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Clinico-physiological effect of ketamine, propofol and Ketofol as constant rate infusion anaesthesia during elective ovariectomy in dogs

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Abstract
The present study was carried out on 18 clinical cases of female dogs irrespective of age and weight presented for ovariectomy operation to evaluate clinic-physiological effect of ketamine, propofol and ketofol as CRI anesthesia. The animals were randomly divided into three experimental groups (n=6), were designated as Group I, II and III on the basis of the induction and maintenance agent for elective ovariectomy. All animals were pre-medicated with glycopyrrolate @ 0.01mg/kg b.wt intramuscularly followed by inj. butorphanol 0.2 mg/kg b.wt and xylazine 1mg/kg b.wt intramuscularly after 5 minutes by using different syringes. After 10 minutes of xylazine, animals were induced (till effect) with propofol and immediately just after induction animals were maintained with constant rate infusion of ketamine, propofol and ketofol 1:1 along with normal saline @ 10 ml/kg/hr. During the present study various physiological and clinical evaluations were carried out to evaluate the CRI ketamine, propofol and ketofol in anaesthetic regimen. On clinical parameters, the mean values of recovery time in groups I, II and III were 47.17±0.94 min, 25.00±1.33 min and 46.83±0.60 min respectively. The mean values of sternal recumbency time in groups I, II and III were 61.17±1.81min, 36.17±1.33min and 58.67±1.05min respectively. The mean values of duration of surgery in groups I, II and III were 58.67±1.56 min, 59.00±0.84 min and 57.00±1.60 min respectively. The mean values of duration of anaesthesia in groups I, II and III were 75.5±2.04min, 73.83±2.53 min and 77.17±1.64 min respectively. Physiological parameters showed that the values of rectal temperature in all three groups showed a decrease at different intervals during the observation period in comparison of the baseline values. The values of respiratory rate in all three groups decreased at different intervals during an observation period in comparison to the baseline values. All three groups showed that respiratory rate value decreased significantly (p<.05) after pre-medication and remained significantly lower throughout the observation period. Value of heart rate significantly (P<0.05) increased after pre-medication in all three groups in comparisons to respective base values after that decreased but remained non-significantly (P>0.05) higher in group I and III, however it become non-significantly lower in group II during maintenance of anaesthesia in comparison to respective base values.

Keywords: ovariectomy, dog, ketamine, Propofol, Ketofol, CRI anaesthesia

Introduction
Anaesthesia and analgesia are interlinked and autonomic parameters like change in respiratory and cardiovascular responses are indicators of the depth of anaesthesia or antinociception (Gruenewald and Ilies, 2013) [8]. The purpose of anaesthesia is to produce a convenient, safe, effective analgesia, sedation and reversible unconsciousness of the animals, so that surgical intervention may be conducted with minimum stress, discomfort, pain and toxic side effects to the patients (Thurmon *et al.,* 1996 and William *et al.,* 2007) [33, 35]. Ideal balanced anesthesia helps in rapid and smooth induction, adequate hypnosis and analgesia for surgical interventions. Pre-anesthetic medications are used to minimize stress, cardiopulmonary depression and the deleterious effect associated with parental and inhalation anesthetics (Habib *et al.,* 2002) [10]. Generally, in animals during minor or major surgery a combination of an anticholinergic, sedative and the tranquilizing agent is used as pre-anesthetic agents. For these purposes, pre-anaesthetic generally used is atropine, diazepam, butorphanol and acepromazine (Mahmud *et al.,* 2014) [21]. These drugs help in overcoming the stress of the animals during examination, maintaining the depth of anesthesia, perioperative analgesia, reducing the amount of any single anesthetic agents, increasing margins of safety and smooth recovery. An anticholinergic agent is most commonly used as a pre-anesthetic agent in combination with xylazine, acepromazine and diazepam to minimize or prevent vagal effects.

The anticholinergic agent also reduces potential muscles spasm, gastrointestinal motility and respiratory secretions as well as decrease tear production during anesthesia (Kovaļčuka and Birģele, 2011) [18]. The administration of pre-anaesthetic agents in combination with general anesthetics is provided better hemodynamic stability because of a lower dose of general anesthetics for induction and maintenance of anaesthesia (Ilkiw *et al.,* 1994) [12]. Butorphanol is a synthetic opioid with agonist-antagonist properties. It is a potent opioid analgesic for managing acute nociceptive pain like injury, peri-operative and post-operative pain, visceral and chronic pain (Ahsam *et al.,* 2020) [2]. In veterinary anesthesiology, xylazine was used in the last sixties in domestic and pet animals. It is an alpha-2 adrenoceptors agonist drug that is widely used to provide dosed ependent sedation, analgesia and muscle relaxation. It is usually used in combination with ketamine during anesthetic applications (Ozkan *et al.,* 2010) [26]. Administration of ketamine alone increases heart rate and means arterial pressure. It can cause undesired effects such as muscular hypertonicity, myoclonus and convulsions. To minimize these unwanted effects, ketamine is generally administered in combination with other drugs like benzodiazepines and alpha-2 agonists (Ozkan *et al.,* 2010 and Dzikiti *et al.,* 2007) [26, 7]. At present time depending on the species, age, breed and physical condition of animals, the drug is commonly used in combination with benzodiazepines tranquilizers and alpha-2-adrenergic agents (Mahmud *et al.,* 2014) [21]. Propofol is a water-insoluble hypnotic alkyl phenol. It is formulated in a lipid emulsion containing extracts of soya and egg protein (Kastner *et al*., 2015) [15]. It is considered to be a suitable drug for the induction and maintenance of anaesthesia by constant rate infusion (CRI) (Musk *et al.,* 2005) [23]. The advantages of propofol include rapid onset of action with smooth induction and recovery. The objective of CRI is to achieve a constant plasma concentration of drugs in the body. This state can be achieved by the administration of a constant rate of ketamine or propofol. CRI prevents the sudden peaks and valleys associated with intermittent I/V boluses and I/M injection and also maintains a stable plane of anaesthesia superiorly to boluses (Pablo, 2011) [27]. Constant rate infusion of propofol minimizes delays in recovery and causes less cardiopulmonary depression than the repeat bolus infusion (Njoku, 2015) [25]. Ketamine and propofol have an additive effect when administered together (Hui *et al.*,1995). The combination of ketamine with propofol nullifies deleterious effects on one another and maintains haemodynamic ability (Kennedy and Smith, 2015) [16]. Single syringe administration of ketamine and propofol as ketofol admixtures was effective and safe for painful procedures in procedural sedation and analgesia (Willman and Andolfatto, 2007) [36]. Combination of glycopyrrolate, butorphanol, xylazine as premedication and induction with propofol and maintenance with ketamine, propofol and propofol mixtures (Ketofol 1:1) as CRI would have the ability to maintain better hemodynamic and also reduce the dose of general anaesthesia for maintenance. There are very few reports regarding ketamine, propofol and ketofol using CRI in dogs along with that appropriate premedication (Intelisano *et al*., 2008) [13]. This technique once gets standardized; it may transfer to field veterinarians for elective ovariectomy under a routine Animal Birth Control (ABC) programme for safe handling of canines. Therefore, the present study was designed to evaluate the clinico-physiological effect of Ketamine, Propofol and Ketofol as CRI anaesthesia undergoing ovariectomy in dogs.

Materials and Methods

The present clinical study was carried out on 18 clinical cases of female dogs irrespective of age and weight presented for ovariectomy operation. The animals were randomly divided into three experimental groups (n=6), were designated as Group I, II and III on the basis of the induction and maintenance agent for elective ovariectomy. All experimental animals were examined with Ultrasonography for any reproductive abnormality. The bitches presented for elective ovariectomy were selected for this study after obtaining written consent from the respective owners. The animals were subjected to preoperative checkups comprising Clinical and physiological parameters. The animals were kept off-fed for a minimum of 12 hours prior to the trial of anaesthesia. After preparation of the animal, blood was withdrawn at 0 min from the cephalic vein and glycopyrrolate (Pyrolate, Neon Laboratories, Palghar, Thane) was given @ 0.01mg/kg b.wt intramuscularly at right lumbar epaxial muscles followed by inj. Butorphanol (Butodol; Neon laboratories, Palghar, Thane, India.) @ 0.2 mg/kg b.wt and xylazine (Indian Immunological Limited, Telangana, India) @ 1mg/kg b.wt were injected intramuscularly after 5 minutes at left lumbar epaxial muscles by using different syringes. After premedication animal was placed on the operation table and canulate with 20 gauges (according to need) intravenous catheter and attached with normal saline infusion. After 10 minutes of butorphanol, animals were induced (till effect) with propofol and immediately just after induction animals were intubated and constant rate infusion of ketamine (Ketmin 50; Themis Medicare Limited, Uttarakhand, India), propofol (Nirfol 1%; Aculife healthcare private limited, Ahmedabad, Gujarat, India) and ketofol 1:1 started along with normal saline @ 10ml/kg/hr by microinfusion set and infusion of anaesthesia was stopped at last skin suture. The animals were kept in a normal environment throughout the study period.

The clinical parameters such as different reflexes, induction time, duration of anesthesia, duration of recovery and quality of recovery along with sternal recumbency time were recorded during this study. Abolition of the palpebral, pedal and corneal reflex was recorded at different intervals in the animals of different groups. In all animals, the plane of analgesia was assessed by observing the response to various painful stimuli. Presence or absences of reflexes were recorded before premedication, 10 minutes after pre-medication, 15, 30 and 60 minutes during maintenance of anaesthesia and after recovery (120 minutes). Palpebral reflexes were tested by observing blinking responses when an eyelid is touched gently with fingers or forceps. The response to palpebral reflex was taken as the measure of the depth of sedation and recorded at 0 minutes before administration of the drug and after 10-minute of premedication and 15, 30 and 60 minutes during maintenance and after recovery (120 minutes). The reflexes was graded on a 1 to 4 scoring scales as: 1 :Intact and strong reflex (quick blink), 2 :Intact but weak reflex (slow response), 3 :Very weak reflex (very slow and occasional, 4 :Abolished reflex. Absence of pedal reflex was recorded by pinching the interdigital webbing of the front and hind limbs approximately for one second with mosquito hemostat forceps. The response to pedal reflex was taken as a measure of the depth of analgesia and it was recorded before premedication, 10 minutes after pre-medication, 15, 30 and 60 minutes during maintenance and after recovery (120 minutes). The reflexes was graded on a 1 to 4 scoring scales as: 1: Intact and strong reflex (strong withdrawal), 2: Intact but weak

reflex (animal responding slowly), 3: Intact but very light reflex (slow and occasional response), 4 :Reflex abolished completely. Corneal reflex was assessed by blinking induced by gently touching the cornea with wet cotton or a drop of normal saline over the cornea and graded as 1 to 4 scales. 1 :Intact and strong reflex, 2 : Intact but weak reflex, 3 :Very weak reflex, 4 :Abolished reflex. The duration of surgical anaesthesia was calculated as the time interval between the time of disappearance of pedal reflex and the time of the return of pedal reflex (Narayanan *et al.*, 2011) [24]. Recovery time was calculated as the time interval between the stoppage of infusion of anaesthetic agent and the return of pedal (Narayanan *et al.*, 2011) [24]. The time from the end of the administration of constant rate infusion to the spontaneous and the regaining of sternal recumbency (minutes). The physiological parameters such as rectal temperature (°F), heart rate (beats per minute) and respiratory rate (breaths per minute) were recorded just before premedication, 10 minutes after pre-medication, 15, 30 and 60minutes during maintenance of anaesthesia and after recovery (120 minutes).

Statistical Analysis

All the collected data were statistically analyzed using SPSS software version 23. Mean ± SE was determined by the descriptive statistics method. Single Factor Analysis of variance (ANOVA), Duncan's multiple range test (DMRT) was used to compare the mean at different time intervals amongst the different groups and compare the mean values at different intervals with their respective base values in each group (Snedecor and Cochran 1994) [31].

Results

In the animals of all three groups, an increase in palpebral reflex was recorded after pre-medication and reaches a maximum depth of sedation after induction. Maximum sedation is maintained during the maintenance of anaesthesia. Comparison among the groups revealed that there was no significant ($p>0.05$) difference between the different groups in the palpebral reflex score at various time intervals. In the animals of all three groups, an increase in pedal reflex was recorded after pre- medication and reach at a maximum depth of analgesia after induction. Maximum analgesia is maintained during the maintenance of anaesthesia. Comparison among the groups revealed that there was no significant ($p>0.05$) difference between the different groups in the pedal reflex score at various time intervals. In the animals of all three groups, an increased corneal reflex was recorded after pre- medication and reaches a maximum after induction. Maximum score maintained during the maintenance of anaesthesia. Comparison among the groups revealed that there was no significant ($p>0.05$) difference between the different groups in the corneal reflex score at various time interval. The mean values of duration of anaesthesia in groups I, II and III were 75.5±2.04min, 73.83±2.53 min and 77.17±1.64 min respectively. Comparison among the groups showed that duration of anaesthesia among group changed non-significantly ($p>0.05$). The mean values of duration of surgery in groups I, II and III were 58.67±1.56 min, 59.00±0.84 min and 57.00±1.60 min respectively. Comparison among the groups showed that the duration of surgery changed non-significantly ($P>0.05$).Mean ± SE. The mean values of Recovery time in groups I, II and III were 47.17±0.94 min, 25.00±1.33 min and 46.83±0.60 min respectively. Comparison among the groups showed that recovery time in group II significantly ($p<0.05$) lower in comparison to groups I and III. Comparison among groups also showed that recovery time in group III non-significantly lower in comparison to groups I. The mean values of sternal recumbency time in groups I, II and III were 61.17±1.81min, 36.17±1.33min and 58.67±1.05min respectively. Comparison among the groups showed that sternal recumbency time in group II significantly ($p<0.05$) lower in comparison to groups I and III. Comparison among groups also showed that sternal recumbency time in group III was non-significantly lower in comparison to group. Value of heart rate significantly ($P<0.05$) increased after pre-medication in all three groups in comparisons to respective base values after that decreased but remained non- significantly ($P>0.05$) higher in group I and III, however it become non-significantly lower in group II during maintenance of anaesthesia in comparison to respective base values. Comparison between the groups showed that heart rate non-significantly ($p<0.05$) change at various intervals of time during the observation period. The values of respiratory rate in all three groups decreased at different intervals during the observation period in comparison to the baseline values. All three groups showed that respiratory rate value decreased significantly ($p<.05$) after pre-medication and remained significantly lower throughout the observation period. Comparison within groups also showed that respiratory rate in group I was significantly lower at 15 minutes, whereas non- significantly lower at 30 and 60 minutes during maintenance of anaesthesia in comparison to after pre-medication. However, in groups, II and III respiratory rates were non-significantly lower during maintenance of anaesthesia in comparison to after pre-medication. Comparison between the groups showed that respiratory rate non-significantly ($p>0.05$) change at various intervals of time during the observation period. The values of rectal temperature in all three groups showed a decrease at different intervals during the observation period in comparison to the baseline values. Groups I showed that rectal temperature gradually decreases after pre-medication and becomes significantly ($p<.05$) lower at 15minute during maintenance of anaesthesia and remained significantly lower up to recovery. However, group II showed rectal temperature gradually decreased after pre-medication and become significantly ($p<0.05$) lower at 30 minutes during maintenance of anaesthesia, after that remained significantly lower up to recovery in comparison to the respective base values. Similar to group I, group III also showed that rectal temperature becomes significantly lower at 15 minutes during the observation period and then remained significantly lower up to recovery. Comparison between the groups showed that rectal temperature non-significantly ($p>0.05$) change at various intervals of time except at 15 minutes during the observation period.

Discussion

In the canine, intramuscular injection is the preferred route for administration of pre- anesthetic agents to attain sedation, as minimal restraint required for IM injection. Besides, cardiovascular responses are attenuated when anticholinergic and α-2-agonists are administered in combination and the adverse actions of any single drug of pre-anesthetic or anaesthetics agents may be diminished due to the lower doses required (Lin *et al.*, 1994) [20]. Intravenous anesthetic drugs are usually first administered as a large bolus to fill the volume of distribution of the central compartment, which is

then followed by continuous lower dosages to maintain effective drug plasma concentrations for the duration of anesthetic procedure (Beths, 2008) [5]. Electrophysiological studies have indicated that pre-and postsynaptic inhibitory mechanisms are responsible for the antinociceptive action of alpha2 -adrenoceptor agonists (Yaksh *et al.*, 1985). Alpha2 and opiate receptors are found in similar regions of the brain and even on some of the same neurons. The binding of either alpha2-agonists or μ-opioid agonists to those receptors results in activation of the same signal transduction systems (membrane-associated G proteins), which induces a chain of events that open potassium channels in the neuronal membrane. Activation of potassium channels in the postsynaptic neuron leads to hyperpolarization of the cell, which ultimately makes the cell unresponsive to excitatory input and effectively severs the pain pathway. Consequently, the alpha 2-agonists and μ- opioid agonists produce analgesia by similar mechanisms. The alpha2-adrenergic agonists are widely used in injectable sedative analgesic combinations because of their potent sedative, muscle relaxant, analgesic and anxiolytic effects. They induce dose-dependent sedation and analgesia in dogs. Synergistic sedative and analgesic activity between alpha 2-agonists and opioid agonist-antagonist has been reported in dogs (Amarpal *et al.*, 1998) [4]. Anaesthesia with propofol has been successfully induced after pre-medication with alpha2- agonists and butorphanol in dogs (Thurmon *et al.*, 1996 and Kim and Jang, 1999) [33, 17]. Palpebral reflex is stimulated by tapping the skin at the medial canthus of the eye or by running the finger along the eyelashes. The reflex disappears in light to the medium plane of surgical anaesthesia in small animals (Tranquilli *et al.*, 2007) [34]. Slow response in palpebral reflex was observed after the administration of glycopyrrolate and butorphanol at 15 min of observation (Gupta, 2010) [9]. In our study during CRI maintenance of anaesthesia in a group, I throughout the observation period from induction to termination of anaesthesia very slow and occasional palpebral reflex observed due to the effect of ketamine (Wright, 1982) [37]. A similar finding was also reported by Ibrahim, (2017) [11] in CRI ketamine. In ketofol 1:1 showing absence of palpebral reflex till CRI termination, further, it was similar to ketamine CRI. As per Tranquilli *et al.* (2007) [34] the corneal reflex varies in different species. The corneal reflex became moderate after the administration of glycopyrrolate and butorphanol in all three groups. The reflex was abolished completely in all the animals after the induction of anaesthesia with propofol. Recovery time was recorded as the time when the pedal reflex reappeared. In the animals of group, I (ketamine), group II (propofol) and group III (ketofol 1:1) the mean recovery time was 47.17±0.94 min, 25.00±1.33 min and 46.83±0.60 min respectively. There is a virtual lack of any cumulative effect of propofol caused rapid recovery after its administration for induction and CRI maintenance (Adetunji *et al.*, 2002) [1]. In the present study, propofol provided rapid induction of anaesthesia, as well as smooth rapid recovery after its administration. Furthermore, the rapid redistribution and metabolism of the drug also explain the rapid, smooth recovery from propofol anaesthesia. Rapid and smooth recovery recorded in the present study was following that reported in the earlier studies in dogs (Ajadi *et al.*, 2007) [3]. On the flip side ketofol 1:1, shows that similar recovery time like ketamine may be attributed to the high dose of ketamine cumulative effect with propofol. The increase of sternal recumbency time in ketamine maybe because of ketamine and its metabolites (Kaka and Hayton, 1980) [14]. Hypothermia has been observed following the use of xylazine in dogs (Surbhi, 2008) [32] also reported a decreased RT after dexmedetomidine administration or its combination with midazolam in dogs. The mean rectal temperature dropped significantly in all the groups following propofol infusion which might be due to a decrease in metabolic rate, inhibition of muscle tone, depression of peripheral circulation, vasodilatation and depression of the thermoregulatory mechanism (Muir and Gadawski, 2002) [22]. One or a combination of these mechanisms might have caused hypothermia by alpha-2 agonists, propofol and ketamine in the present study. The values of respiratory rate in all three groups decreased at different intervals during the observation period in comparison to the baseline values. The findings of this study were in accordance to Silva *et al.* (2010) [29] who observed the significant drop-in respiratory rate ($p<0.05$) after administration of alpha-2 agonist as a pre- anaesthetic to the propofol anaesthesia in dogs. Respiratory depression associated with alpha-2 adrenergic agonists might be secondary to the central nervous system depression produced by alpha-2 adrenoceptors simulation (Sinclair, 2003) [30] or due to direct depression of the respiratory centre in the brain (Kumar and Thurman, 1979). Butorphanol, like other opioids, is known to depress respiration in a dose-related manner by acting on μ receptors. It causes mild lowering of respiratory rate and respiratory depression was observed in dogs (Carpenter *et al.*, 2005) [6]. There is a non-significant difference among the groups. The appropriate premedication and better CRI dose may be the possible reason. Although non-significant, ketofol and ketamine group having a higher respiratory rate than propofol group animals, because ketamine may preserve respiratory tone alone as well as a combination with propofol while administering in CRI. The heart rate increased after pre-medication in all three groups. An initial rise in heart rate may be attributed to the vagolytic action of an anticholinergic agent. In accordance with the present study. Raffe (2015) [28] observed that heart rate increase after pre- medication with atropine, butorphanol and alpha-2 agonist combination and reached the highest level at 15-minute intervals. A non-significant decline in heart rate was observed in group II induction. The non-significant decrease in heart rate after induction in group 2 could be attributed to the typical hemodynamic response of alpha-2 agonists mediated by the baroreflex and due to a decrease in sympathetic activity. Silva *et al.* (2010) [29] reported similar findings and summarized that the intensity of cardiovascular manifestation after administration of dexmedetomidine depends on the dose, route of administration and combination of drugs. However, heart rate remained within the normal physiological limit in all three groups. It might be a combined effect of anticholinergic, alpha-2 agonist, propofol, ketamine and ketofol.

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