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COMPERATIVE STUDY ON ANESTHETIC EFFECT OF XYLAZINE-KETAMINE AND DIAZEPAM-KETAMINE IN RABBIT MODEL

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ABSTRACT

This study was conducted to investigate the anesthetic effects of Xylazine-ketamine and Diazepam-ketamine in rabbits. Twelve adult white New-Zealand rabbits weighing 1.3+0.2 kg, were divided into two groups. A (Xylazine 5mg/kg – ketamine 35mg/kg) and B (Diazepam 5mg/kg – ketamine 35mg/kg). However, the following parameters were observed: analgesic effects (onset and duration) and clinical-parameters (means of heart-rates/BPM, respiratory-rates/BPM and rectal temperature. The onset was significantly $p<0.05$ increased and the duration was significantly $p>0.05$ decreased in A. The heart-rate and the respiratory-rate was significantly $p<0.01$ decreased in A. But the rectal temperature was decreased non-significantly $p>0.05$ in both groups. General observations: in Group A, urination, nasal-discharge, salivation and lacrimation were present, in Group B, defecation, corneal-reflex and pedal-reflex were observed at their peak. It was concluded that the xylazine-ketamine is used for clinical/surgical procedures, while diazepam-ketamine may further be investigated by using other analgesics with this combination.

1. INTRODUCTION

The rabbits can be anesthetized by using injectable general anesthetic agents because the inhalant anesthetic delivery need expensive apparatus and can cause practical problems (Flecknell, 2009) However, General anesthetic agents like ketamine can be used as anesthetizing agent (Hall et al., 2003). Ketamine is a dissociative general anesthetic agent and it is made up of two isomers (Hady et al., 2017). Whereas, ketamine induces anesthesia of voluntary and involuntary accidental stages (I and II) but not surgical stage (III) anesthesia because it is a Gamma amino butyric acid (GABA) binding inhibitor (Muhammad et al., 2014). unlike the other General anesthetic agents, ketamine enhances cardiac rhythm, which ultimately increases heart beats per minute (Avsaroglu et al., 2003). Furthermore, analgesic effects produced greater than anesthetic effects with poor muscle relaxation and increased muscle tone (Annetta et al., 2005), muscular hyper-tonicity, myoclonus and convulsions when used as a single agent (Henke et al., 2005).

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These effects can be reduced when ketamine is used with other sedative agents like alpha-2 agonists and benzodiazepine (Özkan et al., 2010). Xylazine, is a potent sedative drug of the alpha-2 agonist group, which inhibits release of cathecolamines and dopamine, and enhance the alpha-2 adrenergic receptor in the nerve endings of cerebral presynaptic clefts (Jakhrani et al., 2019), the analgesic and sedative effects is produced and delays nerve conduction in the CNS resulting in relaxation of striated muscles (Özkan et al., 2010). Xylazine induces a state of drowsiness with a high dose-dependent degree of analgesia, generalized muscle relaxation of central origin and cardiopulmonary depression (DeRossi et al., 2003). Moreover, xylazine may decrease heart rate, respiratory rate and induce hypotension, the severity depends upon the dose and species (Amarpal et al., 2010). However, there are some adverse effect like hypoxaemia associated with cardiopulmonary suppression is noticed when it is used alone (Udegbunam & Adetunji, 2007). Xylazine is mostly administered in painful surgical anaesthesia in order to obtained safe and effective anaesthetic applications (Celestineet al., 2014).

Diazepam is a benzodiazepine which is also a sedative (a potent hypnotic) drug that is used for muscle relaxation (Oguntoye & Oke, 2014). Unlike other sedative drugs diazepam does not affect the heart rate due to its to its slow metabolism but induce hypotension due to its solvent (propylene glycol) nature (Koshy et al., 2003). While the sedative effect of benzodiazepine depends on the species and sometimes individual dependent. its solvent (propylene glycol) may produce hypotension (Oguntoye & Oke, 2014). Moreover, it has been experimentally observed that mostly rabbits are anesthetized as compared to other species, but the anesthetic mortality rate is greater than dogs and cats (Brodbelt, 2009). Therefore, this experiment was conducted to compare efficacy and safety of intramuscular (im) administration of xylazine-ketamine combination (XK) and diazepam-ketamine comination (DK) for clinical use.

2. MATERIALS AND METHODS

Animal Ethical approval

The present research was conducted as per the rules and regulation of the Animal care and management SBBUVAS, Sakrand.

Experiment Design

In the present study a total 12 adult healthy White New Zealand rabbits weighed 1.3 $\pm$ 0.2 kg (Mean ± SEM) of either sex were used in this study. This experiment was conducted at Department of Veterinary Surgery SBBUVAS Sakrand. All the rabbits were housed in individual cages. The feed and water were provided ad libitum.

Research protocol

All the rabbits were randomly divided into two groups, the groups consist of different anesthetic protocols (A and B treatment) with one-week interval. In treatment A all rabbits were treated with xylazine (Xylaz ®, Farvet laboratories Handelweg 25-5531 AE BLADEL the Netherlands, 20mg/ml) dose rate of 5mg/kg body weight 30 minutes before induction with ketamine (Ketasol ®, indus Pharma (Pvt) Ltd, 65/27, Korangi Industrial Area, Karachi-Pakistan, 50mg/ml) 35mg/kg body weight. Whereas, in the treatment B, all rabbits were treated with diazepam ((Diazomil ®, Mediate Pharmaceutical (Pvt) Ltd, 150-151, Sector 24, Korangi Industrial Area, Karachi-Pakistan, 5mg/ml) 30 minutes before induction with ketamine (Ketasol ®, indus Pharma (Pvt) Ltd, 65/27, Korangi Industrial Area, Karachi-Pakistan, 50mg/ml) 35mg/kg body weight. These anesthetic agents were administered through the intramuscular route.

All the rabbits were monitored after administration of ketamine through analgesia (onset and duration) and physiological parameters (rectal temperature, heart rate and respiratory rate). Analgesia: The analgesia was accessed by pinching of paws with artery forcep (closed to 1st ratchet) after every 5 minutes.

Calculation of anesthetic indices

The following parameters were recorded and calculated as the anesthetic indices: Induction of analgesia was assessed as the period between the induction of anesthesia (ketamine) up to absence of painful stimuli on pinching of hind paws with hemostatic forceps close to the first ratchet. However, the paws of rabbits were pinched after interval of each 10 minutes till the response on pinching of hemostatic forceps to the paw. The whole period is treated as the duration of analgesia.

Onset of analgesia: Time interval between injection of anesthetic agents and loss of pedal reflexes.

Duration of Analgesia: Time interval between loss pedal reflexes to recovery of pedal reflexes.

Physiological parameters

In this study, physio-clinical parameters (heart rates, respiratory rates, and rectal temperature) of all the experimental animals were recorded after every 10 minutes from administration of ketamine till the end of experiment. Furthermore, Heart rate (in beats / min) was calculated by auscultation by placing a stethoscope on the left side over the intercostal space of 2nd and 5th rib. While the respiratory rate (in breaths / min) was recorded by the observing thoracic movement during each respiration (inspiration and expiration) and finally the digital clinical thermometer was inserted into the rectum for determination of rectal temperature (^{0}F)

Statistical Analysis

All the data were statistically calculated as means ± standard error of means (SEM) of 12 rabbits. The means of analgesic parameters (induction and duration of analgesia) and physiological parameters (heart rates, respiratory rates and rectal temperature) were compared using analysis of variance (ANOVA) and followed by LSD test when a significant difference was indicated through computer software SPSS computer software (version 25 for Windows; SPSS, Chicago, USA). The significant level was showed at $P < 0.05$, with a trend that was declared at $0.05<P<0.10$ (Dawson and Trapp, 2004).

3. RESULTS

Analgesics effect

The results of effect of xylaxine ketamine and diazepam ketamine is presented in Table 1. The results showed that the onset of analgesia in group A was significantly

$p<0.05$ increased compared to group B. While the duration of analgesia was significantly $p<0.05$ increased in Group B compared to group A.

Heart rate

Pre-treatment (Control) mean heart rates were 184.8±0.90 and 187.2±0.30 beats per min. in with the intramuscular administration of xylazine-ketamine and diazepam-ketamine respectively. These values were not significant from each other in all rabbits (Table-2).

The heart rate decreased in group A. This decrease was statistically significant between the groups and within the group till 40 minutes after administration and showed the maximum decrease of heart rate 40 minutes and slowly increased till the end of experiment. However, the values showed significant difference from the baseline. While the heart rate in group B decreases non-significantly within group till the end of experiment but these values are significantly different between groups.

Respiratory rate

Pre-treatment (Control) mean respiratory rates were 181.0±2.32 and 185.2±0.76 beats per min. in with the intramuscular administration of xylazine-ketamine and diazepam-ketamine respectively. These values were not significant from each other in all rabbits (Table-3).

The respiratory rate decreased in Group A. This decrease was statistically significant between the groups and within the group up to 40 minutes after administration and showed the maximum decrease of heart rate 40 minutes and slowly increased till the end of experiment. However, the values showed significant difference from the baseline. While respiratory rate was also decreased in group B significantly within group upto 40 minutes after administration and showed the maximum decrease of heart rate 40 minutes and slowly increased till the end of experiment. However, the values showed significant difference from the baseline.

Rectal temperature

Pre-treatment (Control) mean rectal temperature were 104.4±0.00 and 104.6±0.25 ^{0}f with the intramuscular administration of xylazine-ketamine and diazepam-ketamine respectively. These values were not significant from each other in all rabbits (Table-4).

The rectal temperature was decreased in Group A and B till the end of experiment. This decrease was statistically non-significant between the groups and within the group.

General observation

General observations in rabbits after administration of xylazine-ketamine (treatment A) and diazepam-ketamine (treatment B) were examined and presented in Graph-1. The data indicated that in treatment A the following observations viz. urination, nasal discharge, salivation and lacrimation were present. While, in treatment B, the following observations i.e., defecation, corneal reflex and pedal reflex were observed at peak.

4. DISCUSSION

Ketamine is a dissociative General anaesthetic agent that can be used alone or combined with other per-anaesthetic drugs in order to preoperative sedation, onset of anaesthesia and intraoperative anaesthesia maintain the duration of anaesthesia, epidural anaesthesia and also used for postoperative analgesia (Dawson & Trapp, 2004). Some pre-anaesthetic agents can be used for safe and effective anaesthesia like diazepam and xylazine because they reduce the heart and respiratory rates, induce the hypotension and counteract the adverse effects of ketamine such as: increased heart rate, respiratory rate and poor muscle relaxation (Molaei et al., 2010). Ketamine is important to maintain and stimulate respiratory system, induce broncho-dilation and maintain lung esidual capacity (Dzikiti et al., 2007). Ketamine increase the secretions that is undesired effect because it may cause respiratory distress (Biswas et al., 2017). These respiratory secretions can be reduced by inducing anti-muscarinic agents i.e; atropine (Von Ungern et al., 2007; Singh et al., 2005). Benzodiazepines like; diazepam reduce heart rate effects of ketamine depressing the cardiovascular system, likewise, alpha-2 agonists i.e; xylazine also subside cardiopulmonary activity, that was enhanced by administration of ketamine (Hall et al., 2001).

The cardiopulmonary activity and catecholamine levels is altered depend upon the degree of stress when ketamine is used with these sedative agents (Aydİlek et al., 2007). Similar to the findings of other studies, our results showed that clinical findings such as heart rates and respiratory rates reduced from baseline values after induction. The sympathetic effects of ketamine, higher values of the three hemodynamic parameters in the ketamine-diazepam group can be attributed to relatively lesser contribution of diazepam to the induction of anesthesia compared to xylazine (Ismail, 2016). In combination with benzodiazepines and an alpha-2 agonist xylazine, an increase in the quality of analgesia, sedation, anesthesia and recovery, alleviation of anxiety and a decrease in the unwanted ketamine have been demonstrated (Morse et al., 2004). Group B showed prolonged induction and inadequate depth of intraoperative anaesthesia were observed in our study, on other hand group A produced desired anaesthetic effects. As compared to group B, group A produced prolong duration of anaesthesia, adequate depth of surgical anaesthesia and satisfaction at every stage of anaesthesia have been observed (Brohi et al., 2019). The analgesic effects of group A in our study is resembles with the

results of consistent with other studies (Kazemi et al., 2002; Kiliç, 2004). However, our study indicates anaesthetic effect of group A is useful for painful surgical intervention and group B showed lack of analgesia. These findings were agreement with the results of Kazemi and Sumitra (Kazemi et al., 2002; Sumitra et al., 2004).

5. CONCLUSION

In conclusion, both groups (A and B) produced anaesthetic and analgesic effects but only group A provided adequate surgical analgesia for many painful procedures. However, some mild complications were also produced (decreased heart rate) bradycardia, dysphagia (decreased respiratory rate) and salivation (increased secretion of saliva in mouth) after xylazine and ketamine combination, but this can be overcome by addition of atropine injection prior administration of anaesthesia. While diazepam ad ketamine combination cannot produce surgical anaesthesia for painful procedures, because this combination cannot produce adequate analgesia for painful surgical procedures. Therefore, it is recommended that the xylazine and ketamine combination can be used in clinical painful surgical interventions.

6. CONFLICT OF INTEREST

All authors have declared that there is no conflict of interests regarding the publication of this article.

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