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Haemato-Biochemical Comparision of Meloxicam/Ketoprofen in Combination with Atropine-Dexmedetomidine-Butorphanol-Midazolam as Preanasthetic to Ketamine Anaesthesia in Female Dogs

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ABSTRACT

The study was conducted in 12 female dogs undergoing elective ovariohysterectomy divided into two groups of six animals each to evaluate and compare hemato-biochemical findings in meloxicam/ ketoprofen along with atropine - dexmedetomidine - butorphanol - midazolam - ketamine anesthetic combination. Adequate muscle relaxation, sedation and analgesia necessary for surgical intervention were achieved along with smooth and uneventful recovery in all patients. Blood samples were collected at 0min (baseline), 15min, 30min, 45min, 60min and 90min for assessment of Hb, TLC, DLC, plasma urea nitrogen and plasma creatinine. Results were non-significant decrease in Hb, increase in plasma urea nitrogen and increase in plasma creatinine in both the groups. TLC showed non-significant decrease up to 30min followed by gradual increase to baseline. Variation in DLC was clinically insignificant. Both meloxicam and Ketoprofen produced a comparable degree of clinico-physiological and haemodynamic stability in atropine- dexmedetomidine-butorphanol-midazolam - ketamine anaesthetic combination in dogs undergoing elective ovariohysterectomy.

Keywords: Haematobiochemical, meloxicam, ketoprofen, dexmedetomidine, butorphanol, midazolam, dog

Elective ovariohysterectomy is the most frequently performed surgical procedure in companion animal practice (Fox *et al.*, 2000) and the Centre for Veterinary Medicine of the US Food and Drug Administration considers ovariohysterectomy to cause moderate pain, making it suitable for clinical studies of analgesia. An ideal anaesthetic produces sedation, amnesia, analgesia and muscle relaxation. However, all these characteristics cannot be provided by a sole agent and therefore, a combination of drugs is used which is referred to as "balanced anaesthesia" (Thurmon *et al.,* 1996). Premedication makes the patient easier to handle; provides sedative and analgesic effects; and minimizes the total dose of anaesthetics to produce the desired level of anaesthesia (Tranquilli *et al.,* 2007). Injectable anesthetic agents are usually preferred for surgeries of smaller to intermediate duration (Hall and Clarke, 2001).

Atropine causes blockade of acetycholine at postganglionic terminations of cholinergic fibres in the autonomic nervous system which diminishes secretion of mucus in the mouth, throat, respiratory tract and dilates the bronchi (Atkinson *et al.,* 1977). Mostly a lower dose of alpha-2 agonist is associated with a lower degree of sedation and analgesia. Hence, opioids are commonly combined with alpha-2 agonist and benzodiazepines, to increase sedation and analgesia without compromising cardiovascular stability (Rafee, 2013). Administration of dexmedetomidine with butorphanol or ketamine resulted in greater sedative effect, greater muscle relaxation and increased auditory response scores, compared with

administration of dexmedetomidine alone (Selmi *et al.,* 2003).

Meloxicam is COX-2 preferential but not COX-2 specific, which means that at high doses, the specificity of meloxicam for the COX-2 isoenzyme is decreased (Streppa *et al.,* 2002). Meloxicam is in the enolic acid class of NSAIDs. It has analgesic, anti-inflammatory, and antipyretic properties (Brown, 1989). Meloxicam is also efficacious in the management of postoperative pain in dogs and is a safe anti-inflammatory drug used @ 0.2 mg/kg (Andrade *et al.,* 2001).

Ketoprofen inhibits the synthesis of prostaglandin through non-selective COX inhibition, although it appears to be relatively COX-1 selective in dogs (Streppa, 2002). Ketoprofen is a propionic acid derivative of non steroidal anti-inflammatory class of analgesics. It is a inhibitor of both COX-1 and COX-2 and exhibits anti-inflammatory, analgesic, antipyretic and antibradykinin activities (Kay *et al.*, 2000; Streppa *et al.,* 2002).

The present study was undertaken for Haemato-biochemical comparision of meloxicam/ketoprofen in combination with atropine-dexmedetomidine-butorphanol-midazolam as preanaesthetic to ketamine anaesthesia in clinical cases of female dogs presented for ovariohysterectomy.

MATERIALS AND METHODS

The study was conducted on totally 12 healthy female dogs scheduled for elective ovariohysterectomy aged between 1 to 4 years that demonstrated no abnormalities on physical examination. Animals were randomly allocated, via coin toss, into two treatment groups of six animals each. The groups of animals were designated as group A-1 and A-2 on the basis of use of either meloxicam or Ketoprofen for pre-anaesthetic combination with atropine-dexmedetomidine-butorphanol-midazolam during ketamine anaesthesia.

Animals were fasted for 12hrs prior to surgery. Atropine was given @ 0.04 mg/kg body wt. IM and meloxicam @ 0.1mg/kg body wt. SC (group A-1) or ketoprofen @ 1mg/kg body wt. SC (group A-2). After 5minutes, dexmedetomidine @10µg/kg. body wt., midazolam @ 2mg/kg. body wt. and butorphanol @ 0.2mg/kg. body wt. was administered IM. Induction of anesthesia was made after 15minutes of the preanesthetic medication by administration of ketamine intravenously 5mg/kg. body wt. Maintenance of anesthesia was done by incremental doses of ketamine as and when needed during surgery. The animals were left undisturbed for 10 min and oxygen-haemoglobin saturation (SpO2) was monitored with pulse-oxymeter. All surgical procedures were performed by experienced surgeons. Ringer lactate solution was administered IV at a rate of 10 ml/kg body wt.

Blood samples were collected at 0min (base line), 15min, 30min, 45min, 60min and 90min from the time of premedication administration. Haematological and biochemical parameters viz., haemoglobin (Hb), total leucocyte count (TLC), differential leucocyte count (DLC), blood urea nitrogen by diacetyl monoxide (DAM) method and plasma creatinine by alkaline picrate method were estimated at different time intervals. The mean and standard error for all the parameters were computed. The variations in the clinical and biochemical parameters at different time intervals for both the groups were analyzed by two way analysis of variance. The comparison between means of groups within and between groups and periods among the treatments were compared by least square significance difference test (LSD test) using SPSS software.

RESULTS AND DISCUSSION

Mean surgery time was 30 min (standard deviation (*s*) = 8 min) for the group A-1 and 32 min (*s* = 9 min) for the group A-2. The difference was not statistically significant. The mean ± standard deviation values for haematological and biochemical parameters recorded in group A-1 and group A-2 animals at different intervals are presented in Table -1 and Table -2 respectively.

Haemoglobin (Hb) (g/dl)

Hb values decreased significantly in the animals of both the groups in the initial 30min of recording and thereafter increased gradually towards normal. In group A-1 mean baseline (0min) Hb level was 14.15± 0.19 and mean Hb level after administration of anesthetics ranged from 12.20± 0.28 to 12.93± 0.19. In group A-2, the mean baseline (0min) Hb level was 13.95 ± 0.24 mean Hb level after administration of anesthetics ranged 12.25± 0.22 to 12.80± 0.21 g/dl. The variation in mean Hb level from base line to 90min was significant in both group, however,

Table 1: Comparative mean values of haemato-biochemical parameters in dogs administered with meloxicam (group A-1; n=6) / ketoprofen (group A-2; n=6) in anesthetic combination.

Parameters	Time interval					
	0 min	15 min	30 min	45 min	60 min	90 min
Haemoglobin (g/dl)						
A-1	14.15±0.19[a]	12.45±0.26[b]	12.20±0.28[b]	12.48±0.28[b]	12.73±0.26[b]	12.93±0.19[b]
A-2	13.95±0.24[a]	12.25±0.20[b]	12.25±0.22[b]	12.42±0.20[b]	12.65±0.22[b]	12.80±0.12[b]
Total leukocyte count (thousands/µL)						
A-1	12.93±0.22[a]	12.50±0.28[a]	12.54±0.35[a]	12.65±0.38[a]	12.69±0.26[a]	12.79±0.24[a]
A-2	12.25±0.28[a]	11.90±0.28[a]	12.62±0.39[a]	12.94±0.41[a]	12.65±0.37[a]	11.97±0.32[a]
Neutrophils (%)						
A-1	79.50±1.38[a]	76.00±1.65[a]	75.67±1.40[a]	76.83±1.86[a]	77.17±1.68[a]	78.83±1.58[a]
A-2	77.90±1.59[a]	75.50±2.18[a]	74.17±1.42[a]	75.50±1.91[a]	76.67±0.99[a]	77.17±1.11[a]
Lymphocyte(%)						
A-1	16.83±1.38[a]	18.00±1.77[a]	19.83±1.85[a]	19.17±1.92[a]	19.83±1.76[a]	18.50±1.28[a]
A-2	18.50±1.15[a]	19.00±1.44[a]	20.00±1.29[a]	19.67±1.28[a]	18.00±1.29[a]	18.00±1.26[a]
Eosinophils(%)						
A-1	3.50±0.34[a]	4.00±0.36[a]	4.67±0.42[b]	4.50±0.22[b]	4.17±0.31[a]	4.00±0.26[a]
A-2	3.33±0.56[a]	4.00±0.36[a]	4.67±0.42[b]	5.00±0.26[b]	4.67±0.21[b]	3.83±0.17[a]
Monocytes(%)						
A-1	2.67±0.42[a]	1.67±0.21[b]	1.50±0.22[b]	0.33±0.21[b]	0.50±0.22[b]	1.67±0.17[b]
A-2	2.83±0.48[a]	1.50±0.34[b]	0.33±0.21[b]	0.50±0.22[b]	0.83±0.17[b]	0.83±0.17[b]
Plasma urea nitrogen(mg/dl)						
A-1	15.23±2.56[a]	15.72±2.34[a]	17.24±3.13[a]	19.56±2.13[a]	21.76±1.11[a]	22.35±2.23[a]
A-2	15.80±2.12[a]	16.02±2.16[a]	18.02±1.15[a]	19.67±2.25[a]	20.80±2.14[a]	21.23±3.15[a]
Plasma creatinine (mg/dl)						
A-1	0.82±0.05[a]	0.83±0.04[a]	0.84±0.06[a]	0.85±0.04[a]	0.86±0.05[a]	0.87±0.03[a]
A-2	0.84±0.03[a]	0.04±0.04[a]	0.85±0.03[a]	0.86±0.04[a]	0.87±0.04[a]	0.88±0.03[a]

Note: Significant (P≤0.05) – Means bearing common superscript do not differ significantly with each other when compared to baseline (0 min).

in both the groups the reduction was within in normal range. Between the groups the mean Hb level variation within the study period was statistically non-significant. The transient decline was in response to anaesthesia and blood loss during surgery (Coles 1984).

Total leukocyte count (TLC) (thousands/µL)

In both the groups the mean TLC level decreased at 15min recording and thereafter the level gradually increased. The mean base line TLC in group A-1 was 12.93±0.22 and post-anesthetic administration the range of TLC was 12.50±0.28 to 12.79± 0.24. In Group A-2 baseline value was 12.25±0.28 and post-anesthetic mean TLC ranged from 11.90±0.28 to 12.24± 0.32. However, the variation in the leukocyte count at different time interval within the groups and between the groups was statistically non-significant.

Pooling of circulatory blood cells in the spleen or other reservoirs secondary to decreased sympathetic activity may explain the decrease in Hb and TLC recorded in the present study (Wagner *et al*., 1991). Similar observations were recorded in ketamine anesthesia in dogs (Sravanti *et al.,* 2016). Reduced Hb and TLC values have also been reported following administration of dexmedetomidine-pentazocine-midazolam in dogs (Rafee, 2013) .

Differntial leukocyte count

Neutrophils level declined till 30min of recording and then increased gradually. Concurrent increase in lymphocyte, eosinophils and monocytes level was noticed till 30min of recording followed by gradual decrease. The deferential leukocyte count during study period in all the animals of both groups was within normal physiological range thereby rendering them clinical insignificant. Similar observations were also made by Hall and Clarke (2001) and Udegbunam *et al.* (2009).

Plasma urea nitrogen (mg/dl)

The mean base line plasma urea nitrogen values in group A-1 was 15.23±2.56 and in group A-2 was 15.80±2.12. The level gradually increased till 90min ranging from 15.72±2.34 to 22.35± 2.23 in group A-1 and from 16.02±2.16 to 21.23± 3.15 in group A-2. The increased values were non-significant throughout the observation period. The urea nitrogen values increase temporarily due to inhibitory effects of anaesthetic drugs on the renal blood flow, which in turn causes a rise in plasma urea nitrogen level as suggested by Kinjavdekar *et al.,* (2000). A non-significant increase in blood urea nitrogen has been reported following use of medetomidine along with butorphanol in dogs (Ahmad, 2010; Santhosh, 2011). A non-significant increase in BUN values have also been reported following administration of dexmedetomidine-butorphanol/pentazocine as preanaesthetic followed by induction with midazolam and maintenance with ketamine in dogs (Rafee, 2013). A non-significant increase in blood urea nitrogen has been reported following use of midazolam-dexmedetomidine in dogs (Ahmad, 2010; Santhosh, 2011).

Plasma creatinine (mg/dl)

Plasma creatinine values increased non-significantly throughout the observation period in animals of both the groups. However, the values were within the normal physiological range. The mean base line plasma creatinine value in group A-1 was 0.82±0.05. The mean plasma creatinine value ranged from 0.83±0.04 to 0.87± 0.03. In group A-2, the mean base line plasma creatinine value was 0.84±0.03. The mean plasma urea nitrogen value ranged from 0.84±0.04 to 0.88± 0.03. Between the groups the variation in mean creatinine values within the period was statistically non-significant. Creatinine values were reported to increase non-significantly following administration of butorphanol along with xylazine and medetomidine (Surbhi *et al.,* 2010). A non-significant increase in creatinine values have been reported following medetomidine-ketamine anaesthesia in dogs (Chonde *et al.,* 2004). A non-significant variation in blood creatinine value has been recorded following administration of dexmedetomidine along with butorphanol (Ahmad, 2010; Santhosh, 2011) in dogs.

CONCLUSION

Based on the present study, following conclusions were drawn: meloxicam/ketoprofen in combination with atropine-dexmedetomidine-butorphanol-midazolam as preanasthetic to ketamine anaesthesia induced good analgesia, muscle relaxation and sedation in female dogs. Both meloxicam and ketoprofen did not produced significant degree of variation in Haemato-biochemical parameters and haemodynamic stability during ketamine anaesthesia in dogs undergoing elective ovariohysterectomy. Preoperative administration of both meloxicam and ketoprofen are safe and may be recommended for balanced anaesthesia.

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