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S Dharmaceelan
Professor and Head, Department of Veterinary Surgery and Radiology, Veterinary College and Research Institute, TANUVAS, Tirunelveli, Tamil Nadu, India

R Manikandan
Veterinary Officer, Milkymist MCC, Velliyampalayam pirivu, Pukkulam post, Udumalpet Taluk, Tiruppur District, Tamil Nadu, India

K Jayakumar
Assistant Professor, Department of Veterinary Surgery and Radiology, Veterinary College and Research Institute, TANUVAS, Namakkal, Tamil Nadu, India

S Senthilkumar
Assistant Professor, Teaching Veterinary Clinical Complex, Veterinary College and Research Institute, TANUVAS, Orathanad, Tamil Nadu, India

P Selvaraj
Professor and Head, Department of Veterinary Physiology and Biochemistry, Veterinary College and Research Institute, TANUVAS, Namakkal, Tamil Nadu, India

Correspondence
S Dharmaceelan
Professor and Head, Department of Veterinary Surgery and Radiology, Veterinary College and Research Institute, TANUVAS, Tirunelveli, Tamil Nadu, India

Haemato-biochemical alterations and stress response to pre-emptive administration of meloxicam, ketoprofen, tolfenamic acid and flunixin in dogs

S Dharmaceelan, R Manikandan, K Jayakumar, S Senthilkumar and P Selvaraj

Abstract
A clinical research was conducted in 24 dogs which were randomly divided into four groups viz., group I, II, III and IV to evaluate the haemato-biochemical changes and stress response by addition of preemptive meloxicam (0.2mg/kg), ketoprofen (2.0mg/kg), tolfenamic acid (4.0mg/kg) and flunixin (1.0mg/kg) in the anaesthetic protocol following Ovariohysterectomy (OHE) in dogs. After 15 minutes, midazolam was administered at the dose rate of 0.3mg per kg to all the animals. General anaesthesia was induced with propofol at the dose rate of 6 mg/kg in all the animals and maintained with isoflurane. Haemoglobin (Hb) in g per dL, packed cell volume (PCV) in per cent (%), total erythrocyte count (TEC) in millions per microliter (10^6 /µL), total leucocyte count in thousands per microliter (10^3 /µL), platelet count in Lakhs per microliter (10^5/µL), Serum urea nitrogen (mg/dL), serum creatinine (mg/dL), and serum cortisol (ng/ml) were measured before premedication, immediately, 3 h and 12 h after surgery in all animals. The results revealed a significant (p<0.05) reduction in Hb, PCV and TEC immediately after surgery and 3 h of surgery in all the groups. There was no significant difference in platelet count between different time intervals, but difference was noticed among the groups. Biochemical parameters studied were within physiological range but showed a significant increase (p<0.05) immediately after surgery and at 3 h of surgery. The cortisol level increased immediately after surgery and at 3 h of surgery in all the animals.

Keywords: Haematology, biochemical, dogs, meloxicam, ketoprofen, tolfenamic acid and flunixin, general anaesthesia, preemptive

Introduction
Preemptive analgesia refers to the application of analgesics prior to exposing patients to noxious stimuli. This prevents the exposure of spinal cord to the barrage of afferent nociceptive impulses that causes central hypersensitivity. It is considered as the most effective means of controlling post-operative pain (Tranquilli *et al*., 2007) [13]. The 'protective' effect on the nociceptive pathways provided by the preemptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented (Dahl and Moiniche, 2004) [4]. Postoperative pain is commonly treated by administration of opioids and/or nonsteroidal anti-inflammatory drugs (NSAIDs). Opioids are effective analgesics but may be accompanied by sedation, dysphoria, respiratory, and cardiovascular depression, especially at high doses. Considering these adverse effects, the potential for theft and personnel abuse within a practice setting, an alternative to opioid analgesia is desirable from both a medical and an administrative aspect (Mathews, 1996) [9]. NSAIDs have been used successfully to control postoperative pain in dogs for the long period of time, but dogs are more susceptible to the adverse effects. NSAID administration for postoperative analgesia in dogs may be associated with side effects on renal function, on the gastrointestinal tract, and on coagulation. Appropriate dosing may increase the efficiency of NSAIDs, minimize the side effects and can safely be used for the management of postoperative pain in dogs. The present study was formulated to assess the haemato-biochemical and stress response to pre-emptive administration of meloxicam, ketoprofen, tolfenamic acid and flunixin in dogs.

Materials and methods
The study was conducted at Veterinary Clinical Complex, Veterinary College and Research Institute, Namakkal for a period of one year on clinical cases registered for elective

ovariohysterectomy in dogs. Twenty four numbers of healthy, non-oestrus, non pregnant, non lactating female dogs were selected for the study. Twenty four animals were randomly divided into four groups viz., group I, II, III and IV comprising of six animals each. Food was withheld for 12 h and water for 3 h before anaesthetic trials in all the dogs and right flank was prepared aseptically for ovariohysterectomy. All the animals were premedicated with atropine at the dose rate of 0.02mg/kg subcutaneously (s.c). Immediately after atropine administration, meloxicam, ketoprofen, tolfenamic acid and flunixin were administered at the dose rates of 0.2, 2.0, 4.0 and 1.0 mg/kg intravenously in group I, II, III and IV animals, respectively. After 5 min, midazolam was administered at the dose rate of 0.3 mg per kg body weight intravenously to all the dogs. Anaesthesia was induced with propofol at the dose rate of 6 mg per kg body weight in all the dogs intravenously. The maintenance of general anaesthesia was carried out with isoflurane. The haematological parameters were estimated by collecting 5 ml of venous blood from the cephalic vein in EDTA tube before premedication after surgery, 3 h and 12 h after surgery in all animals. Haemoglobin (Hb) in g per dL, packed cell volume (PCV) in per cent (%), total erythrocyte count (TEC) in millions per microliter (10^6 /µL), total leucocyte count in thousands per microliter (10^3 /µL), platelet count in Lakhs per microliter (10^5/µL) were measured. 5 ml of blood sample was collected from the cephalic vein in the sterilized test tubes before premedication, immediately after surgery, 3 h and 12 h after surgery in all the animals and allowed to clot. The clotted blood was centrifuged and serum separated. The separated serum samples were collected in 2 mL vials and stored at –20ºC till analysis. Serum urea nitrogen, creatinine and cortisol levels were estimated.

Results and Discussion

The haemoglobin, packed cell volume, total erythrocyte, total leukocyte and platelet count estimated before premedication, immediately after surgery, 3 h and 12 h after surgery are presented in Tables 1, 2 and 3. A significant ($p<0.05$) reduction in HB and PCV values immediately and 3 h after surgery in all the groups were observed and could be due to red blood cell sequestration to the spleen caused by isoflurane as reported by Bishop (2005) [1] as well as anaesthetic induced adrenergic suppression resulting in splenic capsular relaxation and migration of interstitial fluid into the circulating compartment. Kushwaha *et al.* (2012) [7] observed a significant fall in PCV after 10 min of anaesthesia and the reduced PCV was attributed to haemorrhage and haemodilution as a result of increased secretion of anti-diuretic hormone associated with surgery. The total erythrocyte count was reduced immediately after surgery, 3 h and 12 h after surgery in all the groups. The reduction in red blood cells could be attributed to haemorrhage, haemodilution and administration of intravenous fluids (Rosin, 1981) [11]. The total leucocyte count at all time intervals of anaesthesia did not differ significantly at any of the time interval. But a significant ($p<0.05$) difference in group II was observed when compared to other groups. The higher platelet count with use of meloxicam compared to other group could be attributed to the minimal anti-thromboxane activity of meloxicam which act and inhibit COX-2 receptor than COX-1 (Brainard *et al.*, 2007) [2]. The significant ($p<0.05$) reduction in platelet count in tolfenamic acid group compared to ketoprofen and flunixin could be attributed to the more potent anti-thromboxane activity.

The serum urea nitrogen and creatinine significantly ($p<0.05$) increased immediately after surgery and 3 h after surgery compared to before premedication and 12 h after surgery in all the animals. The values were within the physiological limits. It could be attributed to the preemptive administration of NSAIDs which inhibits the production of prostaglandin E_2 and prostaglandin I_2 responsible for renal blood flow maintenance. The reduction in cardiac output caused by sedative and anaesthetic agents affects the renal blood flow and delays the urea nitrogen clearance. These could be the reason for the increase in serum urea nitrogen and creatinine in all the animals. The results of the study concur with the findings of Forsyth *et al.* (2000) [6], Caulkett *et al.* (2003) [3], Erdogan *et al.* (2003) [5] and Mathews (1996) [6]. However, Luna (2007) [8] reported that, the use of meloxicam in dogs did not modify serum biochemical values and urinalysis. The author further stated renal failure and potential risk for renal damage with the use of flunixin during methoxyflurane anaesthesia.

The cortisol estimation at various time intervals was used to assess the stress level associated with postoperative pain. The prostaglandins were important signal transducers in basal stress conditions and they stimulate the secretion of corticotrophin releasing hormone (CRH), vasopressin and ACTH, but also steroidogenesis and the release of corticosterone by acting directly on the adrenal gland. The decreased cortisol level was reported to be caused by the decreased synthesis of prostaglandins via COX inhibition (Yilamaz *et al.*, 2014) [14]. The serum cortisol level recorded immediately after surgery and 3 h after surgery was significantly ($p<0.05$) higher compared to before premedication and 12 h after surgery values in all the groups. The elevated serum cortisol level indicates that the cortisol release and stress response to anaesthesia and surgery in the immediate postoperative period were not prevented. The serum cortisol after 12 h of surgery was significantly ($p<0.05$) lower in all the groups than before premedication value. This could be attributed to the analgesia provided by the meloxicam, ketoprofen, tolfenamic acid and flunixin resulting in decreased cortisol release and stress response. This concurs with the reports of Nakagawa *et al.* (2007) [10]. However, Selmi *et al.* (2009) [12] observed that post-operative plasma cortisol level after ovariohysterectomy surgery in dogs was significantly ($p<0.05$) increased from preoperative value after one hour of surgery and it reduced to the base line value after 6h of surgery. Yilamaz *et al.* (2014) [14] observed the similar findings in OHE undergone dogs.

Table 1: Mean ± S.E of haematological parameters

Parameter	Group	Before premedication	Immediately after surgery	3 hours after surgery	12 hours after surgery
Haemoglobin (g/dL)	I	13.30^{bp}±1.50	11.22^{ap}±0.46	11.66^{ap}±0.53	12.70^{ap}±0.53
	II	13.01^{bp}±1.35	11.50^{ap}±0.44	11.76^{ap}±0.43	11.96^{ap}±0.48
	III	12.86^{bp}±1.35	10.97^{ap}±0.80	11.27^{ap}±0.71	12.11^{ap}±0.80
	IV	12.64^{bp}±1.24	11.92^{ap}±0.66	10.80^{ap}±0.66	12.17^{ap}±0.69
Packed cell volume (per cent)	I	40.20^{bp}±2.86	33.66^{ap}±1.37	34.98^{ap}±1.50	37.66^{abp}±2.98
	II	39.28^{bp}±2.59	34.50^{ap}±1.33	35.16^{ap}±1.54	35.77^{abp}±2.34
	III	38.58^{bp}±2.77	32.91^{ap}±2.41	33.83^{ap}±2.29	36.35^{abp}±2.69
	IV	37.90^{bp}±2.55	35.76^{ap}±2.52	32.4^{ap}±1.87	36.51^{abp}±2.48
Total erythrocyte count ($x10^6$/µL)	I	6.78^{bp}±0.42	5.90^{ap}±0.38	6.15^{abp}±0.36	6.35^{bp}±0.47
	II	6.75^{bp}±0.47	6.03^{ap}±0.46	6.16^{abp}±0.46	6.20^{bp}±0.45
	III	6.58^{bp}±0.52	5.60^{ap}±0.53	5.81^{abp}±0.54	6.08^{bp}±0.49
	IV	6.28^{bp}±0.47	5.45^{ap}±0.48	5.65^{abp}±0.47	5.93^{bp}±0.43
Total leukocyte count ($x10^3$/µL)	I	12.13^{aq}±1.08	12.15^{aq}±1.02	12.35^{aq}±0.87	12.56^{aq}±1.14
	II	11.68^{apq}±0.87	11.90^{apq}±0.83	12.15^{apq}±0.76	12.51^{apq}±0.79
	III	12.10^{aq}±0.80	12.36^{aq}±0.80	12.60^{aq}±0.80	13.03^{aq}±0.75
	IV	10.73^{aq}±0.64	10.88^{aq}±0.68	11.08^{aq}±0.66	11.30^{aq}±0.71

Column-wise group means with different superscript (pq) differ significantly ($p<0.05$).
Row-wise group means with different superscript (ab) differ significantly ($p<0.05$).

Table 2: Mean ± S.E of platelet count

Parameter	Group	Before premedication	Immediately after surgery	3 hours after surgery	12 hours after surgery
Platelet count ($x10^5$/µl)	I	2.63^{aq}±0.28	2.50^{aq}±0.27	2.56^{aq}±0.28	2.60^{aq}±0.29
	II	2.59^{apq}±0.13	2.39^{apq}±0.10	2.47^{apq}±0.11	2.58^{apq}±0.14
	III	2.64^{ap}±0.20	2.27^{ap}±0.17	2.34^{ap}±0.17	2.48^{ap}±0.17
	IV	2.60^{apq}±0.15	2.37^{apq}±0.14	2.43^{apq}±0.15	2.50^{apq}±0.16

Column-wise group means with different superscript (pq) differ significantly ($p<0.05$).
Row-wise group means with different superscript (a) differ significantly ($p<0.05$).

Table 3: Mean ± S.E of serum urea nitrogen, creatinine, cortisol values

Parameter	Group	Before premedication	Immediately after surgery	3 hours after surgery	12 hours after surgery
Urea nitrogen (mg/dL)	I	26.96^{ap}±1.01	28.11^{bp}±1.19	27.21^{bp}±1.32	26.91^{ap}±1.29
	II	27.15^{ap}±1.28	30.90^{bp}±0.81	28.98^{bp}±0.87	26.23^{ap}±1.13
	III	26.28^{ap}±0.90	30.25^{bp}±0.75	28.15^{bp}±0.78	25.50^{ap}±0.86
	IV	25.75^{ap}±0.64	28.51^{bp}±0.47	26.25^{bp}±0.46	26.41^{ap}±0.75
Creatinine (mg/dL)	I	1.08^{ap}±0.04	1.10^{bp}±0.04	1.08^{bp}±0.03	1.00^{ap}±0.02
	II	1.09^{ap}±0.04	1.14^{bp}±0.03	1.09^{bp}±0.04	1.06^{ap}±0.03
	III	1.12^{ap}±0.04	1.18^{bp}±0.04	1.13^{bp}±0.03	1.08^{ap}±0.02
	IV	1.11^{ap}±0.03	1.20^{bp}±0.03	1.15^{bp}±0.01	1.04^{ap}±0.04
Cortisol(ng/mL)	I	29.06^{ap}±2.26	39.50^{bp}±2.20	51.33^{cp}±2.23	26.30^{ap}±1.71
	II	22.83^{ap}±1.64	47.16^{bp}±2.83	57.23^{cp}±2.83	26.66^{ap}±1.65
	III	25.83^{ap}±1.19	43.66^{bp}±3.20	51.50^{cp}±3.40	26.66^{ap}±1.20
	IV	23.16^{ap}±1.14	45.67^{bp}±1.40	50.83^{cp}±2.17	27.33^{ap}±1.61

Column-wise group means with different superscript (p) differ significantly ($p<0.05$).
Row-wise group means with different superscript (abc) differ significantly (p

Conclusion

To conclude, inclusion of meloxicam, ketoprofen, tolfenamic acid and flunixin in the anaesthetic protocol during ovariohysterectomy in dogs did not produce significant alterations in haemato biochemical parameters.

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Conflict of interest

Authors declare that there is no conflict of interests regarding the publication of this article.

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