanaesthetic and anaesthetic periods. Results indicate that midazolam-ketamine anaesthesia is very useful and safe in dogs.

Valadao *et al.* (2001) studied the combination of nalbuphine with acepromazine or midazolam in dogs. 12 dogs of both sexes, weighing 7 to 18 kg were divided into 2 groups (group 1; n=7 and group 2; n=5). A catheter was introduced into the femoral right artery under local anaesthesia. The baseline (T0) systolic, diastolic, and mean arterial blood pressure (MABP), heart (HR) and respiratory rates (RR) and rectal temperature (RT) were measured. Acepromazine (0.1 mg/kg) or midazolam (0.05 mg/kg) were administered intravenously (IV) to groups G1 and G2 respectively. The same parameters were measured 5 min later, and 1 mg/kg of nalbuphine (IV) was injected to both groups. The parameters and the pedal reflexes were again recorded 5 minutes later (T10) and every 10 minutes (T20-T70). Acepromazine induced sedation and reduced the MABP until the end of the study (T70). Temperature was reduced at T30 until T70. Midazolam injection induced excitability in G2 dogs 5 minutes later, and nalbuphine did not attenuate this effect. Loss of interdigital reflex was not observed in both groups. MABP was lower in group G1 animals than in group G2 animals from T10 to T70. RR increased in G2 dogs. Nalbuphine neither modified the hypotension produced by acepromazine nor the excitability induced by midazolam.

Alkan *et al.* (2001) carried out the study in two groups, each consisting of 6 dogs. In the first group a combination of midazolam (Dormicum, 1 mg/kg IM)-ketamine (Ketalar, 20 mg/kg IM) (M-K) and the

second group a combination of diazepam (Diazem, 0.2 mg/kg IV)-ketamine (20 mg/kg IM) (D-K) was used. The effects of combinations of these injectable anaesthetics on arterial blood pressures, blood gases and some physiological functions of the dogs were evaluated. All baseline measurements were made before the anaesthesia as baseline values and all measurements were repeated at 15, 30, 60, 90 and 120 minutes intervals after the anaesthesia. Heart and respiratory rates were higher than those of baseline levels at all time intervals. Neither anaesthetic combination had any significant effect on body temperature. Mean arterial blood pressure consistently increased in the D-K group compared to M-K group. Mean arterial blood pressure was significantly different between both groups after 60 and 120 minutes. $PaCO_2$ values were significantly different between both groups after 120 minutes administration. There were not any significant differences in PaO_2 due to anaesthetic combination. Arterial pH differed significantly between groups at 15 minutes after administration.

Taylor *et al.* (2001) conducted experiment in which Pre-anaesthetic medication with intravenous (IV) acepromazine (ACP, 20 μg/kg), butorphanol (Torbugesic, 20 μg/kg) and detomidine (Domosedan, 10 μg/kg) was given 30 minutes before induction of anaesthesia with detomidine (10 μg/kg) and ketamine (Vetalar, 2 mg/kg) intravenously. Maternal arterial blood pressure was recorded (facial artery) throughout anaesthesia. Arterial blood gas values and plasma concentrations of glucose, lactate, cortisol and propofol were measured at 20- minutes intervals. Anaesthesia was maintained with propofol infused initially at 200 μg/kg/min, and at 130-180 μg/kg/ minutes after 60 minutes, ventilation was controlled with oxygen and nitrous oxide to maintain $PaCO_2$ between 5.0 and 6.0 kPa (37.6 and 45.1 mm Hg) and PaO_2 between 13.3 and 20.0 kPa (100 and 150.4 mm Hg). During anaesthesia, flunixin (Finadyne, 1 mg/kg

IV), procaine penicillin (Depocillin, 6 IU i.m.) and butorphanol (80 μg/kg i.m.) were given. Lactated Ringer's solution was infused at 10 ml/kg/h. Simultaneous fetal and maternal blood samples were withdrawn at 85-95 minutes. Recovery from anaesthesia was assisted. Results: Arterial blood gas values remained within intended limits. Plasma propofol levels stabilized after 20 min (range 3.5-9.1 μg/kg); disposition estimates were clearance 6.13±1.51 l/min (mean±SD) and volume of distribution 117.1±38.9 l (mean±SD). Plasma cortisol increased from 193±43 nmol/l before anaesthesia to 421±96 nmol/l 60 min after anaesthesia. Surgical conditions were excellent. Fetal umbilical venous pH, PO_2 and PCO_2 were 7.35±0.04, 6.5±0.5 kPa (49±4 mm Hg) and 6.9±0.5 kPa (52±4 mm Hg); fetal arterial pH, PO_2 and PCO_2 were 7.29±0.06, 3.3±0.8 kPa (25±6 mm Hg) and 8.7±0.9 kPa (65±7 mm Hg), respectively. Recovery to standing occurred at 46±17 minutes and was generally smooth. Ponies regained normal behaviour patterns immediately. Conclusions and clinical relevance: Propofol anaesthesia was smooth with satisfactory cardiovascular function in both mare and fetus; we believe this to be a suitable anaesthetic technique for pregnant ponies.

Ozaydin *et al.* (2001) investigate the effects of general anaesthesia obtained by the combination of medetomidin propofol and ketamine on their anaesthetic properties, cardiovascular and respiratory system. Seven dogs were studied. Following 10 μg/kg administration of medetomidine, the combination of propofol 3.5mg/kg and ketamine 10mg/kg were injected intravenously for each animal and therefore general anaesthesia induced. ECG (Electrocardiogram) assessment, heart rate, respiration, body temperature and some blood parameters were evaluated for all animals before and after premedication at 5th minutes, during anaesthesia at 15, 30 and 60 minutes. Hematological analysis, including erythrocyte and

leukocyte counts; haemoglobin and haematocrit values were carried out in 5 ml blood sample taken at each interval of the anaesthesia. The sedative and analgesic effect of the agents were evaluated as to the positioning of the animal, sensitivity to environmental objects and the reflex against pin needle, pedal and palpebral and pupillar. Decrease in rectal temperature and bradycardia were noted throughout the anaesthesia. Similarly, following the administration of the anaesthetic agent, decrease in respiratory rate for all animals and temporary apnea were observe for 3 dogs. No abnormal ECG findings were obtained for all animals except sinus bradycardia arrythymia during the anaesthesia between 6 to 60 minutes. Sedative effects of the premedicated agent commenced within two minutes. However, deep anaesthetic effect started approximately in 8 minutes. The recovery time was recorded between 68 to 100 (mean 86.1) minutes. Non-significant alterations were obtained between hematocrit, haemɔglobin values and erythrocyte and leukocyte counts during the anaesthesia. In conclusion, the anaesthetic agent combinations used in the present study was found to have a reliable anaesthetic properties except causing temporary cardiac and respiratory problems in some dogs.

Yamashita *et al.* (2001) evaluated the effects of Combinations of medetomidine (5 μg/kg IV) with thiopental (12.5 mg/kg IV; MT, n=50), ketamine (5 mg/kg IV; MK, n=50), or propofol (4 mg/kg IV; MP, n=50) as premedication and induction for inhalation anesthesia in 150 dogs (ASA Classes I and II, 6.0±4.2 years old). Surgical anesthesia was maintained with 50% nitrous oxide and 50% oxygen-sevoflurane. All dogs became calm and relaxed after administration of medetomidine. Heart rates decreased in 145 dogs (59.7±21.1% of preanaesthetic values). Vomiting occurred in 29 dogs. One dog demonstrated signs of pain upon being injected with propofol. After administration of ketamine, convulsions

occurred in 8 dogs. An initial period of apnea was observed after intubation in 42 MT, 15 MK, and 15 MP dogs. Controlled ventilation was required for 32 MT and 8 MK dogs. End-tidal sevoflurane concentration during surgery was 1.6-1.7% in MT, 1.9-2.0% in MK, and 2.1-2.3% in MP dogs. During all treatment, heart rate was maintained at approximately 110 bpm and mean arterial blood pressure at between 100 and 120 mmHg. Recovery was rapid and most dogs were extubated within 5 minutes after the end of anesthesia. MT, MK, and MP resulted in smooth induction and rapid recovery from anesthesia in dogs free of severe systemic diseases. Apnea was the most frequently observed side effect.

Gremiao *et al.*(2001) evaluated the probable changes that occur in the mean arterial pressure (MAP) when hyperbaric bupivacaine 0.5% (0.3 mg/kg) was used in the subarachnoid space of 6 healthy female mongrel dogs, between 7 and 15 kg and 1- to 5-years-old. All the animals were physically restrained and a catheter was introduced into the cranial branch of the saphenous artery by a percutaneous procedure to measure MAP. Then, the dogs were pre-oxygenated with air for 5 minutes and then were induced with propofol (6 mg/kg i.v.). Upon the loss of protective reflexes, MAP was measured for the second time. After endotracheal intubation, the third MAP was measured. The animals were then monitored and during the maintenance of a continuous infusion of propofol (0.5 mg/kg/min), MAP was measured every 5 and 10 minutes for 15 minutes. Afterwards, the spinal needle was introduced in lumber6 - lumber7 interspace for the bupivacaine administration. Once the subarachnoid anaesthesia was accomplished, MAP was measured every 5 minutes for 1 hour. Hypotension was not observed in any of the patients.

Aguiar *et al.* (2001) evaluated the cardiopulmonary and clinical effects of three different infusion rates of propofol in dogs premedicated

with methotrimeprazine. Ten healthy adult mixed-breed male and female dogs, weighing 14 to 20 kg. premedicated with methotrimeprazine (Neozine, 1 mg/kg intravenously (IV)) followed by induction of anaesthesia with propofol (Diprivan, 4.5 mg/kg IV) and maintenance with propofol for 60 minutes as follows: T1, 0.2 mg/kg/min; T2, 0.3 mg/kg/min; and T3, 0.4 mg/kg/min. Heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), arterial haemoglobin oxygen saturation, arterial blood gases, and pedal and cutaneous reflexes were measured before and 5, 10, 20, 30, 45 and 60 minutes after the beginning of the propofol infusion. Statistical analysis was performed using an ANOVA. Results: Heart rate increased during anaesthesia in all cases and arterial blood pressure decreased only in dogs in the T3 category. Respiratory depression was proportional to the infusion rate of propofol. Muscle relaxation was satisfactory but analgesia was inadequate in the three treatments. Conclusions: The infusion of 0.2-0.4 mg/kg/ minute of propofol produced a dose-dependent respiratory depression. The presence of a pedal withdrawal reflex and marked cardiovascular responses to this noxious stimulus suggests that anaesthesia may not be of sufficient depth for surgery to be carried out. Clinical relevance: Although several studies had been performed using propofol in animals, few studies have investigated the cardiopulmonary and analgesic effects with different doses. The determination of an adequate propofol infusion rate is necessary for the routine use of this intravenous anaesthetic for the maintenance of anaesthesia during major surgical procedures in dogs.

Zamur and Queiroz (2002) studied to evaluate the antinociceptive and sedative effects of midazolam and diazepam in thoroughbred mares. The sedative effects of midazolam (0.05, 0.1, and 0.15 mg/kg intravenously) and diazepam (0.05, 0.15, and 0.25 mg/kg intravenously)

were investigated by determination of the spontaneous locomotors activity (SLA) in automated behaviour stalls and by measuring the head ptosis (HP). The antinociceptive effect was determined using a heat-projecting lamp by measuring the hoof withdrawal reflex latency (HWRL) and the skin twitch reflex latency (STRL). The differences were evaluated by Turkey's test ($P < 0.05$). A significant increase in SLA was observed only for diazepam at a dose of 0.05 mg/kg in comparison to control (saline). Midazolam decreased the head height ($P < 0.05$), leading to sedation between 5 and 75 minutes after drug administration. Diazepam showed a maximum antinociceptive effect (> 10 s) in all animals tested at a dose of 0.15 mg/kg, within 5 minutes. Midazolam produced a good sedative effect and diazepam, a short-acting antinociceptive effect.

Adamiak *et al.* (2002) had done a trial in which anaesthesia for arthroscopic examination was carried out on 30 dogs. All the animals were premedicated with atropine (Atropinum sulfuricum) and Midazolam (Dormicum). General anaesthesia was achieved using Propofol (5.5mg/kg body wt. I/V).Arthroscopic procedures were performed on all dogs. Blood samples were taken for haematological, biochemical and acid based balance during the operations. The results of clinical, haematological and biochemical examinations show that anaesthesia using Atropine, Midazolam and Propofol is effective and clinically useful in arthroscopic procedures in dogs.

Kojima *et al.* (2002) evaluated dose-sparing effects of medetomidine-midazolam (MM), acepromazine-butorphanol (AB), and midazolam-butorphanol (MB) on the induction dose of thiopental and propofol and to examine cardiopulmonary changes in dogs. 23 healthy Beagles dogs were administered MM (Domitor-Dormicum), AB (PromAce-Stadol), MB, or physiologic saline (0.9% NaCl) solution (PS)

IM, and anaesthesia was induced with thiopental (Ravonal) or propofol (Rapinovet). Cardiopulmonary measurements were obtained before and after administration of medication and 0, 5, 10, and 15 minutes after endotracheal intubation. Results: Induction doses were reduced significantly by pre-anaesthetic administration of MM, AB, and MB (thiopental, 20, 45, and 46% after administration of PS; propofol, 42, 58, and 74% after administration of PS, respectively). Recovery time in dogs administered MM-thiopental or MM-propofol and AB-propofol were significantly prolonged compared with recovery time in dogs administered PS-thiopental or PS-propofol. Relatively large cardiovascular changes were induced by administration of MM, which were sustained even after the induction of anaesthesia. Administration of AB and MB induced cardiovascular changes during and immediately after endotracheal intubation that were significantly decreased by induction with thiopental or propofol. However, mild hypotension developed with AB-propofol. Apnea was observed in dogs administered MM during induction of anaesthesia, but most respiratory variables did not change significantly. Conclusions and Clinical Relevance: Pre-anesthetic medication with MM greatly reduced the anaesthesia induction dose of thiopental and propofol but caused noticeable cardiopulmonary changes. Pre-anaesthetic medication with AB and MB moderately reduced the induction dose of thiopental and propofol and ameliorated cardiovascular changes induced by these anaesthetics, although AB caused mild hypotension.

Tamura *et al.* (2002) reported the effects of different preanaesthetic medications (acepromazine plus either meperidine or butorphenol) given before the induction of anaesthesia with midazolam and ketamine on intraocular pressure, heart rate, and arterial blood pressure were investigated in 20 dogs. Following administration of preanaesthetic and

induction of anaesthesia, dogs were intubated and anaesthesia was maintained with halothane for 10 minutes. Intraocular pressure was significantly higher ($P < 0.05$) at several evaluations for dogs premedicated with acepromazine/meperidine than for those premedicated with acepromazine/butorphanol. Mean heart rate and diastolic arterial blood pressure were significantly ($P<0.05$) higher 5 minutes after administration of acepromazine/meperidine than after acepromazine/butorphanol. Results of this study suggest that acepromazine/butorphanol is a satisfactory preanaesthetic combination to use before induction of anaesthesia with midazolam and ketamine for ophthalmic surgery in dogs.

Koc *et al.* (2002) investigated the effects of anaesthetic-like combination of midazolam and xylazine on respiratory rate, heart rate, temperature, blood pressure, and blood gases in dogs. Six dogs were administered with xylazine hydrochloride at 2 mg/kg intramuscularly, followed by midazolam at one mg/kg, intravenously. Measurements were made immediately before treatment and at 15, 30, 60, 90, and 120 minutes after treatment. Mild respiratory depression was apparent in the dogs. Respiratory rate decreased nonsignificantly at 60, 90, and 120 minutes. Cardiovascular effect was characterized by decrease in heart rate. A slight decrease in temperature (39.17±0.13°C) occurred during anaesthesia, but the decrease was only significant at 120 minutes. Changes in arterial blood pressure were nonsignificantly . Moreover, changes in PaO_2, $PaCO_2$, and arterial pH at all time intervals after midazolam-xylazine administration were nonsignificant. It is concluded that the midazolam-xylazine combination had marked effects on heart rate, respiratory rate, and temperature of dogs.

Ilkiw *et al.* (2002) studied the effects of intravenous administration of variable-dose flumazenil (0, 0.001, 0.005, 0.01, and 0.1 mg/kg) after

ketamine (3 mg/kg) and midazolam (0.0 and 0.5 mg/kg) in 18 healthy unmedicated cats from time of administration until full recovery. End-points were chosen to determine whether flumazenil shortened the recovery period and/or modified behaviours previously identified and attributed to midazolam. Overall, flumazenil administration had little effect on recovery and behaviours. One minute after flumazenil administration, all cats were recumbent but a greater proportion of cats which received the highest dose assumed sternal recumbency with head up than any other group. Although not significant, those cats that received the highest flumazenil dose also had shorter mean times for each of the initial recovery stages (lateral recumbency with head up, sternal recumbency with head up and walking with ataxia) than any of the other treatment groups that received midazolam. For complete recovery, flumazenil did decrease the proportion of the cats that was sedated, but did not shorten the time to walking without ataxia. Based on this study, the administration of flumazenil in veterinary practice, at the doses studied, to shorten and/or improve the recovery from ketamine and midazolam in healthy cats cannot be recommended.

Bayan *et al.* (2002) studied the cardiopulmonary changes during propofol anaesthesia in Mongrel dogs. Six clinically healthy adult Mongrel dogs were used. Anaesthesia was induced with intravenous injection of propofol at 5.5 mg/kg body weight and maintained with intermittent incremental bolus doses of propofol at 0.5-1.0 mg/kg body weight every 3-5 minutes until the end of the observation period. The mean arterial pressure (MAP) showed a significant reduction after induction at the 5th minute (108.33±3.33), which continued until the 30th minute and thereafter, showed a slight increase. The central venous pressure (CVP) decreased significantly (1.08±0.158) after induction, which continued until 45 minutes and thereafter, increased slightly. The respiratory tidal volume

(RTV) and respiratory minute volume (RMV) decreased significantly after induction until the 15th minute (0.17±0.04 and 2.54±0.20) and gradually increased thereafter. It is inferred that a dual depression of central respiratory centre and peripheral respiratory receptor activity occurs during propofol anaesthesia.

Amarpal *et al.* (2002) evaluated the effect of xylazine and medetomidine on the dose of propofol required for the induction and duration of anaesthesia, and some clinical parameters in goats. Xylazine at 0.05 mg/kg and medetomidine at 10 µg/kg as preanaesthetics reduced the dose of propofol for induction of anaesthesia and significantly prolonged the duration of anaesthesia in goats. From an induction dose of 5.65±0.39 mg/kg of propofol, xylazine and medetomidine premedication reduced propofol dose to 4.00±0.54 and 3.73±0.46 mg/kg, respectively. However, bradycardia was more pronounced in goats premedicated with medetomidine.

Thibaut *et al.* (2002) in a research done twenty mongrel dogs of both sexes and aged 1 to 6 years were divided into two groups of ten animals each. A dose of 1.5 mg/kg of acepromazine was administered to the first group with 16.2±1.63 kg body weights. The second group of 11.9±1.7.1 kg body weights received a 3mg/kg intramuscular dose of xylazine. Both groups received atropine at 0.1 mg/kg subcutaneously 10 minutes before the administration of propofol at 5 mg/kg intravenously. The effects of propofol on latency period, surgical anaesthesia duration, recovery period, respiratory rate, heart rate, arterial blood pressure and body temperature were evaluated. Adverse reactions to propofol were registered. The results of the anaesthesiological variable significantly differed between the two groups: induction of anaesthesia was 0.45±0.03 minutes in the first group and 0.26±0.03 in the second group. Surgical anaesthesia period was

12.3±1.89 minutes in the first group and 25.2±1.78 minutes in the second group and recovery period was 4.5±0.63 and 10.1±0.98 minutes in group 1 and 2, respectively. The physiological variables in both groups were maintained without significant modification during the surgical anaesthesia period; respiratory rate had an initial average of 14.3±2.45 and 13.0±1.54 breaths/minute in groups 1 and 2, respectively. The heart rate was 175±11.81 beats/minute in the first group and 148.4±9.04 beats/minute in the second group; the average arterial blood pressure was 102.6±5.69 and 111.8±10.43 mm Hg for the first and second groups, respectively. Body temperature in the first group was 38.5±0.17 and 38.7±0.2°C for the second group. Adverse reactions were muscle twitching (3 cases) and opisthotonus (1 case) in group 1 and transitory apnoea (2 cases) in group 2 during the initial anaesthesia period. It is concluded that a single dose of propofol premedicated either with atropine-acepromazine or atropine-xylazine combination induces an adequate surgical anaesthesia in dogs without significant changes in physiological parameters.

Bayan *et al.* (2002) found that six adult, healthy mongrel dogs received a bolus dose (5.5 mg/kg) of propofol. This induced satisfactory relaxation of pharyngeal and laryngeal muscles, making the endotracheal intubation possible, and loss of other reflexes e.g. palpebral, pedal, toe-web pinch, pin prick and anal reflexes. Clotting time showed no significant difference before and after propofol administration. Haemoglobin levels decreased significantly after induction of anaesthesia, with levels of 7.5±0.66 g% 15 minutes post-induction; this, however, gradually increased to pre-induction levels (10.13±0.59 g%). Total erythrocyte count and total leukocyte count showed a decreasing trend until after 15 minutes of propofol administration but gradually rose towards pre-induction level. Blood glucose level increased significantly after propofol administration

from the pre-induction value of 60.40±2.54 mg/ml to 78.61±2.45 mg/dl at 30 minutes post-administration of propofol. Alanine aminotransferase and aspartate aminotransferase both increased 15 minutes post-induction of anaesthesia (25.00±2.13 and 46.33±3.88 U/ml, respectively); levels, however, gradually decreased to pre-induction levels thereafter (22.17±1.94 and 40.17±3.88 U/ml, respectively). A decrease in total protein levels was observed 30 minutes post-induction of anaesthesia (6.98±0.17 g/dl); however, levels subsequently returned to pre-induction values (7.25±0.22 g/dl).

Venugopal *et al.* (2002) evaluated anaesthetic effects of a combination of propofol and ketamine in 18 clinically healthy dogs, randomly divided into 3 groups. Group 1 dogs were administered propofol and ketamine, both at 5 mg/kg body weight; group 2 dogs were administered triflupromazine hydrochloride at 1 mg/kg bw, followed by propofol and ketamine at 5 mg/kg bw each. Group 3 dogs were administered diazepam at 2 mg/kg bw followed by propofol (5 mg/kg bw) and ketamine (5 mg/kg bw). The duration of anaesthesia in the three groups were 9.92±1.86, 40.17±1.96 and 29.33±1.69 minutes, for groups 1, 2 and 3, respectively. The easy endotracheal intubation in all groups during induction suggested the abolition of cough reflexes and adequate jaw relaxation. The results indicated that propofol, with or without premedication, effectively abolished jaw tone during induction. The recovery from anaesthesia was prolonged in premedicated groups, as compared with the propofol-ketamine group; recovery was longer in group 2 (60.17±1.62 minutes) followed by group 3 (43.86±1.35 minutes) and group 1 (14.72±1.34 minutes). There was a significant decrease in total erythrocyte count, total leukocyte count, haemoglobin and packed cell volume during propofol anaesthesia in all groups.

Kwon *et al.* (2002) assessed the cardiovascular effects of propofol after premedication with xylazine (1.0 mg/kg, intramuscularly) under oxygen supply (200 ml/kg/minute) via a endotracheal tube. 12 adult mixed-breed dogs were divided into 4 groups: 0.2 (Group 1), 0.4 (Group 2), 0.6 (Group 3), and 0.8 mg/kg/minute (Group 4) of propofol, respectively. Arterial blood pressure and electrocardiogram were monitored with a physiograph after an arterial catheter was inserted into the femoral artery. pH, arterial carbon dioxide tension ($PaCO_2$), and arterial oxygen tension (PaO_2) were evaluated with arterial blood collected through the inserted catheter. Diastolic arterial pressure, systolic arterial pressure, and mean arterial pressure decreased slightly in Groups I, II, and III, but decreased significantly in Group IV. However, these increased rapidly after stopping propofol infusion in Group IV. pH was maintained in normal range in Groups I, II, and III, but decreased in proportion to time passing in Group IV. $PaCO_2$ increased significantly only in Group IV, but PaO_2 was maintained in normal range in all groups. Although heart rate was recorded in normal range for 90 min, arrythmia was noted after stopping propofol infusion in all groups. It is concluded that propofol depresses the cardiovascular system in proportion to infusion dosage, and 0.8 mg/kg/minute of propofol infusion rate is not appropriate in canine anaesthesia with xylazine premedication.

Adetunji *et al.* (2002) evaluated changes in heart rate (HR), respiratory rate (RR) and rectal temperature (RT), as well as the quality of anaesthesia and unusual reactions produced by propofol in 5 mongrel dogs premedicated with an intramuscular injection of xylazine (2 mg/kg) and atropine (0.04 mg/kg). Propofol anaesthesia was induced with an intravenous loading dose of 5 mg/kg and maintained either by repeat bolus injections (RBI) of 2.5 mg/kg as needed or a continuous infusion rate (CIR)

of 0.17 mg/kg/minute. With both RBI and CIR techniques, HR increased above pre-induction levels in the first 30 minute only, while RR and RT progressively decreased during anaesthesia. Duration of analgesia was 88.4±2.6 minutes with RBI and 87.8±3.5 minutes with CIR. Duration of recumbency was 122.6±2.2 minutes with RBI and 118.2±3.5 minutes with CIR. Standing times were 6.0±1.8 minutes 4.0±1.3 minutes with RBI and CIR, respectively. Recovery times with RBI and CIR were respectively 18.6±2.3 minutes and 17.0±1.7 minutes. Apnoea, cyanosis, retching, vomiting, paddling and opisthotonus all appeared infrequently. It was concluded that administration of propofol by either RBI or CIR provided rapid anaesthetic induction and recovery with very infrequent occurrence of unusual reactions in local dogs premedicated with xylazine.

Vineet and Singh (2003) done a trial in which 8 clinically healthy dogs (2-4 years old, 10-25 kg) were divided into 2 groups and received midazolam at 1 mg/ml, 0.3 mg/kg + ketamine at 50 mg/ml, 15.543±1.018 mg/kg (Treatment I) and midazolam at 1 mg/ml, 0.5 mg/kg + ketamine at 50 mg/ml, 12.11±0.879 mg/kg (Treatment II) intravenously to induce anaesthesia. Haematological and biochemical observations were conducted before and at 20, 60, 120, 1440 and 2880 minutes after drug administration. It was shown that haemoglobin and haematocrit significantly increased in Treatment II. Serum creatinine and chloride levels significantly increased in both treatment groups, while potassium levels significantly decreased between 10 and 120 minutes intervals in Treatment II. In conclusion, midazolam and ketamine at the dosages used in this study do not have adverse effects and can safely be used in surgery without any risk.

Intelizano (2003) evaluated the haemodynamic, oxygenating, metabolic and ventilatory effects of anaesthesia through continuous infusion of propofol and propofol- ketamine as well as the quality of

muscular relaxation and of the post-anaesthesia recovery. Twenty-one healthy female mongrel dogs, weighing 14 ± 3 kg, underwent ovariohysterectomy. For an adequate instrumentation, the animals were anaesthetized with 50% isoflurane in oxygen. Sixty minutes after the suspension of inhalatory anaesthesia, baseline haemodynamic values were collected and study anaesthesia was induced. The quality of the anaesthetic induction was satisfactory; the process was smooth in all animals and endotracheal intubation was easily performed. Heart rate increased significantly at all time points in the three groups. Muscle relaxation provided by the three anaesthesia protocols was intense. In the post-anaesthesia recovery period an increase was observed in the haemodynamic and ventilatory parameters, with a small variation in relation to extubation time, time until animal lifted its head and sternal recumbence, which, although of no statistical significance. In view of the results obtained it is possible to conclude that, notwithstanding the fact that the three anaesthesia protocols promoted tachycardia and altered the haemodynamic parameters calculated based on the heart rate, in addition to the reduction of blood pressure and important ventilatory alterations leading to respiratory acidosis, the association of racemic ketamine allowed the doses of propofol to be reduced in the induction and maintenance of anaesthesia.

Sano *et al.* (2003) evaluated the effects of acepromazine-butorphanol (AB), midazolam-butorphanol (MB) and medetomidine (Med) on the induction dose of propofol and their compatibility with propofol in client-owned dogs (n=80). All premedications induced well to excellent sedation and the induction dose of propofol was considerably reduced. Among the tested premedicants, Med induced the deepest sedation and the most potent dose-sparing effect. Induction of anaesthesia was excellent to good in all

dogs except for one dog premedicated with MB. Most dogs premedicated with AB or MB showed temporary apnoea. Although other adverse effects such as bradycardia or hypotension may also occur, premedication with MB, AB or Med is a valuable technique for the induction of anaesthesia with propofol in dogs in a clinical setting.

Oku *et al.* (2003) evaluated clinical usefulness of xylazine (1.0 mg/kg)-midazolam (20 μg/kg)-propofol (3.0 mg/kg) anesthesias in horses, 6 adult Thoroughbred horses were examined. The quality of induction varied from poor to excellent and 5 out of 6 horses presented myotonus in the front half of the body. However, paddling immediately after induction observed in other reports of equine propofol anesthesia was not observed. Recovery time was 35.3±9.3 minutes and the quality of recovery was calm and smooth in all horses. Respiration rate decreased after induction and hypoxemia was observed during lateral recumbency. Heart rate also decreased after induction; however mean arterial blood pressure was maintained above approximately 100 mmHg.

Hawkins *et al.* (2003) determine induction doses, anaesthetic constant rate infusions (CRI), and cardiopulmonary effects of propofol in red-tailed hawks and great horned owls and propofol pharmacokinetics in the owls during CRI. Animals: 6 red-tailed hawks and 6 great horned owls. The CRI dose necessary for a loss of withdrawal reflex was determined via specific stimuli. Anaesthesia was induced by IV administration of propofol (1 mg/kg/minute) and maintained by CRI at the predetermined dose for 30 minutes. Heart and respiratory rates, arterial blood pressures, and blood gas tensions were obtained in awake birds and at various times after induction. End-tidal CO_2 ($ETCO_2$) concentration and esophageal temperature were obtained after induction. Propofol plasma concentrations were obtained after induction and after completion of the

CRI in the owls. Recovery times were recorded. Results: Mean±SD doses for induction and CRI were 4.48±1.09 mg/kg/minute and 0.48±0.06 mg/kg/minute, respectively, for hawks and 3.36±0.71 mg/kg/minute and 0.56±0.15 mg/kg/minute, respectively, for owls. Significant increases in $PaCO_2$, HCO_3, and $ETCO_2$ in hawks and owls and significant decreases in arterial pH in hawks were detected. A 2-compartment model best described the owl pharmacodynamic data. Recovery times after infusion were prolonged and varied widely. Central nervous system excitatory signs were observed during recovery. Conclusions and Clinical Relevance: Effects on blood pressure were minimal, but effective ventilation was reduced, suggesting the need for careful monitoring during anaesthesia. Prolonged recovery periods with moderate-to-severe excitatory CNS signs may occur in these species at these doses.

Sano *et al.* (2003) showed that Propofol was used as an induction agent of general anesthesia in 77 dogs and 64 cats, all client owned, for a variety of surgeries/treatments or diagnostic procedures. The mean intravenous doses of propofol required achieving endotracheal intubation in dogs and cats were 6.5±1.4 mg/kg and 10.1±2.8 mg/kg, respectively. Most of the animals could be induced to anesthesia smoothly by the administration of propofol with a high incidence of apnea. Propofol is a clinically valuable anesthetic induction agent in both dogs and cats; however, care must be taken for apnea.

Kilic *et al.* (2003) performed experiment in which ten clinically healthy dogs, average age 3 years (1-5 years) were used. For premedication, the dogs were injected intravenously with a combination of 3 mg/kg ketamine (Ketalar-50) and 1 mg/kg xylazine (Rompum). Propofol at 3 mg/kg was used for continuation of anaesthesia. Blood samples were taken before and at 15 minutes after injection. Respiration and heart rates

CRI in the owls. Recovery times were recorded. Results: Mean±SD doses for induction and CRI were 4.48±1.09 mg/kg/minute and 0.48±0.06 mg/kg/minute, respectively, for hawks and 3.36±0.71 mg/kg/minute and 0.56±0.15 mg/kg/minute, respectively, for owls. Significant increases in $PaCO_2$, HCO_3, and $ETCO_2$ in hawks and owls and significant decreases in arterial pH in hawks were detected. A 2-compartment model best described the owl pharmacodynamic data. Recovery times after infusion were prolonged and varied widely. Central nervous system excitatory signs were observed during recovery. Conclusions and Clinical Relevance: Effects on blood pressure were minimal, but effective ventilation was reduced, suggesting the need for careful monitoring during anaesthesia. Prolonged recovery periods with moderate-to-severe excitatory CNS signs may occur in these species at these doses.

Sano *et al.* (2003) showed that Propofol was used as an induction agent of general anesthesia in 77 dogs and 64 cats, all client owned, for a variety of surgeries/treatments or diagnostic procedures. The mean intravenous doses of propofol required achieving endotracheal intubation in dogs and cats were 6.5±1.4 mg/kg and 10.1±2.8 mg/kg, respectively. Most of the animals could be induced to anesthesia smoothly by the administration of propofol with a high incidence of apnea. Propofol is a clinically valuable anesthetic induction agent in both dogs and cats; however, care must be taken for apnea.

Kilic *et al.* (2003) performed experiment in which ten clinically healthy dogs, average age 3 years (1-5 years) were used. For premedication, the dogs were injected intravenously with a combination of 3 mg/kg ketamine (Ketalar-50) and 1 mg/kg xylazine (Rompum). Propofol at 3 mg/kg was used for continuation of anaesthesia. Blood samples were taken before and at 15 minutes after injection. Respiration and heart rates

and body temperature decreased significantly during surgery, while erythrocyte count also decreased significantly and creatinine content increased significantly. The sedative and analgesic effects of the 3-way combination were most pronounced. All dogs showed excellent relaxation and no reaction to the surgical procedures. It is concluded that this anaesthetic combination is suitable for use in dogs.

Alves *et al.* (2003) assessed several arterial blood chemistry parameters, arterial pressure, and pulse frequency in 12 calves kept under anaesthesia for 13 hours. Propofol and isoflurane were used for induction and maintenance, respectively, in association with intra-thecal injection of morphine. Pulse frequency, arterial pressure, and blood glucose levels had mild oscillations, with values close to the reference range for calves under anaesthesia. There was a mild but significant increase in the packed cell volume, haemoglobin, pCO_2, total CO_2, bicarbonate, and K+, throughout the duration of the anaesthesia, whereas blood pH, pO_2, Na+, and Ca++ levels decreased significantly. This protocol proved safe for maintenance of calves under anaesthesia for prolonged periods of time.

Frias *et al.* (2003) in a research done selected six adult horses (five females and one male). Each horse was anaesthetized four times with either ketamine or propofol in random order at 1-week intervals. Horses were pre-medicated with xylazine (1.1 mg/kg IV over a minute), and 5 minutes later anaesthesia was induced with either ketamine (2.2 mg/kg IV) or propofol (1, 2 and 4 mg/kg IV; low, medium and high doses, respectively). Data were collected continuously (electrocardiogram) or after xylazine administration and at 5, 10 and 15 minutes after anaesthetic induction (arterial pressure, respiratory rate, pH, PaO_2, $PaCO_2$ and O_2 saturation). Anaesthetic induction and recovery were qualitatively and quantitatively assessed. Results: Differences in the quality of anaesthesia were observed;

the low dose of propofol resulted in a poorer anaesthetic induction that was insufficient to allow intubation, whereas the high dose produced an excellent quality of induction, free of excitement. Recorded anaesthesia times were similar between propofol at 2 mg kg-1 and ketamine with prolonged and shorter recovery times after the high and low dose of propofol, respectively ($p < 0.05$; ketamine, 38±7 minutes; propofol 1 mg/kg , 29±4 minutes; propofol 2 mg/kg , 37±5 minutes; propofol 4 mg/kg , 50±7 minutes). Times to regain sternal and standing position were longest with the highest dose of propofol (32±5 and 39±7 minutes, respectively). Both ketamine and propofol reversed bradycardia, sinoatrial, and atrioventricular blocks produced by xylazine. There were no significant alterations in blood pressure but respiratory rate, and PaO_2 and O_2 saturation were significantly decreased in all groups ($p < 0.05$). Conclusion: The anaesthetic quality produced by the three propofol doses varied; the most desirable effects, which were comparable to those of ketamine, were produced by 2 mg/kg propofol.

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CHAPTER - III

MATERIALS AND METHODS

CHAPTER - III

MATERIALS AND METHODS

MATERIALS AND METHODS

The present research work was conducted on 18 White Yorkshire pigs available at Ad.hoc Research project (I.C.A.R) in the department (Animal Reproduction, Gynaecology and Obstetrics) at Bihar Veterinary College, Patna-14.

Selection of experimental Animal:

A total of 18 clinically healthy White Yorkshire pigs ageing in-between six to nine months and weighing in-between 35-45 kg of either sex was selected for the present study. All animals were examined clinically. They were kept under close observation for a fortnight. Routine deworming was done with Albendazole[1]@ 15-20 mg/kg body weight orally. The animals were maintained under similar environmental and managemental condition as far as practicable during entire period of study.

Grouping of Animal:

Animals were randomly divided into three groups each containing six animals. The pigs were medicated as shown in the design of (Table-A).

Preparation of Animals:

Feed and water to the experimental animals were withdrawn 24 hours and 12 hours respectively before start of experiment. The animal was weighted just before the administration of anaesthetics.The site was prepared aseptically by proper clipping, shaving and washing with soap and water. It was dried and painted with Betadine[2] liquid, before administration of drug and drug combination.

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[1] **Albendazole®**–Concept Pharmaceuticals Ltd; Mumbai-98

[2] **Betadine solution®** –Win-Medicare Pvt. Ltd; New Delhi-19.

Table-A_: Showing the design of experiment.

No. of Groups	No. of Animals	Drug used	Dose rate (mg/kg b.wt.)	Route of administration
A	1	Propofol[3]	5	Intravenously
	2	do	,,	,,
	3	do	,,	,,
	4	do	,,	,,
	5	do	,,	,,
	6	do	,,	,,
B	7	Mi azolam[4]	0.5	Intavenously
	8	do	,,	,,
	9	do	,,	,,
	10	do	,,	,,
	11	do	,,	,,
	12	do	,,	,,
C	13	Propofol+Midazolam	(1.5+0.1)	Intavenously
	14	do	,,	,,
	15	do	,,	,,
	16	do	,,	,,
	17	do	,,	,,
	18	do	,,	,,

Methods of Experimentation:

Experimental study was conducted on following parameters: -

1. Clinical findings.
2. Haematological studies
3. Biochemical studies.
4. Anaesthetic effects.
5. Statistical studies.

[3] **PROFOL®**-10mg/ml, Claris Lifesciences Ltd;Ahmedabad.
[4] **Midazolam®**-1mg/ml, Sun Pharmaceutical Ind. Ltd;Vapi,(Gujrat).

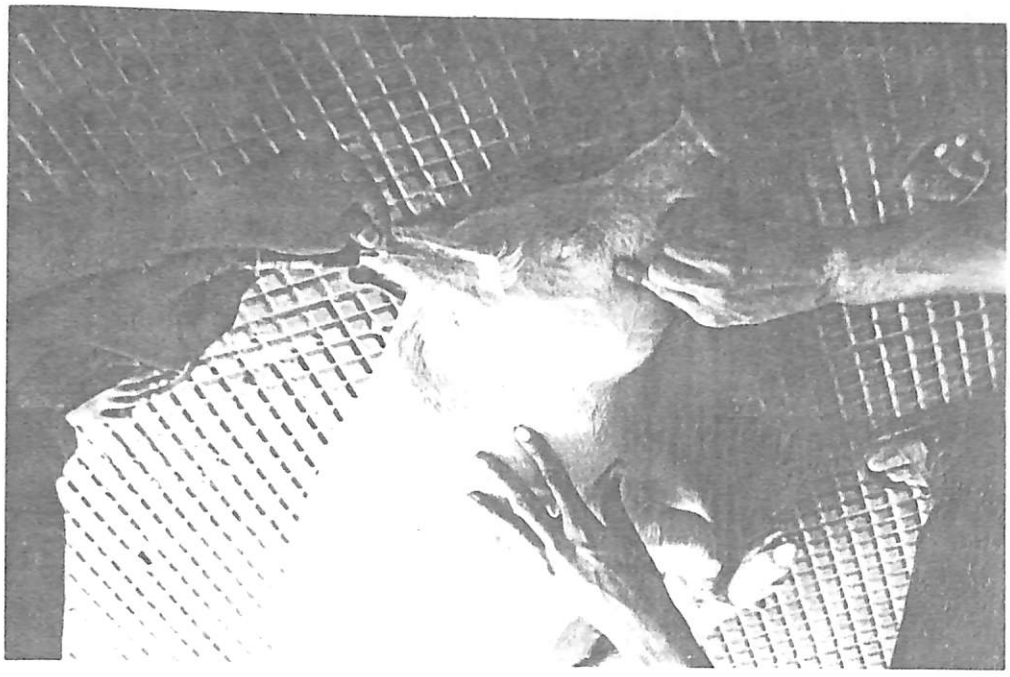

Figure No. 1 Photograph showing collection of blood from the ear vein of experimental pigs of group-C.

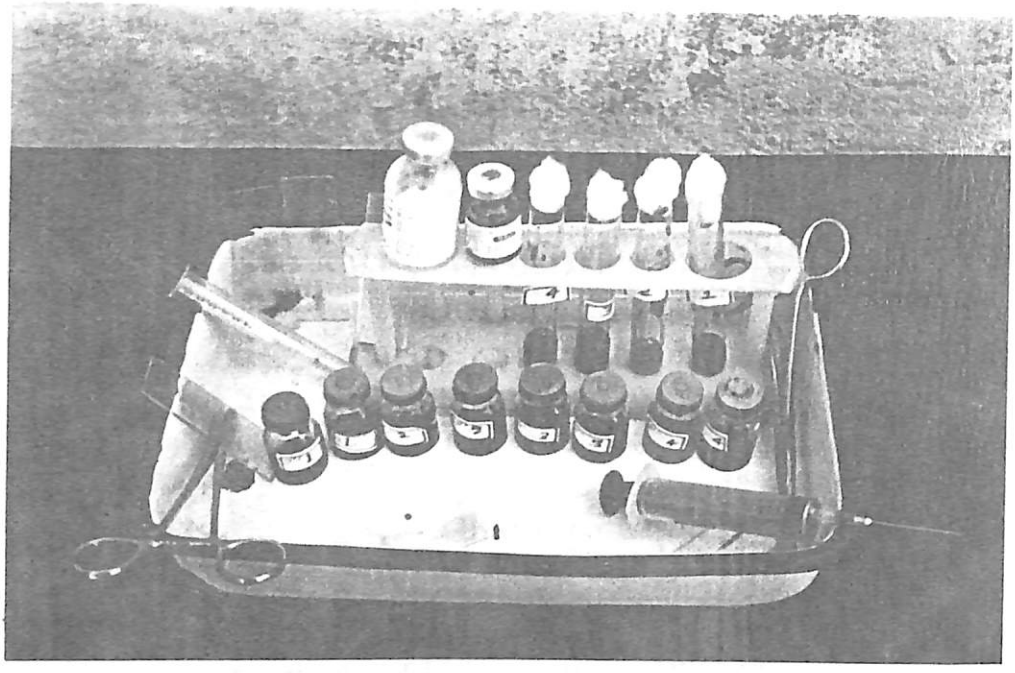

Figure No.2. Photograph revealing collected blood of different interval of time for biochemical estimation.

1. Clinical findings:

In all the animals respiratory rate, heart rate and rectal temperature were recorded, 0 (just before administration of drug), 5, 10, 20, 30, 60 and 90 minutes after intravenous administration of drug.

2. Haematological Studies:

The blood was collected aseptically in EDTA[5] from the ear vein at different time interval i.e. 0(just before administration of drug), 15, 30, and 60 and 120 minutes. After intravenous administration of drug following parameters were examined:

(a) Total Erythrocyte Count (Million/cubic mm): which was done by method as described by Schalm *et al.* (1975).

(b) Total Leukocyte Count (Thousand/cubic mm): It was done by method as described by Schalm *et al.* (1975).

(c) Pack Cell Volume (%): (As described by Schalm *et al.* 1975).

(d) Haemoglobin: Was estimated by method as described by Kolmer *et al.* (1969). Using Sahli's hemometer.

(e) Neutrophil Count (%): Done by method as described by Schalm *et al.* (1975).

(f) Eosinophil Count (%): It was done by method as described by Schalm *et* al. (1975).

3. Biochemical studies:

For analysis of biochemical parameters 5ml of blood was collected aseptically from ear vein 0(just before administration of drug), 15, 30, 60 and 120 minutes after intravenous administration of drug. Then blood was immediately transferred to a clean test tube for clotting. It was kept at room

[5] EDTA® –Qualigens Fine Chemicals Mumbai, Maharastra.

temperature for two to three hours in slanting position for separation of serum. The serum was pipetted out carefully in another clean, sterilized vial for further analysis of different biochemical parameters immediately.

Analytical methods:

(a)The estimation of Total Serum Glucose was done by using the Glucose-Oxidase(GOD) method.

(b) The estimation of SGOT or AST was done by the method as described by Reitman and Frankel (1957).

(c) The estimation of SGPT or ALT was done by the method as described by Reitman and Frankle (1957).

(d) The estimation of total serum protein was done by Biuret method as described by Varley (1967).

4. Anaesthetic effects:

After administration of drug the depth and extent of analgesia was ascertained by pin-pricks response on different body surfaces like coronary band, nasal septum, ear, tail, and thorax were graded in a scale of 0 to 3.

0-No analgesia— strong reaction to pin-prick.

1-Mild analgesia— weak response to pin-prick.

2-Moderate analgesia— occasional response to pin-prick.

3-Strong/complete analgesia— no response to pin-prick.

Effects of drug on the region of limbs, tail, perineum, udder, thigh, digit, posterior flank, anterior flank, thorax, and ear were noted at different time intervals. Response to painful stimuli and pain threshold were assembled by pin-pricks, pinching the cutaneous and deeper structures by towel clamp/ forceps. Onset of anaesthesia, duration of anaesthesia and

recovery from anaesthesia were recorded in all the experimental animals on the basis of different reflexes.

5. Statistical studies:

Statistical analysis of data was done using standard statistical procedure as per Snedecor and Cochran (1967).

Data of rectal temperature, respiratory rate, heart rate, TEC, TLC, PCV, Hb, Neutrophil, Eosinophil, total serum glucose, SGOT, SGPT and total serum protein were subjected to analysis of variance followed by a critical difference test. Mean $\pm$ SE were calculated and analyzed statistically.

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CHAPTER - IV

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

Rectal temperature

Analysis of variance (Table-1) reflects that the effect of anesthetics agents did not have any significant effects on rectal temperature in group A, B and C. However, highly significant effects of anesthetic agents on rectal temperature were found between periods ($P<0.01$).

Mean along with S.E of rectal temperature in anaesthetized pigs at different periods of intervals in different groups had been presented in table-2. The rectal temperature did not vary significantly after induction with Propofol, Midazolam and combination of Propofol and Midazolam in all three different groups. It means rectal temperatures are normal in Propofol, Midazolam and Propofol+ Midazolam treated group. It also revealed significant difference in rectal temperature between periods in each groups upto 10 minutes post induction. However, there was non significant difference between 20 to 30 was found. Also between 60 to 90 minutes temperature differs non significantly. In general rectal temperature tends to increase upto 90 minutes in all three groups except in Propofol+ Midazolam treated group in which at 90 minutes it tends to decrease.

Table –1

Analysis of variance for the effect of different anaesthetic agent on RECTAL TEMPERATURE (^{0}F) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	0.123	0.0615	0.486 ^{NS}
Between period	4	21.09	3.51	27.76**
Error	83	14.79	0.126	

** Highly significant at ($p<0.01$)

NS: Non Significant

Table-2

Mean ±S.E of RECTAL TEMPERATURE (^{0}F) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	**Periods (Minutes)**							**Overall Mean ±S.E**
	0	**5**	**10**	**20**	**30**	**60**	**90**	
A	101.7 ±0.15	101.1 ±0.12	100.6 ±0.10	100.53 ±0.17	100.77 ±0.21	101.0 ±0.20	101.23 ±0.14	100.99^{x} ±0.08
B	101.9 ±0.15	101.27 ±0.18	100.7 ±0.11	100.50 ±0.08	100.53 ±0.13	101.03 ±0.12	101.3 ±0.12	101.03^{x} ±0.09
C	101.87 ±0.13	101.17 ±0.09	100.7 ±0.14	100.67 ±0.16	100.70 ±0.18	101.20 ±0.15	101.17 ±0.20	101.07^{x} ±0.08
Overall Mean ±S.E	100.82^{a} ±0.08	101.18^{b} ±0.07	100.67^{c} ±0.07	100.57^{cd} ±0.08	100.67^{c} ±0.10	101.08^{be} ±0.09	101.23^{bf} ±0.08	

Mean with similar superscript (Columnwise X,Y,.....and rowwise a,b....)did not differ significantly

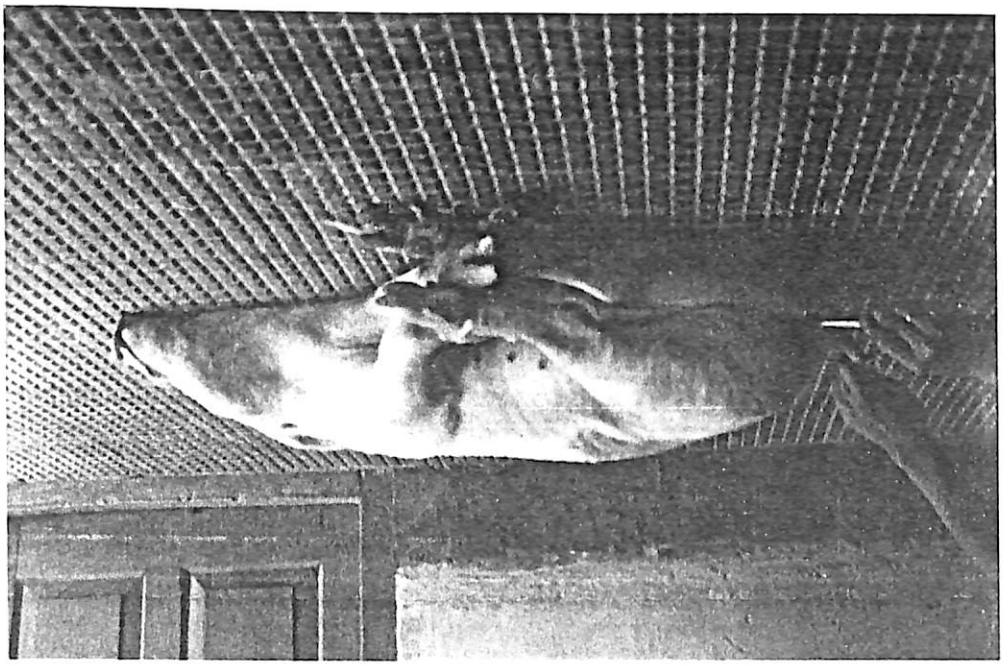

Figure No.3 Photograph showing rectal temperature being taken from experimental pigs of group – C.

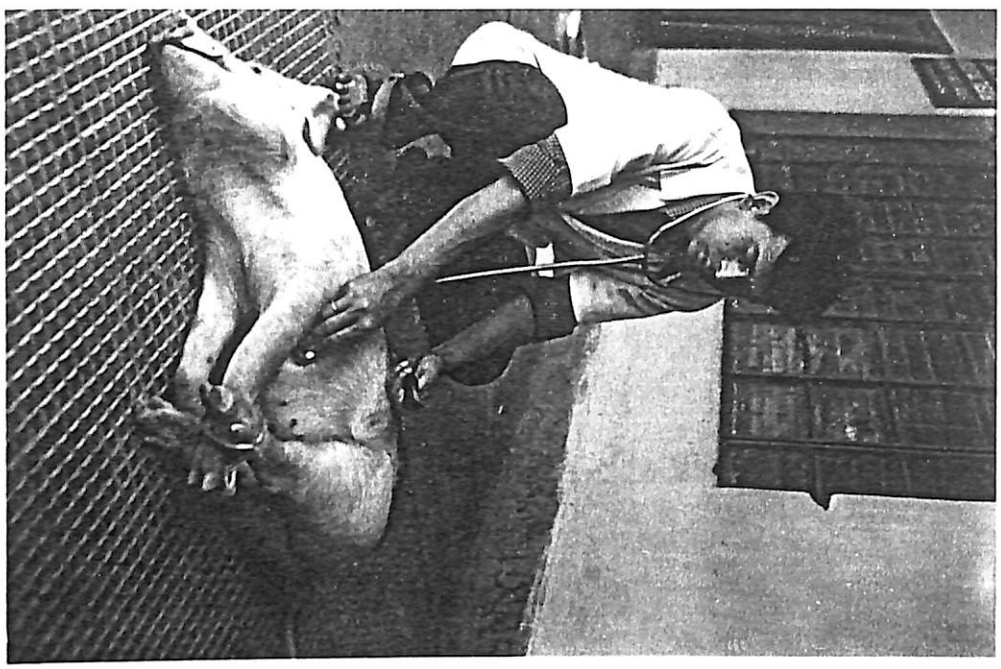

Figure No.4.Photograph showing auscultation of heart for recording its rate in pigs of group- A.

Heart rate

Analysis of variance revealed significant difference ($P<0.01$) among average heart rate in each group at different periods of interval (Table-3).

Mean along with S.E of heart rate in anaesthetized pigs at different periods of intervals in different groups had been presented in table-4. Prior to administration of drugs i.e. at 0(zero) minute, the average heart rate in groups A, B and C were recorded 106.0 ± 3.94, 104.5 ± 2.53 and 101.0 ± 2.06 per minute respectively. This table also showed no significant difference between Propofol treated group and Midazolam treated group on heart rate. However, there was significant difference between Propofol +Midazolam treated groups to rest of two groups. The effects of time duration on different treatment groups varied significantly up to 5 minutes post induction. However, there were non significant effects at 10, 20, and 30 minutes then tends to normalize up to 90 minutes.

Respiration rate

There was significant difference both between treatments ($P<0.05$) and between periods ($P<0.01$). (Table-5)

There was significant ($P<0.05$) difference between Propofol treated group and Midazolam treated group on respiration rate (Table-6). However, no significant difference between Propofol treated group and Propofol+ Midazolam treated groups were marked. The effects of time duration on different treatment group varied significantly up to 10 minutes post induction. However, there were non significant effects up to 30 minutes post induction. The period of 60 and 90 minutes post induction showed slight variation.

Table –3

Analysis of variance for the effect of different anaesthetic agent on HEART RATE (PerMinute) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	682.59	341.29	8.26**
Between period	4	3810.27	635.04	15.38**
Error	83	4831.97	41.29	

** Highly significant at ($p<0.01$)

Table-4

Mean ±S.E of HEART RATE (PerMinute) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Periods(Minutes)							Overall Mean ±S.E
	0	5	10	20	30	60	90	
A	106.0 ±3.94	93.17 ±3.82	91.0 ±3.96	88.5 ±3.89	90.83 ±3.51	93.83 ±3.81	95.83 ±4.23	94.16^{x} ±1.59
B	104.5 ±2.53	92.33 ±02.67	88.83 ±2.32	86.5 ±2.22	88.83 ±1.22	91.83 ±1.25	94.17 ±1.64	92.42^{x} ±1.12
C	101.0 ±2.06	87.16 ±2.24	84.5 ±2.23	82.83 ±1.81	84.66 ±1.70	88.33 ±1.69	91.66 ±1.33	88.59^{y} ±1.11
Overall Mean ±S.E	103.8^{a} ±1.68	90.8^{bd} ±1.74	88.1^{bce} ±1.73	85.94^{c} ±1.61	88.1^{bce} ±1.42	91.3^{de} ±1.47	93.89^{d} ±1.54	

Mean with similar superscript(Columnwise X,Y,.....and rowwise a,b....)did not differ significantly.

Table –5

Analysis of variance for the effect of different anaesthetic agent on RESPIRATION RATE (Per Minute) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	24.11	12.05	3.99*
Between period	4	665.85	110.98	36.80**
Error	83	352.83	3.01	

* Significant at($P<0.05$)

** Highly significant at ($p<0.01$)

Table-6

Mean ±S.E of RESPIRATION RATE(Per Minute) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Periods(Minutes)							Overall Mean ±S.E
	0	5	10	20	30	60	90	
A	17.67 ±0.67	13.5 ±0.76	12.5 ±0.85	12.33 ±0.84	13.0 ±1.21	14.17 ±0.98	16.67 ±0.88	14.26^{x} ±0.44
B	17.83 ±0.60	12.83 ±0.60	11.33 ±0.49	10.83 ±0.30	11.5 ±0.43	13.67 ±0.56	16.0 ±0.68	13.43^{y} ±0.42
C	18.67 ±0.71	14.17 ±1.08	12.33 ±0.80	11.83 ±0.83	12.0 ±0.36	14.33 ±0.42	17.67 ±0.56	14.43^{x} ±0.47
Overall Mean ±S.E	18.06^{a} ±0.37	13.5^{b} ±0.47	12.0^{d} ±0.41	11.6^{d} ±0.41	12.1^{d} ±0.44	14.06^{b} ±0.38	16.78^{c} ±0.42	

Mean with similar superscript(Columnwise X,Y,.....and rowwise a,b....)did not differ significantly

Figure No.7 Photograph showing respiration rate being taken from experimental pigs of group – C.

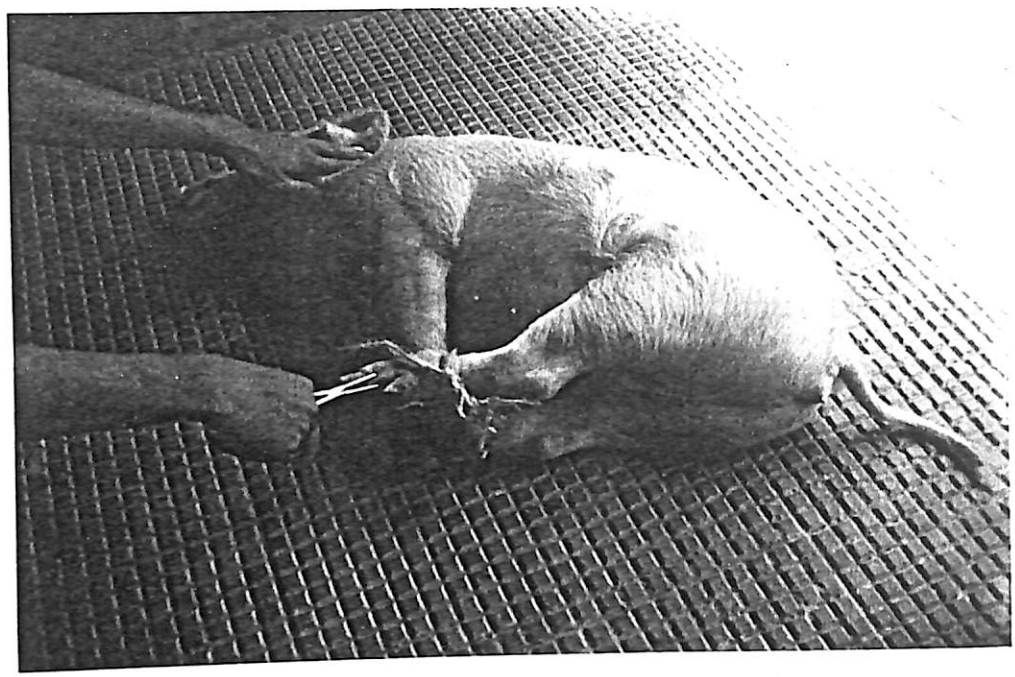

Figure No.8.Photograph showing recording of pedal reflex in pigs after induction of anaesthesia in group –C.

Total erythrocyte count

Analysis of variance (Table-7) revealed highly significant ($P<0.01$) effects of different anaesthetic agent on total erythrocyte count between 0 to 30 minutes but there was non significant effects between treatments.

Table -8 showed that there were no significant differences between different treatment groups but the effects of time duration on different treatment group vary significantly up to 30 minutes post induction. The time period of 30 minutes and 60 minutes, 15 and 120 minutes post induction showed no significant variation. In general total erythrocyte count decreased from 0 to 60 minutes then increased significantly 20 minutes after post induction of anaesthesia.

Total leukocyte count

Analysis of variance (Table-9) presented non significant effects of different drugs on total leukocyte count both between treatments and between periods.

Mean along with S.E of total leukocyte count in anaesthetized pigs at different periods of intervals in all three groups had been presented in table-10. From table it revealed that non significant difference between different treatment groups and different periods of intervals on total leukocyte count. However, in general there was increase in total leukocyte count from 0 to 60 minutes after post induction of anaesthesia, while it was normalized at 90 minutes.

Table –7

Analysis of variance for the effect of different anaesthetic agent on TOTAL ERYTHROCYTE COUNT(Million/cubic mm) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	0.032	0.016	0.91 ^{NS}
Between period	4	2.33	0.582	33.25 **
Error	83	1.458	0.0175	

** Highly significant at ($p<0.01$)
NS: Non Significant

Table-8

Mean ±S.E of TOTAL ERYTHROCYTE COUNT (Million/cubic mm) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	7.08 ±0.08	6.9 ±0.09	6.82 ±0.08	6.79 ±0.08	6.92 ±0.08	6.90 ^{x} ±0.04
B	7.01 ±0.10	6.87 ±0.10	6.79 ±0.10	6.77 ±0.08	6.85 ±0.09	6.86 ^{x} ±0.04
C	7.06 ±0.06	6.90 ±0.07	6.79 ±0.05	6.78 ±0.05	6.89 ±0.05	6.89 ^{x} ±0.03
Overall Mean ±S.E	7.05 ^{a} ±0.04	6.89 ^{b} ±0.05	6.8 ^{c} ±0.04	6.78 ^{c} ±0.04	6.89 ^{b} ±0.04	

Mean with similar superscript (Columnwise X, Y,.....and rowwise a,b....)did not differ significantly.

Table –9

Analysis of variance for the effect of different anaesthetic agent on TOTAL LEUCOCYTE COUN (Thousand/cubic mm) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	0.087	0.0435	0.12 ^{NS}
Between period	4	1.365	0.341	0.948 ^{NS}
Error	83	29.85	0.3596	

NS: Non Significant

Table-10

Mean ±S.E of TOTAL LEUCOCYTE COUNT(Thousand/cubic mm)in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	16.70 ± 0.35	16.86 ± 0.33	16.96 ± 0.36	17.02 ± 0.36	16.85 ± 0.37	16.88^{x} ± 0.15
B	16.58 ± 0.24	16.78 ± 0.20	16.89 ± 0.19	16.95 ± 0.20	16.81 ± 0.20	16.80^{x} ± 0.09
C	16.62 ± 0.19	16.82 ± 0.17	16.94 ± 0.16	17.01 ± 0.16	16.78 ± 0.16	16.83^{x} ± 0.07
Overall Mean ±S.E	16.63^{a} ± 0.14	16.82^{a} ± 0.13	16.93^{a} ± 0.14	16.99^{a} ± 0.14	16.81^{a} ± 0.14	

Mean with similar superscript (Columnwise X, Y,.....and rowwise a,b....)did not differ significantly.

Packed cell volume

As reflected by analysis of variance (Table-11) there was significant ($P<0.05$) effects of anesthetic agents on packed cell volume between treatment and highly significant ($P<0.01$) between periods.

Again table-12 showed that Midazolam treated group did not significantly differ with Propofol treated group and Propofol+ Midazolam treated groups, however Propofol treated group significantly differ with Propofol+ Midazolam treated groups.The effect of time duration on different treatment group varied significantly up to 15 minutes post induction. However, time period of 30 and 60 minutes did not varied significantly.

Haemoglobin

Analysis of variance (Table-13) revealed highly significant ($P<0.01$) effects of different anaesthetic agent on haemoglobin between treatment. However non-significant effects were found between periods.

Mean along with S.E of haemoglobin in anaesthetized pigs at different periods of time in all three groups had been presented in table-14. It revealed that no significant difference between Propofol treatment groups and Propofol+ Midazolam treated groups were observed. However, among the groups significant effects were marked on haemoglobin. The effects of time duration on different treatment group varied significantly up to 15 minutes post induction but after rest of period there was no significant difference.

Table –11

Analysis of variance for the effect of different anaesthetic agent on PACKED CELL VOLUME (%) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	4.76	2.38	4.71*
Between period	4	11.327	2.831	5.60**
Error	83	41.937	0.505	

* Significant at($P<0.05$)

** Highly significant at ($p<0.01$)

Table-12

Mean ±S.E of PACKED CELL VOLUME (%) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	43.70 ± 0.29	43.27 ± 0.27	42.90 ± 0.28	42.37 ± 0.30	43.13 ± 0.26	43.15^{x} ± 0.13
B	43.47 ± 0.36	42.90 ± 0.28	42.37 ± 0.33	42.4 ± 0.32	42.93 ± 0.27	42.81^{xy} ± 0.15
C	43.1 ± 0.30	42.67 ± 0.31	42.2 ± 0.29	42.23 ± 0.30	42.77 ± 0.33	42.59^{y} ± 0.14
Overall Mean ±S.E	43.42^{a} ± 0.18	42.95^{b} ± 0.18	42.49^{bc} ± 0.18	42.45^{cd} ± 0.17	42.94^{b} ± 0.16	

Mean with similar superscript (Columnwise X, Y,.....and rowwise a,b....)did not differ Significantly.

Table –13

Analysis of variance for the effect of different anaesthetic agent on HAEMOGLOBIN (gm/dl) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	2.982	1.491	6.53**
Between period	4	1.704	0.426	1.86 NS
Error	83	18.94	0.228	

** Highly significant at ($p<0.01$)
NS: Non Significant

Table-14

Mean ±S.E of HAEMOGLOBIN (gm/dl) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment Group	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	12.28 ± 0.22	12.18 ± 0.22	11.93 ± 0.22	11.98 ± 0.22	12.18 ± 0.23	12.11^{x} ± 0.10
B	12.02 ± 0.20	11.85 ± 0.19	11.71 ± 0.23	11.60 ± 0.21	11.90 ± 0.20	11.82^{y} ± 0.09
C	11.90 ± 0.18	10.18 ± 0.18	11.50 ± 0.17	11.55 ± 0.18	11.77 ± 0.19	11.34^{x} ± 0.08
Overall Mean ±S.E	12.07^{a} ± 0.12	11.34^{b} ± 0.12	11.71^{c} ± 0.12	11.71^{c} ± 0.12	11.95^{ac} ± 0.12	

Mean with similar superscript (Columnwise X, Y,.....and rowwise a,b....)did not differ Significantly.

Neutrophil

Analysis of variance (Table-15) revealed highly significant ($P<0.01$) effects of different anaesthetic agent on neutrophil between treatments. However, there were non-significant effects in between periods.

Mean along with S.E of neutrophil count in anaesthetized pigs at different periods of time in all three groups had been presented in table-16. Non significant ($P<0.01$) difference between Propofol treatment groups and Propofol+ Midazolam treated groups were marked. However Midazolam treated group and Propofol+Midazolam treated groups had significant effects on neutrophil.The effects of time duration on different treatment group did not vary significantly post induction.

Eosinophil

As reflected by analysis of variance (Table-17) there was significant effects of anesthetics on eosinophil both between treatment ($P<0.01$) and between periods ($P<0.05$). It was evident that Midazolam treated group significantly differ with Propofol treated group and Propofol treated group significantly differ with Propofol+ Midazolam treated groups (table-18). The effects of time duration on different treatment group did not vary significantly up to 15 minutes post induction and also the same was observed upto 30, 60 and 120 minutes.

Table –15

Analysis of variance for the effect of different anaesthetic agent on NEUTROPHIL (%) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	9.446	4.723	9.782**
Between period	4	1.122	0.28	0.58 NS
Error	83	40.072	0.482	

** Highly significant at ($p<0.01$)
NS: Non Significant

Table-16

Mean ±S.E of NEUTROPHIL (%) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	38.30 ±0.36	38.37 ±0.41	38.57 ±0.33	38.35 ±0.29	38.30 ±0.34	38.38^{x} ±0.15
B	38.12 ±0.29	38.13 ±0.30	38.40 ±0.22	38.38 ±0.30	38.14 ±0.34	38.24^{x} ±0.08
C	38.45 ±0.33	38.57 ±0.30	38.83 ±0.29	38.60 ±0.36	38.48 ±0.33	38.59^{x} ±0.14
Overall Mean ±S.E	38.29^{a} ±0.18	38.36^{a} ±0.19	38.60^{a} ±0.16	38.44^{a} ±0.18	38.32^{a} ±0.18	

Mean with similar superscript (Columnwise X, Y,.....and rowwise a,b....)did not differ Significantly.

Table –17

Analysis of variance for the effect of different anaesthetic agent on EOSINOPHIL (%) in swine.

Source of Variation	d.f	SS	MS	F
Between treatment	2	7.85	3.925	8.68**
Between period	4	5.408	1.325	2.992*
Error	83	37.502	0.451	

* Significant at($P<0.05$)

** Highly significant at ($p<0.01$)

Table-18

Mean ±S.E of EOSINOPHIL (%) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	5.35 ±0.29	5.0 ±0.29	4.68 ±0.20	4.67 ±0.28	4.95 ±0.28	4.93^{x} ±0.12
B	5.72 ±0.32	5.3 ±0.32	5.05 ±0.30	5.05 ±0.28	5.38 ±0.30	5.30^{y} ±0.13
C	6.02 ±0.28	5.75 ±0.33	5.38 ±0.31	5.38 ±0.29	5.73 ±0.26	5.65^{z} ±0.13
Overall Mean ±S.E	5.70^{a} ±0.17	5.35^{ab} ±0.18	5.04^{bc} ±0.16	5.03^{bc} ±0.17	5.35^{ab} ±0.17	

Mean with similar superscript (Columnwise X,Y,.....and rowwise a,b....)did not differ Significantly.

Total serum glucose

Analysis of variance (Table-19) revealed highly significant (P<0.01) effects of different anaesthetic agent on total serum glucose between periods but non-significant effects were found between treatments. However, slight significant differences between Propofol and Propofol +Midazolam treated groups were observed (Table-20) but Midazolam treated group and Propofol+Midazolam treated groups had non-significant (P<0.01) effects on total serum glucose. The effects of time duration on different treatment group varied significantly during post induction of anaesthesia.

SGOT

Analysis of variance revealed highly significant difference (P<0.01) among average SGOT in each group at different periods of interval (Table3).

Mean along with S.E of SGOT in anaesthetized pigs at different periods of intervals in different groups had been presented in table-22. Prior to administration of drugs i.e. at 0(zero) minute, the average SGOT in groups A, B and C were recorded 20.48±0.43, 20.38±0.32 and 20.50±0.41 IU/L respectively. This table also showed that there was non significant difference between Propofol treated group and Midazolam treated group on SGOT. However, there was significant difference between Propofol +Midazolam treated groups as compared to two other groups. The effects of time duration on different treatment groups varied significantly in all groups post induction.

Table –19

Analysis of variance for the effect of different anaesthetic agent on TOTAL SERUM GLUCOSE (gm/dl) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	75.089	37.54	2.60 ^{NS}
Between period	4	19311.84	4827.96	334.69**
Error	83	1197.07	14.425	

NS: Non Significant

** Significant at ($p<0.01$)

Table-20

Mean ±S.E of TOTAL SERUM GLUCOSE (gm/dl) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	85.0 ± 1.57	97.83 ± 2.37	109.17 ± 1.83	118.50 ± 2.12	126.50 ± 1.82	107.40^{x} ± 2.85
B	86.17 ± 1.64	100.0 ± 1.15	111.17 ± 1.08	120.0 ± 1.84	127.50 ± 1.61	108.97^{xy} ± 2.79
C	87.17 ± 1.92	100.0 ± 1.41	112.0 ± 1.21	120.50 ± 0.76	128.17 ± 1.25	109.57^{y} ± 2.77
Overall Mean ±S.E	86.11^{a} ± 0.96	99.28^{b} ± 0.97	110.78^{c} ± 0.82	119.67^{d} ± 0.93	127.39^{e} ± 0.87	

Mean with similar superscript (Columnwise X,Y,.....and rowwise a,b....)did not differ Significantly.

Table –21

Analysis of variance for the effect of different anaesthetic agent on SGOT (IU/L) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	8.01	4.005	5.544**
Between period	4	324.056	81.014	112.164**
Error	83	59.949	0.722	

** Highly significant at ($p<0.01$)

Table-22

Mean ±S.E of SGOT (IU/L) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Periods (Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	20.48 ± 0.43	17.08 ± 0.25	15.93 ± 0.28	15.02 ±0.28	19.47 ± 0.38	17.60^{x} ± 0.41
B	20.38 ± 0.32	17.25 ± 0.27	15.65 ± 0.15	14.78 ± 0.17	19.01 ± 0.24	17.41^{x} ± 0.4
C	20.50 ± 0.41	18.28 ± 0.33	17.10 ± 0.41	15.83 ± 0.57	18.88 ± 0.29	18.12^{y} ± 0.34
Overall Mean ±S.E	20.45^{a} ± 0.21	17.53^{b} ± 0.20	16.23^{c} ± 0.22	15.21^{d} ± 0.23	19.12^{e} ± 0.18	

Mean with similar superscript (Columnwise X,Y,.....and rowwise a,b....)did not differ Significantly.

SGPT

Analysis of variance (Table-23) presented non-significant effects of different drugs on SGPT both between treatments and between periods.

Mean along with S.E of SGPT in anaesthetized pigs at different periods of intervals in all three groups had been presented in table-24. From table it revealed that non significant difference between different treatment groups and different periods of intervals on SGPT was found. However, in general there was decrease in SGPT from 0 to 30 minutes after post induction of anaesthesia and then up to 120 minutes, which normalized in due course.

Total serum protein

Analysis of variance (Table-25) showed non-significant effects of different drugs on total serum protein both between treatments and between periods.

Mean along with S.E of total serum protein in anaesthetized pigs at different periods of intervals in all three groups had been presented in table-26. During study it was observed non significant difference between different treatment groups and at different periods of intervals on total serum protein was observed. However, in general there was decrease in total serum protein from 0 to 30 minutes after post induction of anaesthesia and then up to 120 minutes it tended to normalize.

Table –23

Analysis of variance for the effect of different anaesthetic agent on SGPT(IU/L) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	0.0486	0.0243	0.0288 ^{NS}
Between period	4	4.437	1.10925	1.3169 ^{NS}
Error	83	69.91	0.842	

NS: Non Significant

Table-24

Mean ±S.E of SGPT (IU/L) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

Treatment group	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	11.53 ± 0.37	11.22 ± 0.36	10.82 ± 0.38	11.02 ± 0.39	11.35 ± 0.37	11.19^{x} ± 0.16
B	11.51 ± 0.41	11.32 ± 0.37	10.97 ± 0.40	10.98 ± 0.39	11.32 ± 0.40	11.22^{x} ± 0.17
C	11.50 ± 0.40	11.23 ± 0.41	10.97 ± 0.41	10.90 ± 0.42	11.22 ± 0.41	11.16^{x} ± 0.17
Overall Mean ±S.E	11.51^{a} ± 0.21	11.26^{a} ± 0.20	10.92^{a} ± 0.22	10.97^{a} ± 0.22	11.30^{a} ± 0.21	

Mean with similar superscript (Columnwise X,Y,.....and rowwise a,b....)did not differ Significantly.

Table –25

Analysis of variance for the effect of different anaesthetic agent on TOTAL SERUM PROTEIN (gm/dl)in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	0.04895	0.24475	1.79 ^{NS}
Between period	4	0.82	0.205	1.50 ^{NS}
Error	83	11.33	0.136	

NS: Non Significant

Table-26

Mean ±S.E of TOTAL SERUM PROTEIN (gm/dl) in different experimental group of swine due to the effect of different anaesthetic agents at different period of time.

group	Peroids(Minutes)					Overall Mean ±S.E
	0	15	30	60	120	
A	7.29 ± 0.14	7.11 ± 0.14	7.04 ± 0.14	7.09 ± 0.14	7.22 ± 0.14	7.15^{x} ± 0.06
B	7.42 ± 0.15	7.32 ± 0.16	7.18 ± 0.15	7.24 ± 0.16	7.50 ± 0.13	7.33^{x} ± 0.06
C	7.34 ± 0.18	7.22 ± 0.18	7.08 ± 0.18	7.17 ± 0.18	7.28 ± 0.18	7.22^{x} ± 0.08
Overall Mean ±S.E	7.35^{a} ± 0.08	7.22^{a} ± 0.09	7.10^{ab} ± 0.09	7.17^{a} ± 0.09	7.33^{a} ± 0.09	

Mean with similar superscript (Columnwise X,Y,.....and rowwise a,b....)did not differ Significantly.

Onset of action

Time from injection of anaesthetic agents to loss of sensation (recumbency) was considered as onset of action.

Mean along with their S.E of onset of action (in minutes) in anaesthetized pigs in different experimental groups of pigs had been presented in table -30. The average estimates of onset of action (in minutes) were observed 50.50± 1.20, 36.17±1.35 and 27.13±0.83 in group A, B and C respectively. The onset of action was significantly ($P<0.01$) quicker in group C than group A and B, however group B was also highly significantly ($P<0.01$) quicker than group A. Analysis of variance (Table-27) revealed that there was significant difference in between group A, B and C after the induction of anaesthetic agents.

Duration of action

Time from the onset of action to return of sensation on entire body of the experimental animal was considered as duration of action.

Mean along with their S.E for duration of action (in minutes) in anaesthetized pigs in different experimental groups had been presented in table- 30. The average estimates of duration of action (in minutes) were observed 25.0±0.82, 31.67±0.56 and 42.33±0.99 in group A, B and C respectively. The duration of action was significantly ($P<0.01$) longer in group C than group A and B, however, group B was also significantly ($P<0.01$) longer than group A. Analysis of variance (Table-28) revealed highly significant ($P<0.01$) difference in between group A, B and C after the duration of anaesthetic agents.

Recovery period

Time from injection of anaesthetic agents until animal could stand and walk voluntarily was considered as recovery period.

Mean along with their S.E of recovery period (in minutes) in anaesthetized pigs in different experimental groups had been presented in table- 30. The average estimate of recovery periods (in minutes) were observed 72.67±0.08, 55.67±1.05 and 66.50±1.15 in group A, B and C respectively. The recovery period was significantly ($P<0.01$) longer in group C than group A and B, however, group A was also significantly ($P<0.01$) longer than group B. Analysis of variance (Table-29) revealed highly significant ($P<0.01$) difference in between group A, B and C after the duration of anaesthetic agents.

Table –27

Analysis of variance for the effect of different anaesthetic agent at ONSET OF ANAESTHESIA(Seconds) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	2243.11	1121.55	141.173**
Error	15	119.167	7.94	

** Highly significant at ($p<0.01$)

Table –28

Analysis of variance for the effect of different anaesthetic agent at DURATION OF ANAESTHESIA (Minutes) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	917.33	458.665	117.265**
Error	15	58.67	3.91	

** Highly significant at ($p<0.01$)

Table –29

Analysis of variance for the effect of different anaesthetic agent at RECOVERY FROM ANAESTHESIA(Minutes) in swine.

Source of variation	d.f	SS	MS	F
Between treatment	2	888.78	444.39	72.49**
Error	15	91.97	6.13	

** Highly significant at ($p<0.01$)

Table –30

Mean ±S.E of ONSET OF ANAESTHESIA(Seconds) , DURATION OF ANAESTHESIA (Minutes) and RECOVERY FROM ANAESTHESIA in different experimental group of swine due to the effect of different anaesthetic agents.

Treatment group	Onset of anaesthesia(Seconds)	Duration of anaesthesia (Minutes)	Recovery from anaesthesia (Minutes)
A	$50.50^{x} \pm 1.20$	$25.0^{x} \pm 0.82$	$66.50^{x} \pm 1.15$
B	$36.17^{y} \pm 1.35$	$31.67^{y} \pm 0.56$	$55.67^{y} \pm 1.05$
C	$27.13^{z} \pm 0.83$	$42.33^{z} \pm 0.99$	$72.67^{z} \pm 0.08$

Mean with similar superscript(Columnwise X,Y, ...)did not differ Significantly

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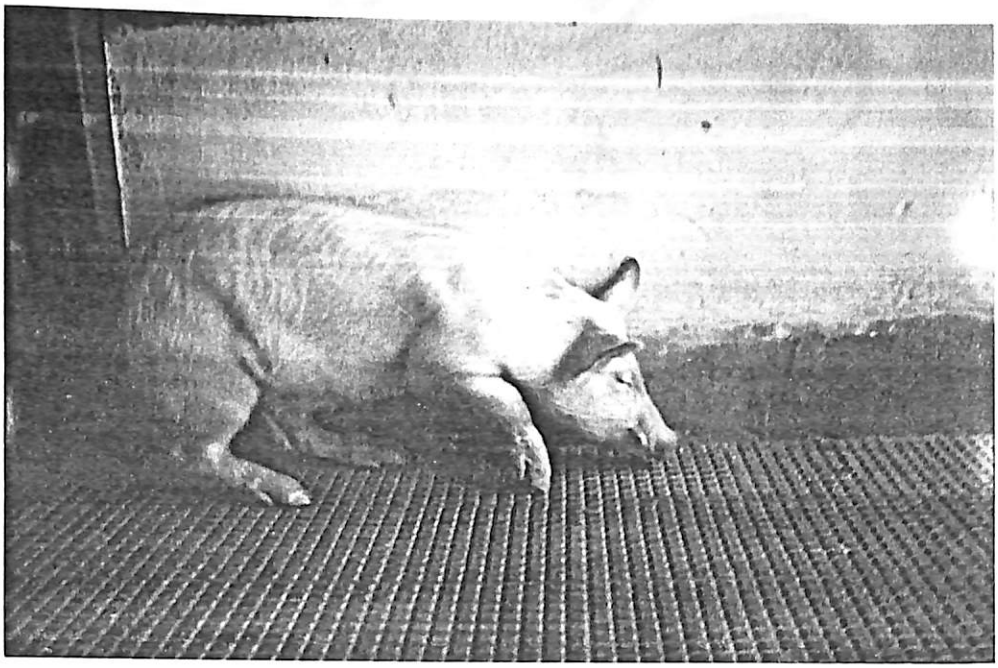

Figure No.5.Photograph revealing pigs of group-A (Propofol) recovering from anaesthesia.

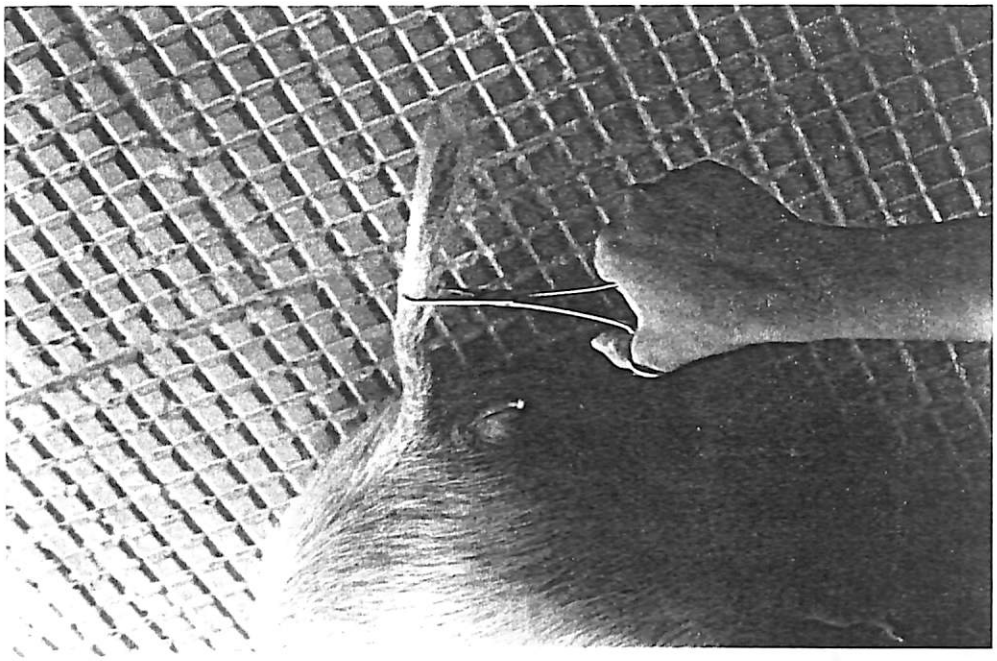

Figure No.6.Photograph showing recording of tail reflex in pigs after induction of anaesthesia in group –C.

CHAPTER - V

DISCUSSION

DISCUSSION

A comparative study was undertaken with Propofol and Midazolam in different dose schedule to evaluate the best dose schedule of the drugs in combination for their safest and most purposeful action in swine.

CLINICAL STUDIES

Rectal Temperature

Rectal Temperature declines significantly ($P<0.01$) in groups of pigs after Propofol and Midazolam administration. Propofol has tendency to decrease rectal temperature by its thermoregulatory depressant effects, as observed by Hargopal, *et al.* (2002) and Ozaydin *et al.* (2001) in dogs. As Midazolam is a benzodiazepine derivative so as like diazepam it can induce hypothermia by exerting a depressing effect on hypothalamic thermoregulatory center. The reduction of rectal temperature could be due to thermoregulatory effects of drugs associated with dissipation of heat from body in the air condition operation theater and reduced basal metabolic rate with suppressed activities of ascending reticular activating system. No malignant hypothermia syndrome was observed (with symptoms of muscles rigor, decrease of temperature of 2^0c or more) in any pigs of all 3 groups under research as seen by Harrison (1988), Zimmermann *et al.* (1994) , Raff and Harrison. (1989) in pigs. The change of temperature is similar to the observation of Hargopal *et al.*(2002), Pypendrop *et al.* (1999) in dogs and Zellner *et al.* (1991) in pigs.

Heart Rate

Values recorded in this study showed that there was a transient significant decrease in heart rate in all the groups. Decrease in heart rate just after Midazolam administration was evident in all pigs in each group, which was also observed by Zellner *et al.* (1991) in pigs.

Significant decrease in heart rate there after as well , correlates with the work done by Akkerdaas *et al.* (2001) in cats, Brussel *et al.* (1989), Quandt *et al.* (1998), Redondo *et al.* (2000), Amarpal *et al.* (2001) in goats and Kenneth *et al.* (1997)in guinea pig and may be due to as Propofol produce negative entropic effects as seen by Brussel *et al.*(1989) in human.

The variation in the heart rate may be explained partially by the direct effect of Propofol on vascular smooth muscles or Propofol represent an alteration in baroreceptor activity that would otherwise lead to an increase in sympathetic nervous outflow. The mechanism for parasympathetic control of heart rate may be stronger than the baroreflex-mediated enhancement of central sympathetic activity. Propofol has been reported to decrease nodal sinus activity, causing decreased heart rate.

As a benzodiazepine derivative Midazolam produces transient arterial hypotensive effects, in pigs Zellner *et al.* (1991) and in mallard duck as seen by Machine and Caulkett (1998). So it may be due to synergistic effects when Midazolam was used in combination with Propofol and there was significant decrease in heart rate through out the period of experiment, which was also supported by the work of Akkerdaas *et al.* (2001) in cats, Zellner *et al.* (1991) in pigs, Machine and Caulkett (1998) in mallard duck, Olson *et al.* (1992) in rabbits and Kenneth *et al.* (1997)in guinea pig.

Respiration Rate

In this study respiratory rate showed significant variation in all the groups. As result showed respiratory rate slightly decreased after Propofol I/V injection. Similar results were found by Nolan and Hall (1985) in ponies. Falls of respiratory rates significantly was also observed by Brearley *et al.* (1988) in cats, Ozaydin *et al.* (2001) and Aguiar *et al.* (2001) in dogs.

There was significant ($P<0.01$) decrease in respiratory rate even after Midazolam I/V injection in pigs. This respiratory depression may be due to reductin in oxygen saturation, Bufalari *et al.*(1998) and attributed to a suppression of central inspiratory system activity.

Respiratory depression was due to synergistic effects of Midazolam and Propofol. Similar findings were observed by Cullen and Reynoldson (1993), Bufalari *et al.* (1996), Quandt *et al.* (1998), Redondo *et al.*(2000), Amarpal *et al.*(2001) and Erhardt *et al.*(1991) in cats.

Haematological observation

From the haematological profile it had been found that total erythrocyte count, packed cell volume, haemoglobin, eosinophil and neutrophil count varied nonsignificantly.

No abrupt change in haematological parameters were observed when Propofol, Midazolam alone and in combination were administered intravenously in pigs.

No abrupt changes in any haematological parameters were observed in any group of pigs. The variation in Total erythrocyte count was nonsignificant in group A, B and C. Total leukocyte count increased little in all groups nonsignificantly but remains more or less same. Packed cell volume decreased nonsignificantly in all groups of pigs but changes are

negligible. Haemoglobin first slightly decreased in all groups then they tend to normalize in all groups of pigs. Neutrophil count remains almost same in all groups with negligible nonsignificant variation. Eosinophil count decreased nonsignificantly in group A, group B and group C pigs. There was a significant decrease in total erythrocyte count, total leukocyte count, packed cell volume and haemoglobin using Propofol anaesthesia (Venugopal *et al.*2002).

These findings correlates with the observation of the other studies using Propofol alone and or in combination with other drugs in animals and human viz. Bayan *et al.*(2002) in dogs, Hargopal *et al.*(2002) in dogs, Bufaleri *et al.*(1996) in dogs, Asskali *et al.*(1994) in human.

The effects of Propofol, Midazolam alone and in combination on haematological parameters may be due to rapid distribution and elimination of both the drugs from the body.

Biochemical analysis

The change in SGOT, SGPT, and total serum protein were nonsignificant decrease in all the groups of pigs, through out the experiment. There was increase in total serum serum glucose from 0 to 120 minutes after induction of anaesthesia. Midazolam was rapidly metabolized to 1-hydroxymethyl midazolam and 4-hydroxy midazolam. The pharmacological activities of these metabolites were negligible as compared to that of the parent compound. There was rapid excretion of Midazolam mainly through the renal routes as glucoronide conjugate (Court *et al.*1991). Propofol was metabolized and eliminated rapidly. Using a subanaesthetic dose of radioactive Propofol in human patients, it was reported that 2 minutes after injection 94% of the radioactive materials in blood were unchanged Propofol but that after 30 minutes 81% of the

radioactivity was in the form of metabolites. Most of the injectable Propofol was excreted as a Propofol conjugate,(approximately 40% urinary excretion product) a conjugate of 4-hydroxy Propofol and a small amount of unchanged Propofol, whereas less than 2% was excreted in the faeces. Results i.e. nonsignificantly decrease of SGOT, SGPT, and total serum protein simulate with findings of Hall and Chamber. (1987) and Bufaleri *et al.*(1996) in dogs. This indicates the drug have minimum effects on liver metabolism.

Anaesthetic observation

The result showed that there was highly significant ($P<0.01$) variation in onset of anaesthhesia between three groups and also in recovery from anaesthesia. Propofol anaesthetic was found smooth during induction and recovery without complication and with no post-anaesthetic hangs over in pigs.

According to Hall and Chambers (1987) the time to onset of drug action depends on both circulation time and biophase kinetics. Result of the present study revealed that onset of the anaesthesia and recovery from the anaesthesia has varied depending on induction dose of Propofol as the other drug schedules were fixed for all the groups. There was smooth recovery from Propofol anaesthesia. These findings correlate with Erhardt *et al.*(1991) and Brearley *et al.* (1988) both in cats, Machine and Caulkett (1998) in mallard duck, Olson *et al.* (1992) in rabbits, Watkins et al.(1987), Zoran *et al.* (1993) in dogs and Taylor *et al.* (2001) in mare.

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CHAPTER - VI

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

Propofol and Midazolam were evaluated alone and in combination as a general anaesthetic in 18 clinically healthy white Yorkshire breeds of pigs, ageing 6 to 9 months. The animals were randomly divided into three groups having six animals in each group. Propofol and Midazolam were injected alone and in combination at a dose rate of 5 mg, 0.5mg and (1.5+0.1) mg per kilogram body weight intravenously in respective groups.The observation were made on the basis of rectal temperature, heart rate, respiration rate, onset of action, duration of action, recovery period, extent and magnitude of analgesia after seeing different reflexes.

Haematological examinations included estimation of TEC, TLC, PCV, Haemoglobin ,Neutrophil count and Eosinophil count .Biochemical examinations included estimation of total serum glucose, SGOT, SGPT and total serum protein. The observation, which was made, and result obtained during the present study revealed that all these anaesthetic are worthy to use in swine.

PROPOFOL: -

Induction of anaesthesia with Propofol was quite,smooth and excitement free in all the treatment group animals.Duration of surgical anaesthesia with Propofol was short. In present trial it ranged from 30-34 minutes. During anaesthesia a little salivation, good cutaneous analgesia with pedal reflex and no bloat were seen in all testing animals.

In present study, rectal temperature of the pig after giving Propofol remains within the normal range. However, heart and respiratory rates were significantly decreased.

MIDAZOLAM: -

Onset of action of Midazolam was rapid, smooth and excitement free in all animals. Duration of surgical anaesthesia with Midazolam was very short. In present trial it ranged from 22-28 minutes.

PROPOFOL-MIDAZOLAM: -

The Propofol-Midazolam combination in pigs induced, excitement free anaesthesia and there was rapid smooth recovery. There was no vomiting, coughing or retching during the recovery from anaesthesia. Desirable degree of analgesia was developed in Propofol-Midazolam combination. Duration of surgical anaesthesia with this combination was found longer and it ranged from 39-46 minutes. No malignant hypothermia was reported in any animal of any group.

Taking all aspects in consideration, such as clinical examination, haematological examination, study of anesthetic effects; it can be concluded that the Propofol -Midazolam combination is safest and most suitable combination of anaesthetic agent in swine.

Study of clinical parameters showed that Propofol in combination with Midazolam had some respiratory and cardiovascular depression effects, which were found to remain, within physiological tolerance level of pigs. Changes in different haematological parameters were nonsignificant, which leads to the conclusion that Propofol-Midazolam combination did not affect the normal anesthesia of pigs.

On the basis of observation made it was clear that there was lack of any type of post complication or death after anesthesia in any group but the efficacy of anesthesia may be concluded as follows: -

1. Propofol alone produced optimal sedation and analgesia in swine.
2. Midazolam alone produced deep sedation and analgesia for short duration (Only for 20-25 minutes) in swine.
3. When combination of Propofol and Midazolam were administered, there was excellent analgesia, deep sedation and abolition of superficial and deep cutaneous reflexes permitting for clinical surgery when needed.
4. NO malignant hypothermia was reported in any animal of any group. Thus, the use of Propofol and Midazolam in combination was suitable whenever needed prior to surgery in swine as compa red to Propofol and Midazolam alone.

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BIBLIOGRAPHY

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Adamiak, Z.; Chyczewski, M.; Jalynski, M.; Brzeski, W.; Mowicki, M.; Depta, A. and Rychlik, A. (2002). Combined anaesthesia with Atropine, Midazolam and Propofol in arthroscopic procedures in dogs. *Medycyna-weterynaryjna.* **58** (2): 120-123.

Adetunji, A.; Ajadi, R.A.; Adewoye, C.O. and Oyemakinde, B.O. (2002). Total intravenous anaesthesia with propofol: repeat bolus versus continuous propofol infusion technique in xylazine premedicated dogs. *Israel Journal of Veterinary Medicine.* **57**(4): 139-144.

Aguiar, A.J.A.; Luna, S.P.L.; Oliva, V.N.L.S.; Eugenio, F.R. and Castro, G.B. (2001). Continuous infusion of propofol in dogs premedicated with methotrimeprazine. *Veterinary Anaesthesia and Analgesia.* **28**(4): 220-224.

Akkerdaas, L.C.; Mioch, P.; Sap, R. and Hellebrekers, L.J.(2001). Cardiopulmonary effects of three different anaesthesia protocols in cats. *Veterinary-Quarterly.* **23**(4):182-186.

Alkan, F.; Koc,Y. and Kul, M.(2001). The effects of midazolam-ketamine and diazepam-ketamine on arterial blood pressure, blood gases and some physiological functions in dogs. *Hayvancilik-Arastirma-Dergisi.* 11(1): 44-49.

Alves , G.E.S.; Hartsfield,S.M.; Carroll, G.L.; Santos, D.A.M.L.; Zhang, S.; Tsolis, R.M.; Baumler, A.J.; Adams, L.G. and Santos, R.L. (2003). Use of propofol, isoflurane and morphine for prolonged general anesthesia in calves. *Arquivo-Brasileiro-de-Medicina-Veterinaria-e-Zootecnia.* **55**(4): 411-420.

Amarpal, Kinjavdekar, P.; Aithal, H.P.; Pratap, K.; Pathak, R. and Singh, V. (2001). Effect of xylazine and medetomidine premedication on propofol anaesthesia in goats. *Indian Journal of Animal Science* . **72**(7): 565-566.

Asskali, F.; Behne, M.; Lischkev.; Probst, S.; Hermaan, R. and Vettermann, J. (1994). Midazolam does not antagonise fentanyl-medicated analgesia in surgical patient. *J. Clin. Anaesthe.* **6**(6):481-486.

Bayan, H.; Sarma, K.K. and Chakravarty, P. (2002). Biochemical and haematological changes during propofol anaesthesia in canine. *Indian Journal of Veterinary Surgery.* **23**(2): 95-96.

Bayan, H.; Sarma, K.K. and Lahon, D.K.(2002). Cardiopulmonary changes during propofol anaesthesia in canine. *Indian Veterinary Journal.* **79**(12): 24-25.

Beswick, W. (1964). Amputation of prolapsed uterus. *Veterinary record.* **76**(35): 930.

Bollwahn, W. (1964). Cesarean section under general anaesthesia. *Tierarztl-Umschau.* **19**(1): 3-11

Brearley, J.C.; Kellagher, R.E.B. and Hall, L.W. (1988). Propofol anaesthesia in cats. *Journal of Small Animal Practice.* **29**(5): 315-322.

Brussel, T.; Theissen, J.L.; Vigfusson, G.; Lunkenheimer, P.P.; Van Aken, H. and Lawin, P. (1989). Hemodynemic and cardiodynamic effects of propofol and Etomidate. *Anesth Analog.* **69**:35-40.

Bufalari, A.; Miller, S.M. and Giannoni, C. (1998). The use of propofol as an iduction agent for Halothane and Isoflurane anaesthesia in dogs. *Journal of the AmericanHospital Association.* **34**:84-91.

Bufalari, A.; Short, C.E.; Giannoni, C. and Vainio, O.(1996).Comparative responses to Propofol anaesthesia alone and with alpha-2 adrenergic medication in a canine model. *Acta Vet.Scand.* **37**(2):187-201.

Buz'ko, A.A. *et al.* (1961). Biostimulation and clitorotomy for fattening. *Veterinariya* . **38**(1):23.

Court, M.H. and Greenbalt, D.J. (1991). Pharmacokinetics and preliminary observations of the behavioral effects of midazolam in dog. *Journal of Veterinary Anaesthesia.* Special supplement.**21**(1) 353-355.

Cullen, L.K. and Reynoldson, J.A. (1993). Xylazine or medetomidine premedication before Propofol anaesthesia. *The Veterinary Record.* **132**:378-383.

Cura, P.; Nastasa, V. and Vulpe, V. (2000). The combination Fentanyl - Midazolam, a new type of vigile anaesthesia to dog. *Lucrai-Stiinifice -Medicina-Veterinara,-Universitatea-de-Stiinte-Agricole-si-Medicina-Veterinara-"Ion-Ionescu-de-la-Brad"-Iasi.* **43**(2): 249-252.

Dyson, J.A. (1964). Anaesthesia for the experimental pig. *British J. Anaesthesia.* **35**(11):736-740.

Erhardt, W.; Lendl, C.; Heuer, H.J.; Trilling, T. and Matis, U. (1991). Comparative investigation of four anaesthetic methods in the cat. *Journal of Vet.Anaesthesia,Spl. Supple. Aug.* 201-203

Frias, A.F.G.; Marsico, F.; Gomez., Segura, I.A.; Nascimento, P.R.L.; Nascimento., Junior, A.; Soares, J.H.N.; Almosny, N.R.; Segura, I.A. and Gomez. (2003). Evaluation of different doses of propofol in xylazine pre-medicated horses. *Veterinary Anaesthesia and Analgesia.* **30**(4): 193-201.

Fussell, R.A.; Watts, R.E. and Carver Alvin T. (1960). Colostomy in a Hog. *Modern Veterinary Practice.* **41**(4): 70-72.

Greene, S.A.; Benson, G.J. and Hartisfield, S.M. (1993). Thiamylal-sparing effect of Midazolam for endotracheal intubation. A clinical study on 118 dogs. *Vet. Surg.* **22** (1): 69-72.

Gremiao, I.D.F.; Nascimento, P.R.L.; Nascimento Junior, A.; Soares, J.H.N.; Ascoli, F.O.; Marsico Filho, F. and Nascimento, P.R.L. (2001). Subarachnoid anaesthesia effects of hyperbaric bupivacaine 0.5% in the mean arterial pressure of dogs induced and maintained with propofol. *Revista-Brasileira-de-Ciencia-Veterinaria.* **8**(3): 151-154.

Gulanber, E.G.; Bastan, A.; Tasal, I.; Aktas, M. and Arikan, N. (2001). General anesthesia in dogs with midazolam and ketamine. *Veteriner-Fakultesi-Dergisi-Istanbul.* **27**(2): 401-409.

Hall, L.W. and Chambers, J.P. (1987). A clinical trial of propofol infusion anaesthesia in dogs. *Journal of Small Animal Practice.* **28**(7): 623-637.

Hargopal, V.; Chandrashekher, E.L. and Venugopal, A. (2002). Effects of Propofol - ketamine anaesthesia with or without premedication in dogs. *Indian Journal of Veterinary Surgery.* **23**(2): 106-107.

Harrison, G.G. (1998). Control of The Malignant Hyperpyrexic Syndrome in MHS Swine By Dantrolene Sodium. *British Journal Anaesthesia.* **81**:626-629.

Hawkins, M.G.; Wright, B.D.; Pascoe, P.J.; Kass, P.H.; Maxwell, L.K. and Tell, L.A.(2003). Pharmacokinetics and anesthetic and cardiopulmonary effects of propofol in red-tailed hawks (Buteo jamaicensis) and great horned owls (Bubo virginianus). *American Journal of Veterinary Research.* **64**(6): 677-683.

Hellebrekers, L.J. (1991). Sulfentanyl – Midazolam anaesthesia in dog. *J. Vet. Anaes.* Special Supplement, 191-193.

Intelizano, T.R. (2003). Haemodynamic and respiratory evaluation of total intravenous anaesthesia with propofol, propofol-racaemic ketamine and propofol-ketamine-S in dogs: experimental study. *Avaliacao-hemodinamica-e-respiratoria-da-anestesia-total-injetavel-com-propofol,-propofol-quetamina-racemica-e-propofol-quetamina-S-em-caes:-estudo-experimental.* Pp 180.

Ilkiw, J.E.; Farver, T.B.; Suter, C.; McNeal, D. and Steffey, E.P. (2002). The effect of intravenous administration of variable-dose flumazenil after fixed-dose ketamine and midazolam in healthy cats. *Journal of Veterinary Pharmacology and Therapeutics.* **25**(3): 181-188.

Kenneth, A.; Schenkman, and shiluo Yan.(1997).propofol impairs Mitochondrial function and cardiac Performance in isolated perfused Guinea pigs hearts. *Abstract #93 Inj./Pharma. Sept.*-20.

Kilic, N.; Pasa, S.; Seyrek, K.and Guzel, N. (2003). Intravenous injection anaesthesia with ketamine/xylazine/propofol in the dog. *Veteriner-Fakultesi-Dergisi-Istanbul.* **29**(1): 77-82.

Koc, Y.; Alkan, F. and Kul, M. (2002). Effects of anesthetic-like combination of midazolam and xylazine on certain clinical parameters in dogs. *Indian Veterinary Journal.* **79**(12): 55-58.

Kojima, K.; Nishimura, R.; Mutoh, T.; Hong-SungHyeok.; Mochizuki, M.; Sasaki, N. and Hong, S.H.(2002). Pets and Companion Animals. Veterinary Pharmacology and Anaesthesiology. Toxicology and Poisoning of Animals. *American Journal of Veterinary Research.* **63:** (12) 1671-1679.

Kolmer, J.A.; Spaulding, E.H. and Robinson, H.W.(1969). "Approved Laboratory technique." Fifth Ed. (Indian ed.).

Kwon, Y.S.; Jang, K.H.; Jang, H.S.; Park, H.J.; Lim, J.H.; Oh, T.H.; Eom, K.D. and Jang, I.H. (2002). Cardiovascular effects of propofol

infused for maintenance of anesthesia in dogs. *Journal of Veterinary Clinics.* **19**(2): 199-203.

Machine, K.L and Caulkett, N.A. (1998).Cardiopulmonary effects of Propofol and a medetomidine-Midazolam-Ketamine combination in Mallard ducks.Ameri. *J. of Vet. Research.* **59**(5):598-602.

Mc Fadden, O.L. (1961). Castration of cryptorchid boars. *Modern Veterinary Practice.* **42**(18): 60.

Nastasa, V.; Cura, P. and Vulpe, V. (2000). Anaesthesia with Midazolam - Ketamine and Xylazine to dog. *Lucrai-Stiinifice -Medicina-Veterinara,-Universitatea-de-Stiinte-Agricole-si-Medicina-Veterinara-"Ion-Ionescu-de-la-Brad"-Iasi.* **43**(2): 253-255.

Nolan, A.M. and Hall, L.W. (1985). Total intravenous anesthesia in the horse with propofol. *Equine Veterinary Journal.* **17**(5): 394-398.

Oku, K.; Yamanaka, T.; Ashihara, N.; Kawasaki, K.; Mizuno, Y. and Fujinaga, T. (2003). Clinical observations during induction and recovery of xylazine-midazolam-propofol anesthesia in horses. *Journal of Veterinary Medical Science.* **65**(7): 805-808.

Oslon W.A.; Benson, G.J.; Tranquilli, W.J,; Thurmon,J.C. and Ko, J.C.H. (1992).A comparison of medetomidine – propofol and medetomidine-Midazolam-propofol anaesthsia in rabbits. *Lab-Animal-Sc.* **42**(5): 503-507.

Ozaydin, I.; Atalan, G.; Uzun, M.; Kilic, E. and Cenesiz, M. (2001). Assessment of anaesthetic properties and clinical, cardiovascular and respiratoric effects of medetomidine, propofol and ketamine combination in dogs. *Kafkas-Universitesi-Veteriner-Fakultesi-Dergisi.* 7(1): 71-76.

Pypendrop, B.; Poncelet, L.. and Verstegen, J. (1999). Use of midlatency auditory-evoked poyentials as indicator of unconsciousness in the dog

and charecterisation of the effects of acepromazine-thiopentone, medetomidine-thiopentone and medetomidine-butrophenol-midazolam combinations. *Research in Vet. Science.* **67**(1): 35-39.

Quandt, J.E.; Rivers, W.J.; Robinson, E.P. and Raffe, M.R.(1998).Cardiorespiratory and anaesthetic effects of Propofol and Thiopental in dogs. *A.j.V.R.* **59**(9):1137-1143.

Raff, M. and Harrison, G.G.(1989). The screening of propofol in MHS Swine, Anaesthesia and Analgesia. *Ane. Res. Soc.* Vol. 68, 750-751.

Redondo, J.L.; Villamandos, G.R.J.; Santisteban, J.M.; Dominguez, J.M.; Ruiz, I. and Avila, I.(2000). Romifidine, medeomidine or Xylazine before Propofol-Halothane Nitrous oxide anaesthesia in dogs. *Can. J.Vet. Res.* **63**(1): 31-36.

Reimann, F.M.; Samson, U.; Derad, I.; Fuchs, M.; Schiefer, B. and Stange, E.F. (2000). Synergistic sedation with low – dose Midazolam and Propofol for colonoscopies Endoscopy. *Journal of Veterinary Medical Science.* 32(3) : 239-44.

Reitman and Frankle (1957). American J. Clin. Patho. 28,56. Cited by Murtuza, M.(1998). Practical Biochemistry, 1st Edition Alpha publication, Patna-14.

Reves, J.G.; Lell, W.A.; Mc Cracken, L. E.Jr.; Kravetz, R.A. and Prough, D.S. (1978). Comparison of morphine and ketamine anaesthetic techniques for coronary surgery: a randomized study. South Med. J. **71**:33-36.

Reves, J.G.; Fragen, R.J.; Vinik, H.R. and Greenblatt, D.J.(1985).Midazolam:Pharmacology and uses. *Anaesthesiology.* **62**:20-324

Rosenberg, H.; Fletcher, J.E. and Seitman, D.(1997). Pharmacogenetics. In, Clinical Anaesthesia, 3rd ed. (Barash, P.G., Cullen, B.F.,

Stoelting, R.K.,eds., transl ator). Lippincott-Raven, Philadelphia, PP.489-517.

Sano, T.; Nishimura, R.; Mochizuki, M.; Hara, Y.; Tagawa, M. and Sasaki, N. (2003). Clinical usefulness of propofol as an anesthetic induction agent in dogs and cats. *Journal of Veterinary Medical Science.* **65**(5): 641-643.

Sano, T.; Nishimura, R.; Mochizuki, M. and Sasaki, N. (2003). Effects of midazolam-butorphanol, acepromazine-butorphanol and medetomidine on an induction dose of propofol and their compatibility in dogs. *Journal of Veterinary Medical Science.* **5**(10): 1141-1143.

Schalm, O.W.; Jain, N.C. and Carrol J.E. (1975). Veterinary Hematology, 3rd ed. Lea and febiger, Philadelphia.

Snedecor, G.W. and Cochran, W.G. (1967). Statistical Methods, 6th Edn. Oxford and I.B.H. publishing Co.

Stegmann, G.F. and Bester, L. (2001). Some clinical effects of midazolam premedication in propofol-induced and isoflurane-maintained anaesthesia in dogs during ovariohysterectomy. *Journal of the South African Veterinary Association.* **72**(4): 214-216.

Stegmann, G.F.; Hofmeyr, M.; Olivier, A.; Lane, E. and Volkmann, D.H. (2001). Rectal prolapse associated with a healed pelvic fracture in a pregnant free-ranging African black rhinoceros *(Diceros bicornis). Journal of the South African Veterinary Association.* **72**(4): 239-241.

Tableman Harvey G. (1960). Claw amputation in the pig. *Modern Veterinary Practice.* **41**(19):62.

Tamura, E.Y.; Barros, P.S.; Cortopassi, S.R.G.; Ambrosio, A.M.; Fantoni, D.T. and Barros, P.S. (2002). Effects of two preanesthetic

regimens for ophthalmic surgery on intraocular pressure and cardiovascular measurements in dogs. *Veterinary Therapeutics.* **3**(1): 81-87.

Taylor, P.M.; White, K.L.; Fowden, A.L.; Giussani, D.A.; Bloomfield, M. and Sear, J.W. (2001). Propofol anaesthesia for surgery in late gestation pony mares. *Veterinary Anaesthesia and Analgesia.* **28**(4): 177-187.

Thibaut, J.; Rivera, T. and Ahumada, F. (2002). Intravenous anaesthesia in dogs using a single dose of propofol premedicated with atropine-acepromazine or atropine-xylazine. *Archivos-de-Medicina-Veterinaria.* **34**(1): 25-35.

Tranquilly, W.J.; Gross, M.E.; Thrumon, J.C. and Benson, G.J. (1990). Evaluation of three Midazolam- Xylazine mixtures. Preliminary Trials in dogs. *Veterinary surgery.* **19**(2): 168-172.

Valadao, C.A.A.; Almeida, P.E. and Oleskovicz, N.(2001). Study of the association nalbuphine with acepromazine or midazolam, in dogs. *Ars-Veterinaria.* **17**(2): 93-97.

Vareley, H. (1967). Practical clinical biochemistry, 4th Edition. William Heineman, Medical Book Ltd. London.

Vineet, B. and Bharat, S. (2003). Haemato-biochemical effects of midazolam and ketamine anaesthesia in dogs. *Indian Journal of Veterinary Surgery.* **24**(1): 44-45.

Venugopal, A.; Chandrasekhar, E.L. and Haragopal, V. (2002). Effects of propofol-ketamine anaesthesia with or without premedication in dogs. *Indian Journal of Veterinary Surgery.* **23**(2): 106-107.

Vulpe, V. and Nastasa, V.(2000). Radiological examination of small animals using anaesthetic techniques. *Lucrai,Stiinifice –Medicina*

Veterinara,-Universitatea-de-Stiinte-Agricole-si-Medicina-Veterinara-"Ion-Ionescu-de-la-Brad"-Iasi. **43**(2): 333-336.

Waterman, A.E. (1988). Use of propofol in sheep. *Veterinary-Record.* **122**(11): 260.

Watkins, S.B.; Hall, L.W. and Clarke, K.W. (1987). Propofol as an intravenous anaesthetic agent in dogs. *Veterinary Record.* **120**(14): 326-329.

Wright, J.G.(1963). Scrotal hernia and castration. *Veterinary Record.* **75**(50): 1352-1367.

Yamashita, K.; Nakashima, M.; Toda, H.; Sasaki, Y.; Tsuzuki, K.; Koike, M.; Izumisawa, Y.; Kotani, T. and Muir, W.W. (2001). Medetomidine with thiopental, ketamine, or propofol as premedication and induction for inhalation anesthesia in dogs. *Journal of the Japan Veterinary Medical Association.***54**(4):282-287.

Zamur, G. and Queiroz, Neto-A. (2002). Comparison of the sedative and antinociceptive effects of midazolam and diazepam in horses. *Ars-Veterinaria.* **18**: 3, 210-217.

Zellner, J.L.; Swindle, M.M.; Smith, A.C. and Spinale, F.G.(1991). Sedative and cardiovascular effects of Midazolam in swine. *Lab Animal Science.* **41**(2):157-161.

Zimmermann, M.; Sampelmann, R.; Botel, R.C,; Strauss, J.M. and Paul, T.(1994). Isoflurane anaesthesia induced porcine malignant hyperthermia. *Deutsche-Tierarztliche-Wocherschrift.* **101**(5):207-208.

Zoran, d.L,; Riedesel, D.H. and Dyer, D.C. (1993). Pharmacokinnetics of Propofol in mixed breed dogs and Greyhounds. *American Journal of Veterinary Research.* **54**(5):655-761.

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