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EVALUATION OF XYLAZINE-MIDAZOLAM-LIGNOCAINE-KETAMINE CONTINUOUS RATE INFUSION (CRI) FOR MAINTENANCE IN XYLAZINE-BUTORPHANOL-MIDAZOLAM-KETAMINE (XBMK) ANAESTHETISED DOGS

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ABSTRACT

Six dogs irrespective of age and sex, categorised as class I or II as per American Society of Anaesthesiologists (ASA) classification, presented to Department of Veterinary Surgery & Radiology for various elective surgeries were selected for this study. All the animals under study were pre-anaesthetised with glycopyrrolate intravenously and anaesthesia was induced using a combination of xylazine-butorphanol-midazolam-ketamine intra-muscularly. An intravenous loading dose of lignocaine was given after which anaesthesia was maintained with xylazine-midazolam-lignocaine-ketamine as continuous rate infusion. Induction of anaesthesia, using the drug combination under study was found to be satisfactory in all the six animals. The time taken for induction of anaesthesia ranged from three to five minutes, with a mean ± SE value of 4.33 ± 0.33 minutes. Quality of maintenance was judged good with good relaxation of abdominal muscles and jaw and good depth of anaesthesia. The time taken for recovery ranged from 22 to 49 minutes with a mean ± SE value of 34 ± 4.35 minutes. Recovery was smooth with out any complications noticed.

Keywords: Xylazine, Ketamine, Glycopyrrolate, Butorphanol, Anaesthesia, Dogs, Maintenance

INTRODUCTION

The concept of balanced anaesthesia is use of multiple agents to produce synergistic effects to provide adequate muscle relaxation, good analgesia and unconsciousness and avoid adverse effects of the individual drugs. Such combinations reduces the dose rates of individual drugs which will reduce the untoward effects and increases the safety. Xylazine and ketamine alone or in combination, are commonly used for anaesthesia in small animal practise. These drugs alone or in combination may

not provide adequate muscle relaxation and profound analgesia. They can be combined with butorphanol an opioid analgesic and midazolam, a benzodiazepine to counter the adverse effects of xylazine and ketamine. But literatures regarding such a combination is very limited.

Continuous rate infusion (CRI) involves use of various intravenous anaesthetic agents in combination at minimal doses to maintain low plasma concentrations of drugs and reduce use of any gaseous agents for maintenance of anaesthesia. This involves use of different drugs to maintain muscle relaxation, analgesia and unconsciousness throughout the period of anaesthesia. Xylazine, lignocaine and ketamine when used in combination or individually for CRI helps to avoid or reduce the MAC of gaseous or intravenous anaesthetics. Use of midazolam in CRI adds to sedative effect of the other drugs required for maintenance. However, there is a paucity of literature when using the anaesthetic combinations using xylazine in CRI.

The present study aimed at studying the quality of anaesthetic maintenance with xylazine-midazolam-ketamine-lignocaine as continuous rate infusions (CRI) in dogs induced with xylazine-butorphanol-ketamine-midazolam combination.

MATERIALS AND METHODS

Six dogs categorised under ASA class 1 and 2 presented for various elective surgeries were anaesthetised using a combination of xylazine-butorphanol-midazolam-ketamine given at a dose rate of 0.4 mg/kg, 0.2 mg/kg, 0.2 mg/kg and 10 mg/kg respectively, mixed together in a single syringe and given intramuscularly. All the animals under study were pre-medicated with glycopyrrolate @ 0.01 mg/kg and meloxicam @ 0.2 mg/kg intravenously thirty minutes prior to induction of anaesthesia. Animals were kept in a calm dark environment, for ease of observation of signs. Quality of anaesthetic induction was judged based on the smoothness of sedation and induction, and was graded as excellent, good, moderate or poor.

Upon induction of anaesthesia, all the animals were intubated using a suitable sized cuffed endotracheal tube, to maintain the airway patent, and connected to a circle system of anaesthesia machine for providing oxygen. A loading dose of lignocaine hydrochloride was given at the dose rate of 2 mg/kg intravenously. Anaesthesia was maintained using a continuous rate infusion of a combination of xylazine (1 mg/kg/hr), midazolam (3 µg/kg/min), lignocaine (50 µg/kg/min) and ketamine (40 µg/kg/min) in normal saline. Calculated volumes of xylazine, midazolam, lignocaine and

ketamine were loaded in separate sterile disposable syringes and mixed in normal saline to make a final volume of 100 ml. The volume of individual drugs was calculated based on the formula given, to deliver xylazine @ 1mg/kg/hr, midazolam @ 3µg/kg/min, ketamine @ 40µg/kg/min and lignocaine @ 50µg/kg/min:

Volume of drug added =

$$\frac{does\ of\ the\ drug\ (\mu g/kg/min)}{rate\ of\ flow\ of\ CRI\ (ml/kg/min)} \mathbf{x}$$

$$\frac{final\ volume\ of\ solution\ (ml)}{concentration\ of\ drug\ (\mu g/ml)}$$

The rate of flow of CRI was fixed at 40ml/hr which was administered by drop count method using a pediatric infusion set.

All the animals were monitored for muscle relaxation, quality of anaesthetic induction, quality of maintenance, degree of anaesthesia and quality of recovery from anaesthesia, by the same individual. The surgeries were performed by the same group of surgeons to avoid variations. The physiological parameters measured during maintenance were rectal temperature, heart rate, pulse rate, rate of respiration and capillary refill time. Physiological parameters and oxygen saturation of peripheral blood, non-invasive blood pressure, end tidal carbon dioxide and electrocardiogram were measured before induction, after induction and every ten minutes thereafter till recovery. Haemato-biochemical parameters and blood gas analysis was done before induction, immediately after induction and after recovery. Blood was collected for analysis in EDTA vials and heparin coated syringes (blood gas analysis). Anaesthetic parameters *viz.* time taken for induction, quality of induction, duration of anaesthesia, quality of maintenance, time taken for recovery and quality of recovery were evaluated for judging the induction, maintenance and recovery using the following anaesthetic combinations.

RESULTS AND DISCUSSION

After the administration of the anaesthetics for induction, quality of induction was judged as excellent in all the six animals. Parameters for the basis of judgement for quality of induction were smoothness of sedation and induction. Deep sedation and profound relaxation of jaw muscles were seen in all the six animals. Laryngeal reflex was absent in all the animals permitting easy intubation. At the time of intubation, position of eyeballs in all the animals were ventro-medial. Signs associated with induction and time taken for each observation in the animals studied are presented in table 1. The time taken for induction ranged from 3 to 5 minutes with a mean ± SE value of 4.33 ± 0.33 minutes.

Signs associated with induction were salivation, ptosis, staggering gait, nodding, sternal and lateral recumbency and head down.

Signs like ptosis, staggering gait, nodding, sternal and lateral recumbency and head down were associated with xylazine as an anaesthetic agent (Ansari *et al*. 2019) when used intramuscularly where glycopyrrolate was a premedication.

The anaesthesia was maintained for a duration of 80 minutes to 150 minutes depending on the surgery performed. Quality of maintenance was judged as smooth based on relaxation of muscles of abdomen, limbs and jaw in all six animals. The excellent muscle relaxation could be attributed to the effects of xylazine and midazolam and their synergism when used together. Sinclair (2003), stated that dexmedetomidine (an α_2-agonist) acts on α_2-adrenoreceptor at the level of interneurons of the spinal cord and caused muscle relaxation. This is similar to the present study where xylazine, an α_2-agonist with similar properties was used. Pedal and palpebral reflex was absent in all animals throughout the duration of anaesthesia, suggesting good analgesia and surgical plane of anaesthesia. All animals had their eyeballs in ventro-medial position over the entire duration of surgery, suggesting a surgical plane of anaesthesia and can be attributed to the analgesia and muscle relaxation produced by the synergistic effect of the drugs, given as continuous rate infusion, for maintenance of anaesthesia (Sahoo *et al.,* 2018). The time taken for recovery ranged from 22 to 49 minutes with a mean ± SE value of 34 ± 4.35 minutes. Quality of recovery was judged smooth in all the six animals.

Table 1. Observations on signs preceding induction and their respective time from administration of anaesthetic combination(mins.)

Animal No.	Salivation	Ptosis	Staggering gait	Nodding	Sternal Recumbency	Lateral Recumbency	Head down	Time taken for induction (min.)
1	2	3	2	2	4	4	4	5
2	NS	2	1	1	2	3	NS	4
3	NS	3	1	3	4	4	4	5
4	NS	NS	1	2	2	3	3	5
5	NS	NS	1	NS	NS	3	3	4
6	NS	NS	1	2	1	2	NS	3
Mean ± SE								4.33 ± 0.33

NS - Not seen

No vocalisation or paddling of limbs was noticed during recovery in any of the six cases. Delirium was absent in all the dogs and could be attributed to the synergistic effects of all the different drugs used in the study.

The core body temperature was observed to be below normal which could be attributed to a decreased basal metabolic rate and muscle activity (Hall *et al*., 2001). The reduction of body temperature could be explained by a study conducted by Mwangi *et al*. (2014) who concluded that xylazine, ketamine and their combination, significantly reduced the core body temperature even though no procedures were undertaken.

Heart rate in all the animals under study increased immediately after induction. This is in accordance with the findings of Richards *et al*. (1989) who stated that glycopyrrolate premedication in dogs could cause an initial increase heart rate. Subsequently after 30 - 45 minutes of induction four dogs showed a reduction in heart rate after the initial increase. Such an observation was made by Sindak *et al*. (2010) which was attributed to the use of xylazine-ketamine combination for induction of anaesthesia.

In five dogs, pulse rate showed an increase after induction much above the baseline values. This is in accordance with the findings Ullah *et al*. (2017) who reported a significant increase in pulse rate in dogs, when xylazine was used in combination with ketamine for induction. In four dogs, after an initial increase in pulse rate it reduced below the pre-induction value by about 35 minutes of induction and later on it increased and was maintained close to their baseline values. Such an observation was made by Abbasi *et al*. (2014) were the pulse rate significantly reduced and reached a minimum of 70.0 beats per minute by about 25 minutes and later on by 55 minutes of administration of xylazine, the pulse rate returned to its baseline values.

In five dogs, respiratory rate reduced after induction below their baseline values. This could be explained due to the use of a combination of drugs like xylazine, butorphanol, ketamine in induction and xylazine-ketamine CRI for maintenance. This is in accordance with Ibrahim (2017) who stated that xylazine-ketamine CRI in dogs also results in a significant respiratory depression.

The colour of visible mucous membrane in all the six dogs was observed to be pale roseate and capillary refill time (CRT) was noted to be less than two seconds in all the dogs. This was in accordance with Narayanan *et al*. (2011) who observed that the colour of the visible

mucous membrane remained pale roseate and CRT < 2 seconds in all dogs which were given glycopyrrolate, xylazine, midazolam, and ketamine throughout the observation period, indicating the stability of peripheral circulation.

The values of SpO_2 values in all the six dogs didn't differ from the baseline and mean value stayed above 96 per cent in all dogs. This is in accordance with De-Carvalho *et al*. (2016), who stated that the SpO_2 levels of the dogs did not differ significantly when compared to their baseline values in xylazine sedated dogs.

The mean arterial blood pressure in all the dogs showed an initial increase (114.67 +/- 8.10 mmHg) but returned to the baseline values over the course of anaesthesia. This is in accordance to the study conducted by Ilback and Stalhandske (2003) who reported that after administration of xylazine, the mean arterial blood pressure increased immediately.

The end tidal carbon dioxide ($EtCO_2$) in five dogs was increased immediately after induction. Manual assisted ventilation was required to maintain eucapnia.

The heart rate in all six dogs remained higher than the baseline preinduction values during the period of anaesthesia, but no variations could be detected in electrocardiogram (ECG).

All haematological parameters were within normal range and there was no significant changes ($p>0.05$) in the parameters seen in any of the animals before induction, immediately after induction and after recovery. A slight decrease was seen in all the hematological parameters after induction but reached close to their pre-induction values. This was in accordance with the findings of Demirkan *et al.* (2002) who reported that in dogs anaesthetised with ketamine-butorphanol combination, the haematological parameters did not alter significantly, although a decrease in haematocrit at 5 minutes and in haemoglobin levels from 15 minutes onwards were observed.

The blood gases pH, HCO_3^-, base excess, blood lactates and electrolytes showed no significant changes from their normal values. The partial pressure of oxygen (P_vO_2) values varied significantly ($p<0.05$) from the time of the induction (62.57+/-3.20) till recovery (77.90 +/- 5.42). In five animals there was a steady increase in P_vO_2 seen immediately after induction and after recovery. This could be due to the flow of 100 % oxygen given throughout the period of anaesthesia. The P_vCO_2 values showed significant changes ($p<0.05$) before induction (42.03+/- 1.29 mmHg), immediately after induction (49.65+/- 1.06 mmHg) and post recovery (42.93

+/- 1.59mmHg). A significant increase in P_vCO_2 values could be seen immediately after induction, which also showed significant increase after recovery. This was in conjunction to the study conducted by Ismail *et al*. (2010) who reported an increase in P_vCO_2 values at various time intervals during anaesthesia, observed with a combination of xylazine, ketamine, and diazepam in dogs. The increase in P_vCO_2 values with a corresponding decrease in pH values refers to respiratory acidosis seen in dogs in the study.

In serum biochemistry, blood glucose levels significantly increased in all the animals from time of induction (138.33 +/- 21.98 mg/dL) to recovery (224.33 +/- 35.01 mg/dL). The significant increase in blood glucose levels could be attributed to xylazine and ketamine which were used in induction of anaesthesia, which is similar to the study conducted by Changmin *et al*. (2010) who reported that insulin levels decreased and serum glucose concentration elevated after administration of xylazine alone or in combination with ketamine during the anaesthetic period. While blood potassium levels showed no significant changes throughout the surgical period.

CONCLUSION

The present study deals with signs of induction, time taken for induction and signs associated with induction of anaesthesia using xylazine-butorphanol-midazolam-ketamine combination when used intramuscularly and maintained with continuous rate infusion of xylazine-midazolam-lignocaine-ketamine after a loading dose of lignocaine, intravenously.

The anaesthetic combination provided smooth induction of anaesthesia allowing easy intubation, safe induction of anaesthesia with no anaesthetic emergencies seen. The anaesthetic combination provided deep and safe anaesthesia with adequate analgesia and muscle relaxation for various surgical procedures including ophthalmic, orthopaedic and soft tissue surgeries. The anaesthetic maintenance was good with good depth of anaesthesia, excellent relaxation of muscles, loss of pedal and palpebral reflexes and safe and smooth recovery from anaesthesia.

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