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

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ABSTRACT:
The purposes of present study was to select 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, and 10mg/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 Ca pnography 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 B were 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 smoothly in (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 present study to compare between two regime of general anesthesia and select 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 received Detomidine Hydrochloride at dose (0.04 mg/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 Detomidine HCL (D)(Dormosedan® the vial contains 20ml (10 mg/1ml), Pfizer- Zoetis- Pharma, American multinational Pharmaceutical Corporation), Butorphanol Tartrate (B) (Torbugesic® the vial contains 50ml (10 mg/1ml), Pfizer- Zoetis- Pharma, American multinational Pharmaceutical Corporation) and Ketamine HCL (K): Ketamine Fresenius® Vial contains 10 ml (50 mg/1ml). Fresenius kabi Pharmaceuticals 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 Physiological signs in base line

Figure 1-C : Evaluate after anesthesia Figure 1-D Evaluate Rectal Temperature
**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 incision about 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, 30 and 60 minutes after injection (Albozachriet al 2012). Onset of analgesia, its intensity and duration were recorded.

**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. The comparisons between groups were performed with two way analysis of variance (ANOVA) by using computerized SPSS program (Statistical Program for Social Sciences). P<0.05 was considered to be least 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>
<thead>
<tr>
<th>Anesthetic agent</th>
<th>Dosage</th>
<th>Onset of Action (Min)</th>
<th>Duration of Action (Min)</th>
<th>Total Recovery Time (Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BK*</td>
<td>0.1 mg/kg B, 10 mg / kg K</td>
<td>* 2.010 ± 0.09274</td>
<td>* 38.40 ± 1.122</td>
<td>* 65.80 ± 0.8367</td>
</tr>
<tr>
<td>DK**</td>
<td>0.04 mg/kg D, 10 mg / kg K</td>
<td>* 1.500±0.05099</td>
<td>* 63.80±1.393</td>
<td>* 93.80±0.6000</td>
</tr>
</tbody>
</table>

*: Symbol referred to significant differences among treatment groups P < 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 continued 38.40 ± 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.

<table>
<thead>
<tr>
<th>Anesthetic agent</th>
<th>Dosage</th>
<th>Righting Reflex (min)</th>
<th>Palpebral Reflex (min)</th>
<th>Corneal Reflex (min)</th>
<th>Pedal Reflex (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BK</td>
<td>0.1 mg/kg B, 10 mg / kg K</td>
<td>2.010 ± 0.09274</td>
<td>2.070 ± 0.09274</td>
<td>2.070 ± 0.09274</td>
<td>2.170 ± 0.05831</td>
</tr>
<tr>
<td>DK</td>
<td>0.04/kg B, 10 mg / kg K</td>
<td>1.500 ± 0.05099</td>
<td>1.580 ± 0.06000</td>
<td>1.580 ± 0.06000</td>
<td>1.640 ± 0.08718</td>
</tr>
</tbody>
</table>

*: 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 with group 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).
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 and Gad, 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 and Gad, 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 38 minutes in group A and disagreed with (Demirkan et al., 2002) 63 minutes in group B this might be due to wide distribution of alpha 2 adrenoceptors 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 2 minutes after I-V injection and continues 38 minutes during this time can be achieving operation. In group B there was analgesia starting from 1.5 minute and continues for 63 minutes 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 αα-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 with a 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 O2 rate disagrees with walker et al (2001).

In group B decrease in level of respiratory rate and O2 due to effect of Ketamine action which depression of respiratory rate with poor muscle relaxation. In combination Ketamine and Alpha-2 adrenoreceptors to prolong general anesthesia.

Detomidine was also cause depression in respiratory rate and O2 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 α2-adrennergic 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 B agree 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


