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EFFECTS OF COMBINATION OFDETOMIDINE, AND BUTORPHANOL WITH KETAMINE ON THE BODY REFLEX AND PHYSIOLOGICAL PARAMETERS IN GERMAN SHEPHERD DOGS

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ABSTRACT:

The purposes of present studywasto selective the best anesthesia, and evaluated the anesthesia agent to induce anesthesia in dogs, through a combination of detomidine, butorphanol and ketamine. German Shepherd dogs were carried in present study 10 adult male clinically health. Two drug combinations were applied as Detomidine HCL with Ketamine (DK) at the dose of 0.04 mg/ kg , and 10mg/ kg B .W, respectively, and Butorphanol tartrate with Ketamine (BK) at the dose 0.1 mg/ kg , and10mg/ kg B .W, respectively. All drugs were injected intravenously.

The effects of the drug were studied on body reflex and physiological parameters such as Righting reflex, corneal reflex, palpebral reflex and pedal reflex. Also the evaluation nature of induction, analgesia, and recovery as well as oxygen level (OL), Temperature(T), Respiratory rate (RR) and Heart rate (HR) at period zero (base line),5,10,15,20,25,30 and 60 minute after injection of anesthesia agent by using Capnography system. The HR increase in (BK) compare with (DK) it was gradually increased at time 5, 10, 15 and 20 minutes. The results revealed that significant differences in HR increase in (BK) compare with (DK). But the OL and RR between (BK) and (DK), was gradually decrease in two groups at all time compare with base line, same result in temperature.

The evaluation of onset of induction, after injection the drug (BK) the dogs are characterized with slight excitation but in group Bwere smoothly. In analgesia in (BK) was a starting in 2.010 ± 0.09274 minutes after injection and continues 38.40 ± 1.393 minutes but in (DK) analgesia starting from 1.500± 0.05099 minute and continues for 63.80± 1.393 minutes during the induce wound. The nature of recovery was at a nature smoothlyin (BK). While in (DK) smoothly and difficult to standing position.

It is concluded that (DK) anesthesia in dog is a safe and reliable anesthesia protocol for surgery.

Key word: Butorphanol tartrate, Detomidine Hydrochloride, Ketamine Hydrochloride, body reflex, Physiological parameters, Dogs.

I. INTRODUCTION

The goal in the administration of general anesthesia is to provide a stage of reversible unconsciousness with adequate analgesia and muscle relaxation for surgical procedures in such a way that it does not jeopardize the patient's health. Providing safe anesthesia requires knowledge, technical skill and anastute awareness of the patient's status at all times. (Miller and Pardo, 2011). There is no available anesthetic drug which can provide proper anesthesia alone nowadays. Therefore, combinations of sedatives and other anesthetics have been widely used in animal practice. The anesthetic combination should combine various characteristics, such as adequate sedation and a deep unconscious state, without significantly altering the patient's physiologic parameters. (Alma et al., 2002). General anesthesia is needed for certain surgical procedures which are otherwise cannot be performed under regional and local anesthesia (Flecknell2015).

Ketamine as an injectable dissociative anesthetic is commonly used in combination with α2-agonists for achieving balanced anaesthesia in small animal (El-Sherif2018). Ketamine has negative ionotropic effect on heart, and cardiovascular stimulation after intravenous administration, minimal effect on the respiratory system (Adams et al., 2015) and direct depressive action at thermoregulatory center (Rafee et al., 2015). Alpha-2

agonists; like Detomidine are commonly used in veterinary practice (Hall 2014). Combinations of opioids with α2-agonists show synergism (Boehm et al., 2010; Ahmad et al., 2013). Butorphanol tartrate is a synthetic opioid, possessing an agonist and antagonist activity at the μ-opioid receptor, as well as partial agonist activity at the κ-opioid receptor properties (Gharagozlou et al., 2006).. Panting and respiratory depression has been reported with Butorphanol (Peeters et al., 2012). It can cause a decrease in heart rate, arterial blood pressure and intestinal motility (Schnellbacher 2010). The aims of presntstudy to compare between two regime of general anesthesiaandselective the best regime.

II. MATERIALS AND METHODS

Present study was carried out on ten adult male, clinically healthy German -Shepherd dogs, aging 7 years, weighing (29- 33 kg). They were divided randomly and equally into two groups two drug combinations were set as Group A (Five dogs received Butorphanol tartrate at dose (0.1 mg/kg) and Ketamine Hydrochloride at dose (10 mg / kg) intravenously (BK) and Group B(Five dogs receivedDetomidineHydrochloride at dose (0.04mg/kg) and Ketamine Hydrochloride at dose (10 mg / kg) intravenously (DK group) .

The animals were maintained in individual cages under normal environment including climate and management. Twelve hours before each experiment, the animals withheld from food and water. Under aseptic conditions, two 18- gauge, 1.3 x 45 mm, 95ml/ min, intravenous cannula was set in the cephalic vein for administration of anesthetic drugs.

The anesthetic drugs used included DetomidineHCL (D)(Dormosedan® the vial contains 20ml (10mg/1ml), Pfizer- Zoetis- pharma, American multinational Pharmaceutical Corporation), Butorphanol Tartrate (B) (Torbugesic® the vial contains 50ml (10mg/1ml), Pfizer- Zoetis- pharma, American multinational Pharmaceutical Corporation) and Ketamine HCL (K): Ketamine Fresenius® Vial contains 10 ml (50 mg/1ml). Fresenius kabiPharmaceuticals Corporation).

Evaluation of Physiological Parameters: Oxygen level, respiratory rate and heart rate by oximeter on tongue, Temperature by rectal thermostat,After intravenous injection of anesthetic agents by using Capnography system were recorded before, during induction anesthesia and recovery period at base line and 5, 10, 15, 20, 25, 30 and 60 minute (Albozachri et al., 2012). (Fig.1-A) (Fig.1-B) (Fig.1-C) (Fig.1-D) (Fig.1-E) (Fig.1-F).

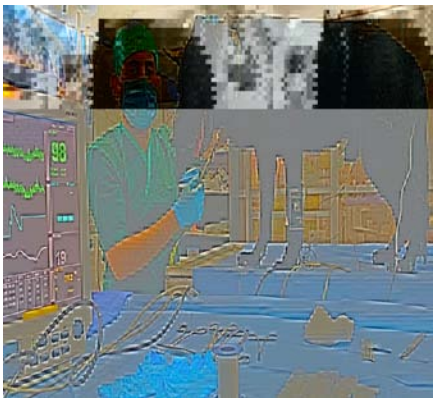
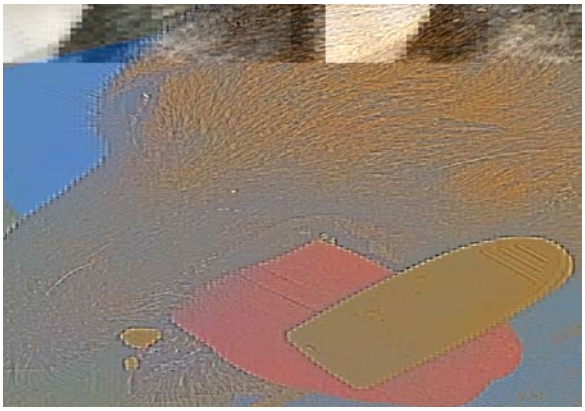


Figure 1-A: Capnography system Figure 1-B:Evaluate Physiologicalsigns in base line

Figure 1-C : Evaluate after anesthesiaFigure 1-D Evaluate rectal Temperature



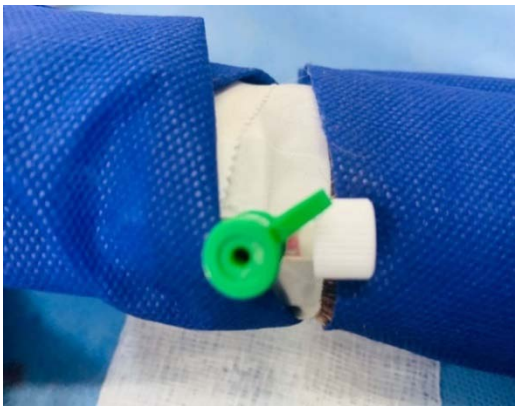


Figure 1-E Oxygen sensorFigure 1-FCannula for anesthetic injection

Nature and Time of Induction

The animals were carefully observed from the moment of anesthesia administration until the reflexes were disappeared to evaluate the induction type if it was smooth, shivering or struggling movements.

Anesthetic Time (Surgical Time)

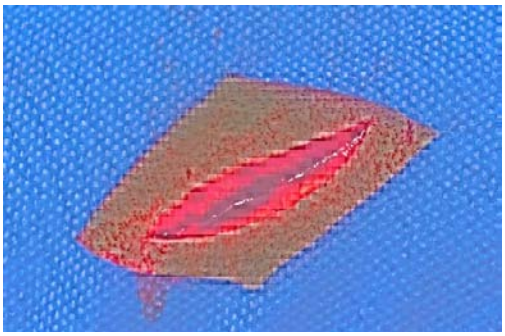
The total anesthetic period between disappearance and reappearance of reflexes were recorded.

The Nature and Time of Recovery

The recovery was observed from the time of reappearance of the reflex until complete consciousness if it was smooth, staggering and nature of standing.

Evaluation of Analgesia

Induce incisionabout 4 cm (fig.2-A) and then suturing (fig.2-B) which used to evaluate the analgesic action of anesthetic combination at times 5, 10, 15, 20, 25, 30and 60 minutes after injection (Albozachriet al 2012). Onset of analgesia, its intensity and duration were recorded.



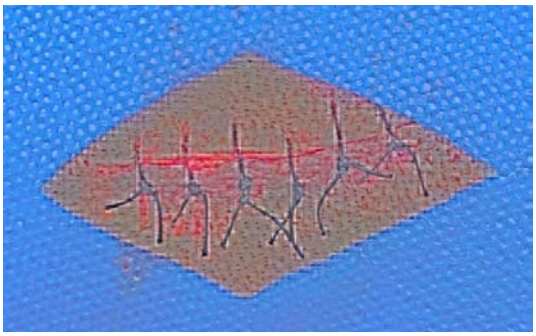


Figure (2-A) Incision about 3-4 cmFigure (2-B) suturing the wound

Evaluation of Body Reflex

In the current study, the various body reflex activities were assessed during anesthesia in order to determine the depth of anesthesia.

Rightening Reflex:

The Rightening reflex was elicited by squeezing or pinching a forelimb digit and observing whether the dog flexed the leg or withdrew the digit from the investigator during the examination after the anesthetic combinations were administered. (Yohannes, 2018).

Corneal Reflex:

The Corneal reflex was tested by touching the cornea with a finger (Albozachriet al., 2012).

Palpebral reflex:

The palpebral reflex was tested by lightly taping the lateral or medial canthus of the eye and observing whether the dog blinks in response after the anesthetic combinations were administered. (Yohannes, 2018).

Pedal reflex:

After administering the anesthetic combinations, the pedal reflex was elicited by squeezing or pinching a digit of the hind limb and observing whether the dog flexed the leg or withdrawn the digit from the investigator during the examination. (Yohannes, 2018).

Statistical analysis:

The results were expressed as mean ± SD.Thecomparisonsbetweens groupswereperformedwith two way analysisofvariance(ANOVA)byusing computerizedSPSSprogram(StatisticalProgramforSocialSciences). P<0.05 was considered to be lest limit of significance. Least Significant Different Test (LSD) was calculated to test the difference among means (groups) for (ANOVA) using SPSS .

III. RESULTS:

Evaluation of analgesia and anesthesia.

Evaluation of onset, duration action and recovery time

Table _ 1: Mean values (± Standard Error) of subjective scores qualifying anesthesia (Induction time, surgical Time (Duration of Action) and recovery time)/minute

Anesthetic agent	Dosage	Onset of Action (Min)	Duration of Action (Min)	Total Recovery Time (Min)
BK*	0.1 mg/kg B, 10 mg / kg K	* 2.010 ± 0.09274	* 38.40± 1.122	* 65.80± 0.8367
DK**	0.04mg/kg D, 10 mg / kg K	* 1.500±0.05099	* 63.80± 1.393	* 93.80± 0.6000

*: Symbol referred to significant differences among treatment groupsP < 0.05.

BK*: Butorphanol+Ketamine

DK**: Detomidine+ Ketamine

The analgesic effects of anesthetic drugs in two groups were determined by incised wound, in order to confirm for the entrance to the surgical stage, generally all animals not response to these test.

Evaluation nature of induction.

The experimental animals represented slight excitation in group A, and smoothly induction in group B.

Evaluation of Analgesia.

In group A analgesia started in 2.010 ± 0.09274 minutes after I-V injection, and continued38.40 ± 1.393 minutes. In group B,started 1.500± 0.05099 minute after the induction, and continued for 63.80± 1.393 minutes.The duration of analgesia may convey that during this time, the operation can be achieved, however after that the analgesia would be absent.(Table-1).

Evaluation nature of recovery.

The recovery was completely smooth for the dogs in group A, and the pedal reflexes were normal. However, the group B the recovery nature was characterized smooth and difficult to standing position. Then was standing position and alert in all animals.

Evaluation of body reflex activity

Table 2: Loss of body reflexes activity.

Anesthetic agent	Dosage	Righting Reflex (min)	Palpebral Reflex (min)	Corneal Reflex (min)	Pedal Reflex (min)
BK*	0.1 mg/kg B, 10 mg / kg K	* 2.010 ± 0.09274	* 2.070 ± 0.09274	* 2.070 ± 0.09274	* 2.170± 0.05831
DK**	0.04/kg B, 10 mg / kg K	* 1.500± 0.05099	* 1.580 ± 0.06000	* 1.580 ± 0.06000	* 1.640± 0.08718

*: Symbol referred to significant differences among treatment groups P < 0.05.

BK*: Butorphanol+Ketamine

DK**: Detomidine+ Ketamine

The Body Reflex activity remained unchanged throughout the anesthesia in every group. Absent the reflexes as time in (Table-2).

Evaluation of physiological parameters

The results revealed significant (P < 0.05) decrease in the means of respiratory rate between groups A and B at all time compared with base line(Fig. 3).

The results revealed that significant (P < 0.05) differences in the means of heart rate between groups (A)and(B) the heart rate was increase in group A in compare withgroup B, as well as was significant differences in the means of heart rate withingroup A , it was gradually increased at times 5 ,10,15 and 20 minute then return close to base line at 25,30 and 60 minute while in group (B) the means of heart rate were increased at all times in compared with base line (Fig. 4).

The results revealed that significant slowly decrease in the means of oxygen rate between groups (A) and (B) at all time compared with base line (Fig.5).

In both groups the body temperature mildly decreases during the period of observation followed the injection of these agents. Significant (P < 0.05)decreaseat all time compare with base line(Fig. 6).

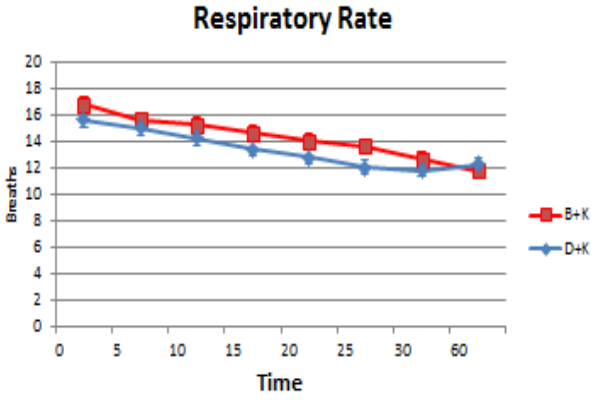


Fig. (3) Respiratory Rate

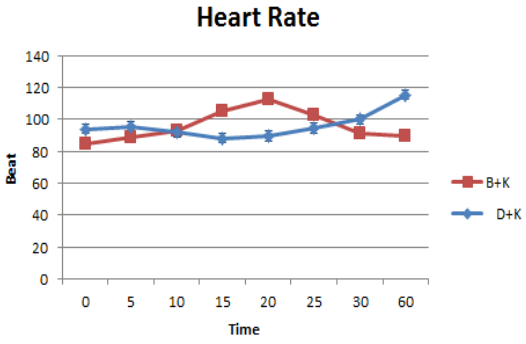


Fig. (4) Heart Rate

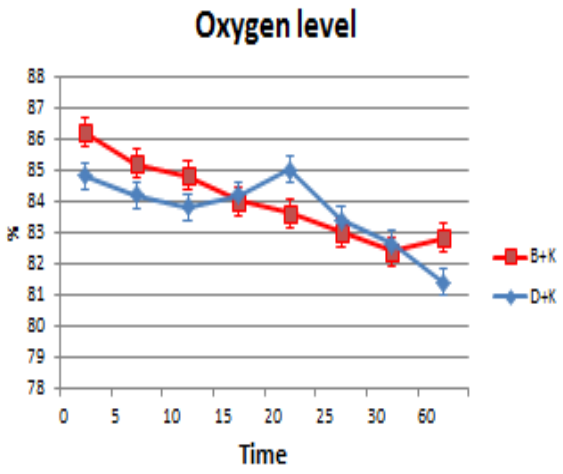


Fig. (5) Oxygen Rate

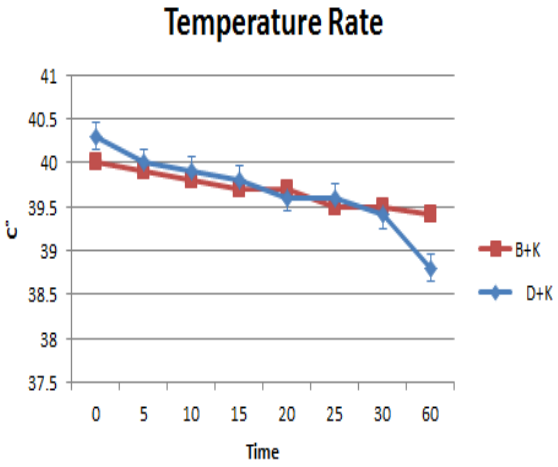


Fig. (6) Temperature Rate

IV. DISCUSSION:

After injection the drug the nature of induction in group A the animals characterized with slight excitation was effect by outer physical impulses agree with (Demirkan et al., 2002). In group B the animals characterized with smoothly induction agree with (El-Kammar andGad, 2014).

The onset of time as in (Table-1) in group A which agree with (Demirkan et al., 2002). But other group which Intravenous injection of detomidine induced the most rapid onset and longest duration of sedation and analgesia in animals compared to i.v. injection of each drug alone. These effects may be the result of a synergistic effect of the 2 drugs agree with (El-Kammar andGad, 2014) and disagree with (Yayla et al., 2015).

There are a number of pharmacokinetic studies of ketamine reported in some species(Craigmill., 2018). According to these findings, ketamine is poorly bound to plasma proteins, allowing it to leave the brain quickly and redistribute into other tissues. This redistribution of ketamine to other body tissues, primarily body fat, lung, liver and kidney is attributed to the rapid recovery from anesthesia,.The result of present study duration time about 38minutes in group Aand disagreed with (Demirkan et al., 2002) 63minutes in group Bthis might be due to wide distribution of alpha 2 adenoreceptors and ketamine combination in the body, because they are highly soluble in lipid and can be redistributed into muscles and adipose tissues agree with (Azizpour and Hassani,2012). And disagree with (Yayla et al., 2015)

The nature and time of recovery as in (Table 1) in group A which smoothly and not excited dogs agree with (Demirkan et al., 2002) While the group B the recovery nature was characterized smooth and difficult to standing position agree with (Kamiloglu et al., 2008).

Ketamine provides the state of dissociative anesthesia (Schauer et al.,2021) and effectiveness of butorphanol or detomidine which cause the body reflexes abolished in all group at time as in (Table 2). Agree with (Yayla et al., 2015;Yohannes, 2018). And disagree with (Amin and Najim, 2011).

The changes which occur in the nervous system during anesthesia were due to interference with the conduction of impulses in nerve fibers, the oxidation process in nerve cells. In group A analgesia was a starting in 2minutes after I-V injection and continues 38minutes during this time can be achieving operation. In group B there was analgesia starting from 1.5minute and continues for 63minutes during this time can be achieve operation then that the analgesia was loss. The analgesic effect of detomidine via binding to alpha-2 receptors in the locus ceruleus on the pons and lower in the brain steam and spinal cord (Daunt and Steffey, 2002) and butorphanol which increase the intensity and duration of the analgesia which are dose dependent with duration of analgesia ranging from 15-90 minutes (Hutton et al., 2000). Agree with (Hutton et al., 2000; Daunt and Steffey, 2002).

These results group B agreed with the result of other researches that attributed to the effect of α-2 agonist drugs which causes depression of heart rate that lead to arrhythmogenic include sinoatrial block first and second atrioventricular (AV) block, bradycardia, and sinus arrhythmia. Bradycardia occurred after administration of the anα-2 agonist drugs (Freeman et al., 2002 and Machado et al., 2006). In time 5 minute, of the experiment the

heart rate increased due to the ketamine effect on cardiovascular stimulating properties. Wong and Jenkins(1974) revealed that ketamine causes high blood pressure, tachycardia and increased cardiac output are primarily sympathomimetic actions as a result of stimulation of the central sympathetic nervous system.

The group A result agreement witha sympathomimetic drug, ketamine stimulates the cardiovascular system which is characterized by increases in heart rate, mean aortic pressure, pulmonary arterial pressure, central venous pressure and cardiac output (Branson, 2001), Ketamine is a dissociative compound which causes an increase in HR attributable to stimulation of the central nervous system(Hartsfield, 1992).Butorphanol, like other opioids. It may increase the heart rate for 1 h or keep it slightly higher than the normal range (Demirkan et al., 2002).

Decrease respiratory rate due to a significant decrease in O2 (Schroeder and Smith, 2011). In group (A), significant decrease in respiratory rate which agree with Schroeder and Smith (2011), (Demirkan et al., 2002). Both respiratory and O_2 rate disagrees with walker et al (2001).

In group B decrease in level of respiratory rate and O_2 due to effect of Ketamine action which depression of respiratory rate with poor muscle relaxation. In combination Ketamine and Alpha-2 adenoreceptors to prolong general anesthesia.

Detomidine was also cause depression in respiratory rate and O_2, group B was agree with (Hopfensperger et al., 2013;Vigani and Garcia, 2014; Rosa et al., 2014), but its shorter effectiveness on increase respiratory rate, then decrease after reduce of CNS activity or by the fact that animals under the effect of these regimes anesthesia and required a lower oxygen supply and α_2-adernergic agonists due to the ability of these drugs to promote bronchodilation disagree with (Yayla et al., 2015)

Decrease in rectal temperature observed during post anaesthetic period might be attributed to a decrease in the skeletal muscle tone, reduced metabolic rate, depression of thermoregulatory centers and vasodilation (Malik et al., 2011) agree with group A.And disagree with Walsh et al., (2001) increases skin temperature like typical opioid agonists.

In group Bagree with Sinclair (2003) Temperatures may decrease in animals sedated with a2-agonists. In general, the reduction in temperature with a2-agonists can be attributed to CNS depression, in combination with a reduction in muscular activity .However, in dogs, only slight reductions in rectal temperature were observed, Alpha2-agonists may allow for better maintenance of body temperature due to the peripheral vasoconstriction and central redistribution of blood, with a consequent reduction in cutaneous heat losses, in contrast to the consistent reductions in body temperature reported with the use of other anesthetic agents that induce vasodilation.

The conclusion is group B anesthesia in dog is a safe and reliable anesthesia protocol for surgery.

REFERENCES

1. **Adams J G, Figueiredo J P, and Graves T K (2015).** Physiology,pathophysiology, andanesthetic management of patients with gastrointestinal and endocrine disease. Veterinary Anesthesia and Analgesia, 1, 641.
2. **Ahmad R A, Kinjavdekar P, Aithal H P, Pawde A M, and Kumar D (2013)**. Potential use of dexmedetomidine for different levels of sedation, analgesia and anaesthesia in dogs. VeterinarniMedicina, 58(2).
3. **Albozachri J M K, Al-faris A A, and Majeed S K (2012).** Effect of Use Two General Anesthetic Regimes on Some Clinical and biochemical Parameters in Donkeys. Kufa Journal For Veterinary Medical Sciences, 3(2).
4. **Alma A G, Héctor S, and Enrique N (2002).**Pharmacological Basis of Short-Term Endovenous General Anesthesia Ee El EquinoVeterinaria México, July-September, Universidad Nacional Autónoma de México Distrito Federal, México, 33(3):309-333.
5. **Amin A, andNajim I (2011).** Use of detomidine, butorphanol and ketamine for induction of general anesthesia in donkeys. Al-Anbar JournalVeterinarySciences, 4, 1-8.
6. **Azizpour A, and Hassani Y (2012)** Clinical evaluation of general an aesthesia with a combination of Ketamine HCL and Diazepam in pigeons. Journal of Agriculture 7: 101-105.
7. **Boehm C A, Carney E L, Tallarida R J, and Wilson R P (2010).** Midazolam enhances the analgesic properties of dexmedetomidine in the rat. Veterinary anaesthesia and analgesia, 37(6), 550-556.
8. **Branson, K.R. (2001).** Injectable anesthetics, In: Veterinary Pharmacology and Therapeutics, 8th ed., H.R. Adams (Ed.), Iowa State University Press, Iowa, P: 213-267.
9. **CraigmillA L (2018).** Handbook of comparative pharmacokinetics and residues of veterinary therapeutic drugs. CRC press.
10. **Daunt DA and Steffey EP (2002).** Alpha-2 adrenergic agonists as analgesics in horses. veterinary ClinicallyNorth America Equine Practice, 18: 39-46..
11. **Demirkan İ, Atalan G,Gökce H İ, Özaydin İ, andÇelebi F (2002).** Comparative study of butorphanol-ketamin HCl and xylazine-ketamin HCl combinations for their clinical and cardiovascular/respiratory effects in healthy dogs. Turkish Journal of Veterinary and Animal Sciences, 26(5), 1073-1079.
12. **El-Kammar, M. H., & Gad, S. B. (2014).** Evaluation of the sedative, analgesic, clinicophysiological and haematological effects of intravenous detomidine, detomidine-butorphanol, romifidine and romifidine-butorphanol in standing donkeys. Equine Veterinary Education, 26(4), 202-207.
13. **El-Sherif MW (2018).** Evaluation of clinical anaesthetic effect after tramadol hydrochloride addition to xylazineketamine total injectable general anaesthesia in cats undergoing scrotal castration. Indian Journal of Applied Research, 2: 1-6.
14. **Flecknell, P. (2015).** Laboratory animal anaesthesia. Academic press.4th Edition**,** Elsevier, pp.5-10
15. **Freeman S L, Bowen I M, Alibhai H I K and England G C (2002).** Cardiovascular effects of romifidine in the standing horse. Research in Veterinary Science, 72: 123-129.
16. **Gharagozlou P, Hashemi E, DeLorey T M, Clark J D, and LamehJ(2006).** Pharmacological profiles of opioid ligands at kappa opioid receptors. BMC pharmacology, 6(1), 1-7.
17. **Hall LW (2014).**veterinary anaesthesia (11th ed). UK: Elsevier Ltd, pp. 85-91.
18. **Hartsfield, S. M. (1992).** Advantages and guidelines for using ketamine for induction of anesthesia. *The Veterinary clinics of North America. Small animal Practice*, *22*(2), 266-267.
19. **Hopfensperger M J, Messenger K M, Papich M G, and Sherman B L (2013).** The use of oral transmucosal detomidine hydrochloride gel to facilitate handling in dogs. Journal of Veterinary Behavior, 8(3), 114-123.
20. **Hutton P, Cooper G M, James F M, and Butterworth J (2000).** Fundamental Principles and Practice of anesthesia. DUNIT. pp. 621-625.
21. **Kamiloglu A, Atalan G, and Kamiloglu N N(2008).** Comparison of intraosseous and intramuscular drug administration for induction of anaesthesia in domestic pigeons. Research in veterinary science, 85(1), 171-175.
22. **Machado L, Cortopassl G, Fantonl T, Cruz D, and Silva D (2006).** Cardiovascular and pulmonary effects of romifidine and butorphanol combination in horses. Brazilian Journal of Veterinary Research and Animal Science, (4) 34:568-575.
23. **Malik V, Kinjavdekar P, Aithal H P, and PawdeA M (2011).** Continuous intravenous infusion anaesthesia with ketamine in medetomidine, midazolam, butorphanol premedicated and thiopental induced buffaloes. Indian Journal of Animal Sciences, 81(2), 116-122.
24. **Peeters E, Porters N, Bols P E J, NelissenM, Moons C P H, De Rooster, H, and Polis I (2012).** Anesthesia in kittens a review of the literature with stress on the possibilities in Belgium. VlaamsDiergeneeskundigTijdschrift, 81(3), 129-137.
25. **Rafee M A, Kinjavdekar P, and Amarpal H P (2015).** Effect of dexmedetomidine with or without butorphanol on the clinico-physiological and haemodynamic stability in dogs undergoing ovariohysterectomy in midazolam and ketamine anaesthesia. International Journal of Scientific and Research Publications.
26. **Miller RD, Pardo MC, (2011)** Basic of anesthesia, Philadelphia,PA 19103-2899,
27. **Rosa A C, Lopes C, Quarterone C, Rocha R N, Quevedo D A C, Padovani C R, and Aguiar A J A (2014).**Sedative effects of xylazine and detomidine in northeastern donkeys (Equusasinus): Preliminary results.. Veterinary Anaesthesia and Analgesia, 41(2).
28. **Schauer S G, Naylor J F, Davis W T, BorgmanM A, and April M D (2021).** An Analysis of Prolonged, Continuous Ketamine Infusions. Military Medicine. https://doi.org/10.1093/milmed/usaa481
29. **Schnellbacher R (2010).** Review: Butorphanol. Journal of Exotic Pet Medicine, 19: 192-195.
30. **Schroeder C A, and Smith L J (2011).** Respiratory rates and arterial blood gas tensions in healthy rabbits given buprenorphine, butorphanol, midazolam, or their combinations. Journal of the American Association for Laboratory Animal Science, 50(2): 205-211.
31. **Sinclair, M. D. (2003).** A review of the physiological effects of α2-agonists related to the clinical use of medetomidine in small animal practice. The Canadian veterinary journal, 44(11), 885.
32. **Vigani A, and Garcia-Pereira F L (2014).** Anesthesia and analgesia for standing equine surgery. Veterinary Clinics: Equine Practice, 30(1): 1-17.
33. **Walker EA, Picker MJ and Dykstra LA (2001)** Three-choice discrimination in pigeons is based on relative efficacy differences among opioids. Psychopharmacology (Berl), 155:389-396.
34. **Walsh SL, Geter-Douglas B, Strain EC and Bigelow GE (2001)** Enadoline and butorphanol: evaluation of kappa-agonists on cocaine pharmacodynamics and cocaine self-administration in humans. Journal of pharmacology and experimental therapeutics, 299:147-158.

35. **Wong D and Jenkins L (1974).** An experimental study of the mechanism of action of ketamine on the central nervous system. Canadian Anesthesiologists' Society Journal, 21:57-67.
36. **Yayla S, KamilogluN N, Kamiloglu A, Ozaydin I, and Ermutlu C S (2015).** Comparison of the effeCts of intramusCular and intraosseal administration of detomidine/Ketamine Combination for General anaesthesia in Quails (Coturnix Coturnix Japonica). Bulgarian Journal of Agricultural Science, 21(1): 220-224.
37. **Yohannes, G. (2018).** Hematological and Physiological Effects of Ketamine with and without Xylazine in Dogs. International Journal of Cell Science and Molecular Biology, 5(1): 17-23.