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RESEARCH ARTICLE

Efficacy of Medetomidine Hydrochloride Alone and In Combination with Ketamine Hydrochloride for Surgical Anesthesia in Cats

Hamid Akbar, Muhammad Arif Khan, Shehla Gul Bokhari, Mansur Ud Din Ahmad[1]*, Muhammad Nawaz[2], Aftab Ahmad Anjum[2] and Humaira Majeed Khan[3]

Department of Clinical Medicine and Surgery; [1]Department of Epidemiology and Public Health; [2]Department of Microbiology, University of Veterinary & Animal Sciences, Abdul Qadir Jillani Road, Lahore, 54000-Pakistan; [3]Department of Pharmacy, Lahore College for Women University, Lahore, 54000-Pakistan
*Corresponding author: mansuruddin@uvas.edu.pk

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Efficacy of medetomidine HCl (Med-HCl) as sedative/analgesic alone and in combination with ketamine HCl (Ket-HCl) was clinically evaluated during ovariohysterectomy in cats. Clinically healthy cats (n=60) divided randomly into groups A, B and C (n=20 each). Cats in groups were administered normal saline (control), Med-HCl alone and combination of Med-HCl and Ket-HCl respectively. It was observed that body temperature, pulse and respiratory rates tend to decrease overall in treated cats compared to control. In group C, the onset of anesthesia was significantly shorter ($P<0.05$) whereas duration of recumbency and recovery prolonged in relation to other groups, suggesting superior efficacy of the combination. The analgesia and sedation scores at 15, 30 45 and 60 minutes post administration indicated significantly better efficacy of Med-HCl and Ket-HCl combination. The effects of the anesthetic drugs on liver enzymes (serum alkaline phosphatase and alanine aminotransferase) and kidney functions (urea, creatinine and uric acid) were non-significant showing no harmful effects on liver and kidney functions. Significant increase in the creatinine values were seen in group C. Hematological parameters such as uric acid, hemoglobin, total leukocyte count, differential leukocyte count showed non-significant changes in groups B and C as compared to control, group A. No untoward effects of Ket-HCl were appeared on use in combination with medetomidine. It was concluded that combination of medetomidine with ketamine is safe and effective anesthesia for feline surgical interventions.

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INTRODUCTION

In past chloroform and ether vapors were used to achieve anesthesia by inhalation (Askitopoulou *et al.,* 2000). The main purpose of general anesthesia is to perform surgery of any patient under quiet conditions with minimum movement (Sebel *et al.,* 2004). Anesthesia must produce reliable degree of sedation, muscle relaxation and analgesia in different animal species (Weinbroum and Abraham, 2001; Ripamonti and Dickerson, 2001). Ketamine is a dissociative anesthetic used as one of the most preferred injectable agents providing excellent analgesia and amnesia (Azizpour and Hassani, 2012). Medetomidine HCl is a latest drug of new millennium and has gained the attention of many animal practitioners as a sedative-analgesic (Kastner *et al.,* 2001; Morgaz *et al*., 2013; Akbar *et al.,* 2014; Lu *et al*., 2014). It has many advantages over xylazine (Kanda and Hikasa, 2008) on account of its better activity for sedation, analgesia and muscle relaxation in cats (Selmi *et al.,* 2004).

Med-HCl can counteract the effects of Ket-HCL (Sinclair, 2003). Hence, Med-HCl and Ket-HCl combination may be a better choice for animal anesthesia (Jang *et al.,* 2009). The combination has been used in the past for anesthesia in mice (Baker *et al.,* 2011). In routine ketamine, atropine and xylazine (KAR) combination is used as anesthesia in cats for all kinds of major and minor surgical problems. This combination does not fulfill the requirements of complete anesthesia as it is short term, risky and offers limited analgesia (Wellington *et al.*, 2013). Xylazine is sedative and hypnotic in nature with minimal analgesia compared to Med-HCl. Present study was planned to evaluate the sedative, analgesic and hematologic effects Med-HCl alone and in combination with Ket-HCl.

MATERIALS AND METHODS

Sixty adult client-owned female cats selected from cases presented for ovariohysterectomy surgery at the Pet Centre, UVAS Lahore, over a period of six months were included in the study. The plan was approved by the Animal Ethical Committee, University of Veterinary and Animal Sciences Lahore, Pakistan.

The selected cats were divided randomly into three groups A, B and C (n=20, each). Cats of group A (control) were administered normal saline. In group B, Med-HCl (Domitor® Vet., Orion Pharma Animal Health, Turku, Finland) was injected at dose rate of 15 µg/kg body weights alone to induce anesthesia. Meanwhile, in group C, combination of Med-HCl and Ket-HCl 2mg/kg BW (Narketan®, Chassot, Dublin, Ireland) was used to induce and evaluate anesthesia for the major surgical procedure. During anesthesia, corneal desication was prevented by an eye gel (Viscotears®, CIBA Vision AG, Hetlingen, Switzerland). In case of spontaneous recovery during surgery supplementary dose was injected intramuscularly. The cats were prepared aseptically for surgery and the peritoneal cavity accessed by a ventral midline incision using surgical procedure (Ko *et al*., 2007).

The physical parameters included for assessment of anesthesia efficacy were body temperature, pulse and respiratory rates. Rectal temperature, pulse and respiratory rates were recorded by digital thermometer (Welch Allyn Diatek 600, Welch Allyn Inc, New York, USA), stethoscope and manual monitoring of chest movements, respectively. The complete process of anesthesia induction, recording of observations and monitoring the recovery was managed at an isolated, quiet place to avoid any disturbance. Depth of sedation and analgesia was evaluated on the basis of scoring system allocated based on number of reflexes present or lost. Reflexes were monitored and scores allotted from (1-5) on the basis of number of reflexes lost, following the same protocol of numerical sedation score (NSS) ranging from 1-3 (Selmi *et al.*, 2003; Valverde *et al.*, 2004). The reflexes for analgesia evaluation included were ear twitch, toe pinch, tail, anal and patellar reflex (Fahlman *et al*., 2006). The degree of analgesia was graded in relation to presence/absence of analgesia reflexes by scoring system. Sedation depth was scored in relation to time as for analgesia. Reflexes monitored for sedation included were neck down, head down, jaw tone, palpebral reflex, gait in-coordination, and saliva drooling. Sedation scores were allocated based on degrees of sedation reflexes.

Blood samples were collected during optimal anesthesia at 12-15 minutes post-anesthetic drug administration and dispatched to the laboratory for analysis. The blood samples were collected from the femoral artery using disposable syringes with and without heparin (PICO^{TM} 70, Radiometer Copenhagen, Denmark). SAP and AST were measured using commercially available kits (Crescent Diagnostics, Saudi Arabia) having Cat # CZ901U, CZ904L and CZ902L, respectively. Urea, creatinine and uric acid levels were monitored to evaluate the effect of drug on kidney function. Level of urea was measured by Urease-GLDH enzymatic UV test using a commercially available kit "Urea UV" (Merck Pvt. Limited, France, Ref. # 5.17610.0001). Serum creatinine concentration was determined by kinetic method without de-proteinization–Jaffe reaction using "Creatinine Test Kit" (Crescent Diagnostics, Saudi Arabia; Cat. # CS604-8). Uric acid was measured by Uricase/PAP method using "Globals' Uric Acid Kit" (Global In vitro LLP, London, UK. Ref. # UAC62150). Hemoglobin concentration, total leukocyte count, differential leukocyte count and erythrocyte sedimentation rate were determined using automated hematology analyzer (Abacus Junior Vet Serial No 130076 Austria). Data was analyzed statistically using one-way ANOVA followed by Duncan's multiple range post hoc test using SPSS version 10.0.

RESULTS

The body temperature showed the highest decline in group C (Med-HCl and Ket-HCl combination), with a mean value of 100.6±0.66°F (Table 1). Statistically, the value was significant when compared with the control group A ($P<0.05$). Decline in pulse rate was statistically significant in groups C (133.1±5.9/minute) and B (136.2±6.0/minute), respectively, as compared to control group A (143.0±9.6/minute). Likewise, the respiratory rate also decreased significantly in group C (23.2±2.0/minute) and group B (25.0±2.8/minute) when compared with the control group A (27.0±3.5/minute). Onset of anesthesia was earlier in the group B than C and statistically, all three groups showed significant difference with each other (Table 1). The duration of anesthesia and recovery time were significantly prolonged in cats of group C than to B and control A.

Analgesia scores depicted moderate analgesia in group C, injected with combination at 15 minutes, to deep analgesia at 30, 45 and 60 minutes, respectively. Contrarily, analgesia scores in group A showed mild to moderate analgesia at different time intervals, while the control group A did not show any signs of analgesia at any time. Statistically, all three groups differed significantly ($P<0.05$) with each other at each time interval (Table 2).

Serum alkaline phosphataseand Alanine aminotransferase increased with statistical non-significant difference between the three groups, viz. groups A, B and C respectively. This indicated that enzymes remained almost unaffected. Indices for renal function, included significant increases in urea and creatinine values in group C, as compared with control group A, viz. (24.99±2.1) and (0.98±0.11), respectively (Table 3). Increase in urea and creatinine values in group B were non-significant on comparison with groups A and C, respectively. Contrarily, the mean statistical value of uric acid showed a non-significant difference between the treated groups indicating that this enzyme remained unaffected.

Blood analysis depicted non-significant increases in the values of most indices including hemoglobin, TLC, polymorphs counts, lymphocytes counts, monocytes and ESR. However, only the eosinophil count showed significant

Table 1: Effects of medetomidine and medetomidine-ketamine combination on clinical parameters in experimental cats

Groups	Drugs used	Temperature °F	Pulse (minutes)	Respiration (minutes)	Onset (minutes)	Duration (minutes)	Recovery (minutes)
A	No drugs	101.1±0.59[a]	143.0±9.6[b]	27.0±3.5[b]	0.00±.00[a]	0.00±0.00[a]	0.00±0.00[a]
B	Med-HCl	100.8±0.56[ab]	136.2±6.0[a]	25.0±2.8[a]	3.70±.80[b]	47.90±4.4[b]	56.55±5.4[b]
C	Med-HCl+Ket-HCl	100.6±0.66[b]	133.1±5.9[a]	23.2±2.0[a]	2.65±0.58[c]	54.00±4.4[c]	63.60±7.3[c]

Mean±SD carrying different superscripts in a column differed significantly (P<0.05). Med-HCl: medetomidine HCl; Ket-HCl: ketamine HCl

Table 2: Effects of medetomidine alone and in combination with ketamine on analgesia and sedation scores in experimental cats (n=20 each)

Parameter	Groups	Drugs used	15 min	30 min	45 min	60 min
Analgesia	B	Med-HCl	3.45±.51[b]	2.95±.75[b]	2.90±.64[b]	3.15±.58[b]
	C	Med-HCl+Ket-HCl	4.05±.60[c]	5.15±.58[c]	5.65±.48[c]	4.90±.64[c]
Sedation	B	Med-HCl	1.85±.48[b]	2.60±.50[b]	2.80±.61[b]	2.25±.44[b]
	C	Med-HCl+Ket-HCl	2.50±.51[c]	4.20±.61[c]	4.90±.64[c]	3.55±.68[c]

Mean±SD carrying different superscripts in a column and a parameter differed significantly (P<0.05). Med-HCl: medetomidine HCl; Ket-HCl: ketamine HCl

Table 3: Effects of medetomidine alone and in combination with ketamine on blood profile, liver and kidney function in experimental cats

Parameter	Unit	Groups (n=20 in each group)		
		A (no drugs)	B (Med-HCl)	C (Med-HCl+Ket-HCl)
Serum alkaline phosphatase	IU/L	186.24±22.6	193.13±24.2	199.58±27.4
Alanine aminotransferase	IU/L	13.15±5.0	14.03±5.2	14.92±5.2
Urea	mg/dl	22.62±2.0[a]	23.75±2.0[ab]	24.99±2.1[b]
Creatinine	mg/dl	0.87±0.07[a]	0.93±0.11[ab]	0.98±0.11[b]
Uric acid	mg/dl	2.32±0.11	2.31±0.32	2.36±0.33
Hemoglobin	mg/dl	10.78±2.5	11.26±1.0	11.14±1.1
Total leukocyte count	10^3/mm^3	6442±36	6532±36	6474±36
Polymorphs	10^3/mm^3	25.55±6.5	26.30±6.6	26.95±6.9
Lymphocytes	10^3/mm^3	64.60±7.0	65.40±6.9	67.10±7.0
Monocytes	10^3/mm^3	3.30±0.81	2.95±0.82	3.30±0.81
Eosinophils	10^3/mm^3	1.57±0.50[a]	1.70±0.47[ab]	1.90±0.44[b]
Erythrocyte sedimentation rate	mm/hour	1.65±0.48	1.80±0.61	1.95±0.39

Mean±SD carrying different superscripts in a row differed significantly (P<0.05).

increases in group C, as compared with group A with a mean value of (1.90±0.44). Eosinophil count showed non-significant increase (Table 3) in group B, as compared with either group A or Group C respectively.

DISCUSSION

Medetomidine and ketamine combination has been used for induction of anesthesia in different animal species (Burnside *et al.,* 2013). Med-HCl combination with Ket-HCl provided muscle relaxation and abolishment of reflexes superior than ketamine alone (Lee *et al.,* 2010). Med-HCl caused significant fall in temperature of cats in treated groups as compared with normal. Findings of present study were in agreement with similar findings regarding more pronounced effects of Med-HCl on body temperature in smaller species of animals (Sinclair, 2003). Both Hypothermia and hyperthermia can complicate physiological response of body therefore this can be minimized by selecting the appropriate anesthetic combination. Heart rate values decreased initially and remained stable later while pulse rate declined significantly in group C injected with Med-HCl and Ket-HCl combination than control. Comparable observations in relation to anesthesia had been reported (Lamont *et al.,* 2001: David and Shipp, 2011). Bradycardia induced by the Med-HCl cocktail in the initial stages was in accordance with the findings of Selmi *et al.* (2003), who logically present a justification that bradycardia is induced by alpha-2 adrenoreceptor agonists due to increase in arterial pressure and inhibition of central sympathetic activity. Similar reports have been presented by other scientists demonstrating stimulation of central and peripheral adrenoreceptors by alpha 2-adrenoreceptor agonists and their effects on cardiovascular function (Ko *et al.,* 2000). No doubt, Med-HCl counteracts the poor muscle relaxant and analgesic effects of Ket-HCl however; cardiac stimulating properties are partially compensated. In present study, respiratory rate decreased significantly in cats of group C which is in agreement with findings of Ko *et al.* (1997) that alpha-2 adrenreoceptor agonists and Ket-HCl depress respiratory rate. In contrast, Kuusela *et al.* (2000) observed that Med-HCl tends to maintain respiratory rate near to normal baseline values in cats although a slight decrease in respiratory rate of dogs occurs. Immobilizing drugs may interfere with the normal respiratory function and lead to respiratory depression and hypoxemia (Suzuki *et al.,* 2001).

Induction of anesthesia was very smooth in present study and same results were recorded by Selmi *et al.* (2004). Duration of anesthesia recorded in present experiments was of long lasting (average 63 minutes) in cats of group C enabling smooth surgical procedure. Comparable observations have been reported by Kuusela *et al.* (2000) in dogs. The same pattern of attaining recumbency in less than five minutes has been recorded in dogs post administration of Med-HClin adults (Fahlman *et al.,* 2006) as observed in present study by the injection of combination. Recovery times showed significant difference among various groups and significantly better in cats receiving combination than others as has been reported earlier (Grint *et al.,* 2009).

Higher analgesia scores throughout the experimental duration were recorded in group injected with Med-HCl and Ket-HCl combination than others. This may be due to stimulation of receptors in the pain pathway within the brain and spinal cord. The methodology of checking the toe-pinch reflex for effective analgesia evaluation coincides with that considered valid by other scientists

(Kuusela *et al.,* 2000) for evaluation of analgesia induced by alpha-2 adrenoreceptors agonists.

In agreement to present findings, despite strong analgesia, effects of Med-HCl observed by Ko *et al.* (1997), were of much shorter duration than sedation. Reliable sedative/analgesic effects following Med-HCl administration have been recorded in cats (Anash *et al.,* 2000). The sedative and anxiolytic effects by alpha-2 adrenoreceptors are produced by receptors located primarily in locus ceruleans neurons on the pons and lower brainstem (Selmi *et al.,* 2003). During sedation dogs or cats may suddenly become aggressive on disturbance (Ko *et al.,* 2000). Sedation accompanied with muscle relaxation is reported as a beneficial property of anesthetics due to inhibition at alpha 2-adrenoreceptors. Sedation with Med-HCl induces muscle twitching in cats and this property was also observed in group B cats during present study. The effect of Med-HCl on liver enzymes did not show any significance which is an indication of safety for liver. The renal profile, however, manifested a significant increase in urea and creatinine in the Med-HCl and Ket-HCl combination as compared to control.

The hematological profile depicted only a significant increase in eosinophils in group C as compared with the control. All other variables (hemoglobin, TLC, polymorphs, lymphocytes, monocytes and ESR) indicated a non-significant difference. Ket-HCl has the major drawback that it is unable to relax skeletal muscles, due to which co-administration of other anesthetic drugs is frequently required (Prassinos *et al.,* 2005).

Conclusion: It was concluded that for surgical interventions especially in cats Med-HCl and Ket-HCl combination is a better choice. Most of the side effects can be controlled which are being faced during surgery by use of single anesthetic. Use of combination particularly in complex surgeries of longer duration may prefer to reduce the risks of anesthetic side effects.

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