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

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ABSTRACT

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.

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-analgescic (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 (PICOTM 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 using Urease-GLDH enzymatic UV test using a commercially available kit “Urea UV” (Merek 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 hematometry 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 phosphatase and 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
the Med-HCl cocktail in the initial stages was in
2001: David and Shipp, 2011). Bradycardia induced by
HCl combination than control. Comparable observations
significantly in group C injected with Med-HCl and Ket-
remained stable later while pulse rate declined
heart rate values decreased initially and
minimized by selecting the appropriate anesthetic
physiological response of body therefore this can be
Both Hypothermia and hyperthermia can complicate
temperature in smaller species of animals (Sinclair, 2003).
regarding more pronounced effects of Med-HCl on body
findings of present study were in agreement with similar findings
2010). Med-HCl caused significant fall in temperature of
cats in treated groups as compared with normal. Findings
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
over 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 adrenoreceptor 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.
Comparative 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-HCl in 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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Groups</th>
<th>Drugs used</th>
<th>Temperature °C</th>
<th>Pulse (minutes)</th>
<th>Respiration (minutes)</th>
<th>Onset (minutes)</th>
<th>Duration (minutes)</th>
<th>Recovery (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No drugs</td>
<td></td>
<td>101.1±0.59</td>
<td>143.02±9.8</td>
<td>27.0±3.5</td>
<td>0.00±0.0</td>
<td>0.00±0.0</td>
<td>0.00±0.0</td>
</tr>
<tr>
<td>B</td>
<td>Med-HCl</td>
<td></td>
<td>100.8±0.56</td>
<td>136.26±6.0</td>
<td>25.0±2.8</td>
<td>3.70±8.0</td>
<td>47.90±4.4</td>
<td>56.3±5.4</td>
</tr>
<tr>
<td>C</td>
<td>Med-HCl+Ket-HCl</td>
<td></td>
<td>100.6±0.66</td>
<td>133.1±5.9</td>
<td>23.2±2.0</td>
<td>2.65±0.58</td>
<td>54.00±4.4</td>
<td>63.60±7.3</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Groups</th>
<th>Drugs used</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>A</td>
<td>No drugs</td>
<td>3.45±0.51</td>
<td>5.15±0.58</td>
<td>5.65±0.48</td>
<td>4.90±0.64</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Med-HCl</td>
<td>2.95±0.58</td>
<td>2.90±0.64</td>
<td>3.15±0.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Med-HCl+Ket-HCl</td>
<td>4.05±0.60</td>
<td>5.15±0.58</td>
<td>5.65±0.48</td>
<td>4.90±0.64</td>
</tr>
<tr>
<td>Sedation</td>
<td>A</td>
<td>No drugs</td>
<td>1.85±0.48</td>
<td>2.60±0.50</td>
<td>2.80±0.61</td>
<td>2.25±0.44</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Med-HCl</td>
<td>2.50±0.51</td>
<td>2.40±0.61</td>
<td>2.90±0.64</td>
<td>3.55±0.68</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Med-HCl+Ket-HCl</td>
<td>5.05±0.51</td>
<td>5.40±0.61</td>
<td>4.30±0.64</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Groups (n=20 in each group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A (no drugs)</td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
<td>IU/L</td>
<td>186.24±22.6</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>IU/L</td>
<td>13.15±5.0</td>
</tr>
<tr>
<td>Urea</td>
<td>mg/dl</td>
<td>22.62±2.0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dl</td>
<td>0.97±0.07</td>
</tr>
<tr>
<td>Uric acid</td>
<td>mg/dl</td>
<td>2.32±0.11</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>mg/dl</td>
<td>10.78±2.5</td>
</tr>
<tr>
<td>Total leukocyte count</td>
<td>10³/mm³</td>
<td>644±36</td>
</tr>
<tr>
<td>Polymorphs</td>
<td>10³/mm³</td>
<td>25.5±6.5</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>10³/mm³</td>
<td>64.0±6.7</td>
</tr>
<tr>
<td>Monocytes</td>
<td>10³/mm³</td>
<td>3.0±0.81</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>10³/mm³</td>
<td>1.57±0.50</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>mm/hour</td>
<td>1.65±0.48</td>
</tr>
</tbody>
</table>

Mean±SD carrying different superscripts in a row differed significantly (P<0.05).
(Kuusela et al., 2000) for evaluation of analgesia induced by alpha-2 adrenoceptor 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 adrenoceptors 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-adrenoceptors. 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.

REFERENCES


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