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Review Article

Comparison of Intravenous and Inhalation Anesthesia for Performing Minor and Major Surgeries in Sheep and Goat: A Review

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CHEMICAL CHARACTERISTICS OF KETAMINE

Ketamine has two resolvable isomers or enantiomers that are S-(+)-ketamine and R-(+)-ketamine (Rossetti *et al*., 2008). It is a white crystalline powder having molecular weight of 238kd. It has more lipid solubility as compared to thiopental so it is rapidly distributed into the body tissues. Ketamine is prepared in slightly acidic solution and the racemic mixture comes in concentration of 10, 50 and 100 mg ketamine base per millilitre of sodium chloride solution. Ketamine is metabolized by hepatic microsomal enzymes. The major pathways involve N-de-methylation to form nor ketamine, which is then dehydroxylated to form hydroxyl norketamine. These products are conjugated to water soluble glucuronide derivatives and are excreted in urine (Rossetti *et al*. 2008).

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TISSUE DISTRIBUTION AND ELIMINATION

Ketamine is a potent sedative and analgesic agent in several animals. Its distribution and elimination study after administration into rat s/c, dogs IV ,calves IV revealed that ketamine due to its high lipophilic activity is rapidly distributed into body tissues including brain, lungs ,liver and fat. Plasma protein binding is about 52% in horses, 55%

in dogs and 38-54% in the calves. The high lipid solubility of ketamine is reflected in its large volume of distribution. Clearance is also relatively high which accounts for the relatively short elimination half life.

The clearance of drug depends upon the blood flow towards liver .Those drugs which affect hepatic blood flow also cause delay in clearance time of anesthetic drugs. Those drugs which reduce blood flow towards liver also cause delay in ketamine clearance (Hedenqvist *et al*., 2008). Low dose diazepam increases the volume of distribution and clearance of ketamine, thereby resulting in higher plasma concentration. Diazepam also increases the distribution of ketamine into the brain. The distribution and elimination of two isomers is also different as S-ketamine has larger elimination and larger volume of distribution than R-ketamine (White *et al*., 2001).

Xylazine with ketamine anesthesia: The use of anesthetic agents such as propofol and ketamine has gained increasing popularity in recent years (Rodrigo *et al*., 2012). Because of convulsion and poor muscle relaxation activity of ketamine, it can be used only after a suitable sedation (Grubb *et al*., 1997). The pre-anesthetic effect of xylazine has been evaluated only in very small number of animals. Seerinan *et al*. (2002) reported the use of xylazine as a pre-anesthetic before ketamine in 48 horses. Recumbancy ensured after IV administration of ketamine. The interval between injections was 15-20 min in all. Xylazine is a potent alpha-2 adrenergic agonist with sedative and analgesic properties. It has been found to produce prolonged analgesia and deeper stage of sedation. The study showed significantly prolonged induction time in xylazine premedicated animals. Xylazine premedication also seemed to lengthen the induction phase in horses casted with guaifenesin and thiopentone. Halothane has been found to increase the sensitivity of myocardium to adrenaline (Khan *et al*., 2005). The effect is further enhanced by alpha adrenergic agonist. The secretion of adrenaline may increase as a result of surgical stimulation during insufficient anesthesia or because of increased carbon dioxide tension (Marshal *et al*., 2001). The administration of xylazine has been found to initial decrease in carbon dioxide tension with a subsequent increase above the control level approximately 40 min post injection (short *et al*., 2005). A state of hypoxia was found to develop during the period of post anesthesia recumbancy. In an effort to minimize it (Clarke *et al*., 2003) used xylazine as a pre-anesthetic before ketamine anesthesia in horse.

Effects of Xylazine-Ketamine administration on arterial blood pressure: The effects of xylazine-ketamine administration on arterial blood pressure, arterial blood pH, blood gases, rectal temperature, and heart and respiratory rates were recorded in 5 healthy female goats weighing 17-29 kg. Xylazine (0.2 mg kg^{-1}, i.m.) was administered 15 min prior to ketamine (10 mg kg^{-1}, i.v.). All baseline measurements were taken before the xylazine administration and were repeated at 5, 15, 30, 45, and 60 min intervals after induction of anaesthesia with ketamine. nIt was found that heart rate decreased at 15 to 60 min and rectal temperature decreased significantly at 30 to 60 min but respiratory rate did not change significantly. Mean arterial blood pressure declined significantly at 15 to 60 min after anaesthesia. $PaCO_2$ did not change significantly but $PaCO_2$ values increased significantly at 5, 15 and 60 min. Values of pH decreased significantly at 5 and 15 min. According to this study, xylazine-ketamine combination is responsible for declined arterial blood pressure, bradycardia, increased $PaCO_2$, decreased pH and hypothermia in anaesthetized goats (Afshar *et al*., 2005).

Cardiopulmonary effects of xylazine: The cardiopulmonary effects of an intramuscular xylazine (0.088 mg kg^{-1})-ketamine (4.4 mg kg^{-1}) drug combination were evaluated in calves. Heart rate, central venous and mean pulmonary artery blood pressures, and cardiac output did not change after drug administration.

Mean arterial blood pressure decreased significantly ($P \leq 0.05$) 15 minutes after drug administration. Respiratory frequency increased significantly ($P \leq 0.05$) whereas arterial partial pressure of oxygen (PaO2) decreased significantly ($P \leq 0.05$) after drug administration. The duration of lateral recumbency was 55.7 +/- 10.4 minutes. Immediate or long-term adverse effects were not observed (Rings and Muir, 1982)

Effect of Ketamine–xylazine on cerebral blood flow: Ketamine–xylazineis a commonly used anesthetic for laboratory rats. Previous results showed that rats anesthetized with ketamine–xylazine can have a much lower cerebral partial pressure of oxygen (P_tO_2), compared to unanesthetized andisofluraneanesthetized rats. The underlying mechanisms for the P_tO_2 reduction need to be elucidated. In this study, regional Cerebral Blood Flow (CBF) using Nuclear Magnetic Resonance (NMR) perfusionimaging and cortical P_tO_2 using electron paramagnetic resonance (EPR) oximetry in the forebrain of rats under isoflurane, ketamine, ketamine-xylazine and isoflurane–xylazineanesthesia was measured. The results showed that in ventilated rats ketamine at a dose of 50 mg kg^{-1} does not induce significant changes in CBF, compared toisoflurane. Ketamine–xylazine in combination causes 25-65% reductions in forebrain CBF in a region-dependent manner. Adding xylazine to isoflurane anesthesia results in similar regional reductions in CBF. EPR oximetry measurements showketamineincreases cortical$P_tO_2$whilexylazinedecreases corticalP_tO_2. The xylazine induced reduction in CBF could explain the reduced brain oxygenation observed in ketamine–xylazine anesthetized rats (Lie *et al*., 2001).

Pharmacokinetics of ketamine and xylazine: To compare the pharmacokinetics of coadministered intraperitoneal ketamine and xylazine in young (8 to 10 wk; n= 6) and old rats (2 to 2.4 y; n = 6), blood samples obtained at 15 and 30 min and 1, 2, and 4 h after drug administration were analyzed by HPLC–tandem mass spectrometry. In both groups, the withdrawal reflex was absent during anesthesia and was present at 1.1 (± 0.2) and 2.6 (± 0.7) h after drug administration in young and old rats, respectively, with the first voluntary movement at 1.5 ± 0.2 and 4.9 ± 1.0 h. Drug availability of ketamine and xylazine was 6.0 and 6.7 times greater, respectively, in old than young rats. The rate constant of elimination of both drugs was greatly decreased and the elimination half-life was significantly greater in old compared with young rats. In conclusion, age and associated factors affect the availability of ketamine and xylazine when coadministered to attain clinical anesthesia, changing the pharmacokinetics of these drugs and prolonging anesthesia duration and recovery times with aging. Compared with their young counterparts, aged rats required much higher doses to attain a similar level of anesthesia. Finally, the long half-life of both ketamine and xylazine, when coadministered to old rats, may be a factor in research protocols because residual plasma concentrations could still be present for as long as 3 and 5 d, respectively, after administration (Veilleux-Lemieux, Castel *et al*., 2013).

Effect of xylazine- ketamine on renal functions: To evaluate the effect of an increased dose of ketamine on some renal function indices of ketamine–xylazine anaesthetized dogs. Five adult

female mongrel dogs assigned to two different treatment groups in a randomized cross over design were used for this study. Each of the dogs received either 10 mg kg^{-1} or 20 mg kg^{-1} ketamine at a week interval. The mean glomerular filtration rate (GFR) of creatinine, absolute and fractional excretion of sodium (UNaV, FE_{Na}), urine flow rate (UFR), and plasma sodium clearance were all found to be insignificantly increased in dogs that received the higher dose regime of ketamine. All the dogs in the two treatment groups exhibited levels of glycosuria and hyposthenuria. When plasma sodium concentration of dogs treated with 10 mg kg^{-1} was correlated with UNaV it was found to be significant and strong ($P < 0.05$; $r = 0.86$). It was however strong but insignificant with sodium clearance ($P > 0.05$; $r = 0.82$) and creatinine clearance ($P > 0.05$; $r = 0.39$). At 20 mg kg^{-1}, the UNaV, sodium clearance and glomerular filtration rate all correlated weakly and insignificantly with plasma sodium concentration. The enhanced diuresis and natriuresis observed in the two treatment groups could be attributed to the effect of xylazine on either the alpha-2 adrenoceptor of the brain or those on the tubules of the kidney. These effects of xylazine could not be reversed by attempting to competitively antagonize it with a 100% increase in ketamine dose (Ajibola *et al*., 2014).

Sedative and clinical effects of xylazine: To investigate the sedative and clinical effects of the pharmacopuncture with xylazine, compared to the conventional dose of a intramuscular injection in dogs. Twelve dogs were randomly distributed in two groups of six animals and treated as follows: control group (X-IM): 1mg $kg^{-1}$of xylazine given intramuscularly (IM); pharmacopuncture group (X-Yintang): 0.1 mg kg^{-1} of xylazine diluted to 0.5 mL of saline injected into the Yin Tang acupoint. Heart rate, cardiac rhythm (ECG), systolic arterial blood pressure (SABP), respiratory rate (RR), rectal temperature (RT), blood glucose concentration, degree of sedation and adverse effects were evaluated. Sedative effect was observed in both groups. The degree of sedation was greater in X-IM only at 15 min when compared with X-Yintang group. Cardiovascular established was observed in X-Yintang group, while marked reduction in the HR and increased incidence of ECG abnormalities were detected in X-IM. In both treatment groups, minimal changes were observed in relation to SABP, RR, RT and blood glucose. High incidence (66%) of vomiting was observed in X-IM, while this adverse effect was absent in X-Yintang. Pharmacopuncture with xylazine induced clinically relevant sedative effects in dogs, with the advantage of reduction of undesirable side effects associated with α2-agonists, including bradycardia, cardiac arrhythmias, and emesis (Cassu *et al*., 2014).

CARDIOPULMONARY EFFECTS OF SEVOFLURANE, ISOFLURANE AND HALOTHANE

The anesthetic potency and cardiopulmonary effects of sevoflurane were compared with those of isoflurane and halothane in goats. The (mean +/- SD) minimal alveolar concentration (MAC) was 0.96 +/- 0.12% for halothane, 1.29 +/- 0.11% for isoflurane, and 2.33 +/- 0.15% for sevoflurane. Cardiopulmonary effects of sevoflurane, halothane and isoflurane were examined at end-tidal concentrations equivalent to 1, 1.5 and 2 MAC during either spontaneous or controlled ventilation (SV or CV). During SV, there were no significant differences in respiration rate, tidal volume and minute ventilation between anesthetics. Dose-dependent decreases in both tidal volume and minute ventilation induced by halothane were greater than those by either sevoflurane or isoflurane. Hypercapnia and acidosis induced by sevoflurane were not significantly different from

those by either isoflurane or halothane at 1 and 1.5 MAC, but were less than those by halothane at 2 MAC. There was no significant difference in heart rate between anesthetics during SV and CV. During SV, all anesthetics induced dose-dependent decreases in arterial pressure, rate pressure product, systemic vascular resistance, left ventricular minute work index and left ventricular stroke work index. Systemic vascular resistance with isoflurane at 2 MAC was lower than that with sevoflurane. During CV, sevoflurane induced dose-dependent circulatory depression (decreases in arterial pressure, cardiac index, rate pressure product, systemic vascular resistance, left ventricular minute work index and right ventricular minute work index), similar to isoflurane. Halothane did not significantly alter systemic vascular resistance from 1 to 2 MAC (Hikasa *et al*., 1998).

ISOFLURANE INHALATION ANAESTHESIA

Chemical characters: (CHF2-O-CHCl-CF3) Isoflurane, an isomer of enflurane, is metabolized even more slowly than halothane or enflurane. Isoflurane is a colourless, stable liquid and non-flammable. It has pungent smell. Specific gravity of isoflurane is 1.496 and vapour pressure is 238 mm Hg (Hikasa *et al*., 2000).

Tissue distribution and elimination: Along with volatile anaesthetics usually used in veterinary anaesthesiology are the isoflurane, sevoflurane and desflurane (Sakai *et al*., 2005). For delivery, the volatile liquids are vaporized and mixed with a carrier gas. The vapours are wrapped up through lungs alveoli into blood and circulated to the central nervous system and other organs. Isoflurane has sooner induction and quick recovery activity due to less solubility in blood. Therefore, the induction of anaesthesia is frequently quick as well as the level of anaesthesia is easily controlled. The removal of inhalation agents is principally by exhalation of unaffected compounds. The isoflurane is metabolized to 0.2% during the preservation of anaesthesia; balance is reached through the same regular partial pressure in the alveoli as the brain. The quick special effects are additional accentuated in small animal, in which equilibrium is reached greatly faster than in large animal (Brunson *et al*., 1997).

Effects of isoflurane on cardiovascular system: The significant effects of isoflurane and sevoflurane anaesthesia on CVS, haematology and serum biochemistry were experimental in sheep undergoing minor surgical procedures. After induction, preservation was performed on gas pour rate of 1.5L /min in isoflurane. As a consequence as compared to isoflurane, sevoflurane showed additional recovery time than isoflurane anaesthesia. Cardiovascular and serobiochemical parameters showed no change in both anaesthetics drugs treatment.

For the period of apnoeic period, animal showed considerable reduction in heart rate through isoflurane anaesthesia. Improvement time with sevoflurane is additional quick than isoflurane. Respiratory and cardiovascular functions are similar in isoflurane and sevoflurane anaesthesia (Hikasaa *et al*., 2002). Similarly heart rate, mean arterial pressure, haemoglobin oxygen infiltration as well as respiratory rate, in rabbits undergoing surgery are exaggerated by propofol to its combination with ketamine (Cruze *et al*., 2010).

After both normotensive and hypertensive haemorrhage in sheep, Isoflurane stop transcapillary refill (Hahn, Brauer *et al*., 2006) and sevoflurane is a better anaesthetic when combine with N_2O alongside through epidural block for cirrhotic patients than isoflurane (Nishiyama, Fujimoto *et al*., 2004). Thus isoflurane was not used a behavioural

measure of tinnitus as it mainly inhibits provisional noise-induced tinnitus (Norman *et al*., 2012).

Effects of isoflurane anaesthesia on renal and hepatic function: In the septic conditions as well as results of inflammatory process, anaesthetics drugs influence function of different organs in reply to these pathological changes. Various anaesthetics drugs called as less hepatoprotective such as isoflurane for the reason that it shows further response towards these pathological changes and cause liver injuries (Suliburk *et al*., 2005). Administration of isoflurane had no effect on hepatic enzyme activities whereas; there was small boost in AST value by ketamine- xylazine administration (Thompson *et al*., 2002). Administration of isoflurane causes increase in serum triglyceride, phosphorus and chloride concentrations by decreased serum calcium and potassium levels (Gil *et al*., 2010). Post operative renal as well as hepatic function was affected by isoflurane and sevoflurane in term of serum creatinine, BUN, urinary protein and glucose excretion, ALT and AST between anaesthetic groups remains constant 24-72 h (Kharasch *et al*., 2001). Also, isoflurane cause more increase in serum concentration of liver enzymes subsequent surgery than sevoflurane (Nishiyama *et al*., 2004). Both Isoflurane and Sevoflurane concentrations cause transient to reasonable special effects on a few hepatobiliary enzyme concentrations (Yuan *et al*., 2012).

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