Research Article

Comparison of the Sedative, Analgesic, Behavioral, Hematological and Serum Biochemistry Effects of Four Analgesics in Dogs

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Abstract | This study compares the sedative, analgesic and behavioral effects with the detection of changes in vital signs and blood values following injection of Nalbuphine HCl, Fentanyl citrate, Tramadol HCl and Meloxicam in dogs. Forty clinically healthy mongrel dogs were randomly divided into 4 groups (10 dogs each) according to the analgesic agent used. Doses of 0.5mg/kg Nalbuphine HCl, 5µg/kg Fentanyl citrate, 2mg/kg Tramadol HCl and 0.2mg/kg Meloxicam were given IV in groups A, B, C and D, respectively. The zero time for evaluation was 10 min for Nalbuphine HCl, 45 min for Tramadol HCl, 7 min for Fentanyl citrate and one hour for Meloxicam. The dogs were evaluated every15 min interval for up to 90 minutes. Assessments included the degree of analgesia, sedation, behavioral abnormalities and changes on vital signs, hemogram and serum biochemistry. Statistical analysis was carried out by paired samples *t*-test. Unlike Nalbuphine HCl, Fentanyl citrate and Tramadol HCl, Meloxicam induced better analgesia, no significant changes in total leukocytes, neutrophil, eosinophil, lymphocyte and monocyte counts, serum levels of total protein (TP), albumin, urea, creatinine, creatinine clearance and serum enzymatic activities of alanine transaminase (ALT) and aspartate transaminase (AST) along the whole experiment. Meloxicam induced no sedation, no behavioral changes, insignificant increase in heart rate, significant increase in systolic, diastolic and mean blood pressure and significant increase in respiratory rate after 15 and 30 minutes. In conclusion, meloxicam is more safe and effective analgesic than Nalbuphine HCl, Fentanyl citrate and Tramadol HCl in dogs.

Keywords | Dogs, Fentanyl citrate, Meloxicam, Nalbuphine hydrochloride, Tramadol hydrochloride

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INTRODUCTION

In veterinary practice, it is necessary to alleviate sings of pain in animals undergoing different surgeries. For several decades opioids have been used as the sole analgesic agents for this aim. Later, nonsteroidal anti-inflammatory drugs (NSAIDs) with preferential cyclo-oxygenase-2 (Cox-2) inhibition properties, such as Carprofen and Meloxicam, have been applied in the preoperative period (Mathews et al., 2001; Slingsby et al., 2001).

Analgesics can be given before surgery as preemptive analgesia that aims at inhibition of central sensitization (Raffe, 1997; Lascelles, 1999). Also, adding of these

analgesics to anesthetic protocols has many advantages like decreasing the amount of anesthetics required to induce surgical anesthesia, stabilizing anesthetic depth, reducing overall patient morbidity associated with surgery and anesthesia and reduction of post-operative pain (Muir, 2002; Abu-Seida, 2012).

Opioids are morphine-like agents that bind to opioid receptors and raise the pain threshold through acting at the receptors in the dorsal horn of the spinal cord and mesolimbic system (Benson, 2002). There are at least three different receptors for opioids: mu, delta, and kappa (μ, δ, κ) (Heavner and Cooper, 2008).

Nalbuphine HCl is agonist-antagonist opioid that is competitive μ-receptor antagonists, but exerts its analgesic effects by acting as agonists at κ receptors. Moreover, Nalbuphine HCl induces mild analgesia with minimal sedation, little reduction of ventilation and miosis (Benson, 2002; Lamont and Mathews, 2007).

Fentanyl citrate is a synthetic μ-opioid agonist with an analgesic potency that is 75 to 125 times the potency of morphine (Hellyer et al., 2001). Moreover, Fentanyl citrate is more lipid soluble than morphine with rapid onset and short duration of action. Its peak analgesic effect occurs in about 5 minutes and lasts approximately for 30 minutes (Gutstein and Akil, 2001). Therefore, it is suitable as an intra-operative analgesic (Mendes and Selmi, 2003).

Tramadol HCl is a centrally acting 'atypical' opioid analgesic with a dual mechanism of action, namely, the interaction with opioid μ receptors and the monoaminergic effect through inhibition of the reuptake of norepinephrine and serotonin (Haeseler et al., 2006). Moreover, Tramadol HCl has lower tolerance in animals than morphine because of its non-opioid mechanism of action (Miranda and Pinardi, 1998). One of the active metabolites of Tramadol HCl is Odesmethyltramadol (M1), which has a 200 times higher μ-opioid receptor binding action than Tramadol HCl so that its production is necessary for the anti-nociceptive actions of Tramadol HCl (Ide et al., 2006). Tramadol HCl induces analgesia equivalent to morphine (Mastrocinque and Fantoni, 2003) and it is recommended in chronic pain conditions that have opioid resistance (Raffa, 2001).

Meloxicam is NSAID that derives much of its anti-inflammatory actions from its ability to inhibit the synthesis of prostaglandins (PG) by inhibiting the effect of cyclooxygenase (Jones and Budsberg, 2000). In addition, it inhibits the actions of inflammatory mediators such as histamine, bradykinin, and other kinins on peripheral sensory receptors (Amadio et al., 1997). Central antinociceptive actions have also been suggested because NSAIDs may act on excitable membranes, on second messenger systems, or in the expression of inflammatory mediators (Budsberg, 2002).

Many analgesics have adverse effects on the cardiovascular and respiratory systems, hepatic, renal and gastrointestinal functions, hematology, serum biochemistry, animal's behavior and vital signs (Day, 2002; Lamont and Mathews, 2007; Heavner and Cooper, 2008; Torad and Hassan, 2018). Therefore, this study compares the sedative and analgesic effects as well as the changes in animal's behavior, vital signs and blood values following injection of Nalbuphine HCl, Fentanyl citrate, Tramadol HCl and Meloxicam in dogs.

MATERIALS AND METHODS

Ethical approval

The study was approved by the Institutional Animal Care and Use Committee at Faculty of Veterinary Medicine, University of Sadat City, Egypt.

Animals

This experiment was carried out on 40 mongrel dogs of different ages (1.92±0.45 years), weights (18.24±1.4 kg) and of both sexes. Each dog was subjected to complete physical, hematological and biochemical examinations in order to exclude any diseased dog.

Before the experiment, all dogs were fasted (withholding of food for 12h and water for 2h). Both cephalic veins were catheterized through intravenous catheters (18 gauges) for blood samples collection and administration of analgesics. The middle third of the tail was clipped for placement of pulse oximetry probe.

Experimental design

Dogs were acclimated to the examination room at 27°C for one hour before the experiment. The dogs were randomly divided into 4 groups (10 dogs each) according to the type of the analgesic agent used. These groups included:

Group (A): Nalbuphine HCl (Nalufin®, Amoun Pharmaceutical Company, Cairo, Egypt) was given IV at a dose of 0.5mg/kg (Murphy and Hug, 1982).

Group (B): Fentanyl citrate (Fentanyl-Janssen ®, ADWIA Company, 10th of Ramadan city, Egypt) was given IV at a dose of 5 μg/ kg, IV (Psatha et al., 2011).

Group (C): Tramadol hydrochloride (Amadol®, Janssen Pharmaceutica, Beerse, Belgium) was given IV at a dose of 2 mg/kg (Vettorato et al., 2010).

Group (D): Meloxicam (Meloxi Del®, Delta Pharma, 10th of Ramadan city, Egypt) was given IV at a dose of 0.2mg/kg (Mathews et al., 2001).

All animals were injected by the same experienced veterinarian (AAH) throughout the study. Also, the

animals were evaluated by two veterinarians who were blind with the given analgesic (SMG and FAT).

The zero time for starting evaluation of these analgesics was 10 min for Nalbuphine HCl (Murphy and Hug, 1982), 45 min for Tramadol HCl (Seddighi et al., 2009), 7 min for Fentanyl citrate (Hall et al., 2001a) and one hour for Meloxicam (Lemke and Creighton, 2010). After these points, the dogs were evaluated every15 min interval for up to 90 min.

Methods of evaluation

Each analgesic was assessed through the following parameters:

Degree of analgesia

Analgesia was assessed according to the dog's response to painful stimuli such as pinprick and pressure from hemostat clamp on the skin of thoracic and abdominal wall and toe pinch response. Deep muscles prick was evaluated when no response to superficial skin bricks was reported to confirm complete analgesia.

The response to standard noxious stimulus was used to assess the degree of analgesia according to the following scale (Torad et al., 2009):
Grade 0: Normal response to a painful stimulus.
Grade 1 (Mild analgesia): depressed reaction to a painful stimulus.
Grade 2 (Moderate analgesia): no response to skin pricks
Grade 3 (Complete analgesia): no response to muscle pricks.

Degree of sedation

The degree of sedation was assessed using the following scale (Valverde et al., 2004):
Grade 0 (No sedation): Active animal
Grade 1 (Mild sedation): Less alert but still active
Grade 2 (Moderate sedation): Drowsy and recumbent but can walk
Grade 3 (Intense sedation): Very drowsy and unable to walk.

Behavioral evaluation

After injection, any abnormal behavior like vomiting, diarrhea, panting, defecation, salivation, nasal secretion, struggling, rigidity, biting, wide-eye expression, vocalization, shivering, leg withdrawal, orienting, hiding, or abnormal respiration was reported according to Lester et al. (2003).

Determination of vital signs

Vital signs including heart rate, blood pressure, respiratory rate, oxygen saturation and rectal temperature were evaluated.

Heart rate (HR) was measured via auscultation (Ko et al., 2006). Respiratory rate (RR) was measured by visual observation to thoracic motion (Lemke et al., 2002).

Noninvasive measurements of systolic arterial pressure (SAP), diastolic (DAP) and mean arterial pressure (MAP) were performed via a calibrated oscillometric blood pressure monitor (Contec patient monitor®, CMS 5000, Contec medical systems Co, Qinhuangdao, China) and metatarsal site was selected for cuff placement (Reusable neonate NIBP cuff, 7-13cm) according to Psatha et al. (2011).

Oxygen saturation (SPO_2) was estimated by placing the pulse oximetry probe (infant SPO_2 pulse oximeter of Contec patient monitor®) on the clipped portion of the tail (middle third).

Rectal temperature was determined using clinical thermometer.

All vital signs were assessed at triplicates and the mean was calculated.

Determination of hematological parameters

The evaluated hematological parameters included red blood cell count (RBCs), packed cell volume (PCV), hemoglobin concentration (Hb), total leucocytic count (TLC), differential leucocytic counts and platelet count (Feldman et al., 2000).

Determination of serum biochemical parameters

Serum samples were assessed for concentrations of TP, albumin, glucose, urea, creatinine, and serum enzymatic activities of ALT and AST. Study of creatinine clearance was also performed. These variables were determined by spectrophotometer and commercial kits (Biodiagnostic, Egypt).

The previously mentioned variables were determined at baseline, start time, and every 15 min along an observation period of 90 min from the start time (15, 30, 45, 60, 75 and 90 min).

Statistical analysis

The statistical analysis of the data was carried out using paired samples *t*-test to compare cardiorespiratory, temperature, hematologic and biochemical parameters at baseline with the following measurement times. Values obtained were expressed as mean±SE. The differences were considered to be significant when $P < 0.05$. Statistical analysis was done with IBM® SPSS® Statistics Version 20 for Windows (IBM Corporation, NY, USA).

RESULTS AND DISCUSSION

Analgesic effects

The grades of analgesia of the four tested analgesics at different evaluation times are collected in Table 1.

Sedative effects

The grades of sedation of the four tested analgesics at different evaluation times are collected in Table 2.

Table 1: Analgesic effect of the tested analgesics at different evaluation times.

Times	Nalbuphine HCl	Fentanyl citrate	Tramadol HCl	Meloxicam
Baseline	Grade 0	Grade 0	Grade 0	Grade 0
Start time	Grade 0-1	Grade 1-2	Grade 0-1	Grade 1-2
15 min	Grade 0-1	Grade 1-2	Grade 0-1	Grade 1-2
30 min	Grade 0-1	Grade 1-2	Grade 0-1	Grade 1-2
45 min	Grade 0-1	Grade 0-1	Grade 0-1	Grade 1-2
60 min	Grade 0-1	Grade 0	Grade 0-1	Grade 1-2
75 min	Grade 0-1	Grade 0	Grade 0-1	Grade 1-2
90 min	Grade 0-1	Grade 0	Grade 0-1	Grade 1-2

Table 2: Sedative effect of the tested analgesics at different evaluation times.

Times	Nalbuphine HCl	Fentanyl citrate	Tramadol HCl	Meloxicam
Baseline	Grade 0	Grade 0	Grade 0	Grade 0
Start time	Grade 0-1	Grade 0-1	Grade 0	Grade 0
15 min	Grade 0-1	Grade 1	Grade 0	Grade 0
30 min	Grade 0-1	Grade 1	Grade 0	Grade 0
45 min	Grade 0-1	Grade 1	Grade 0	Grade 0
60 min	Grade 0-1	Grade 0	Grade 0	Grade 0
75 min	Grade 0-1	Grade 0	Grade 0	Grade 0
90 min	Grade 0-1	Grade 0	Grade 0	Grade 0

Behavioral effects

In group A (Nalbuphine HCl), group C (Tramadol HCl) and group D (Meloxicam), no behavioral abnormalities were recorded in all dogs during the entire observation period.

In group B (Fentanyl citrate), defecation was demonstrated in six dogs while no vomiting was recorded in any dog. Moderate salivary and nasal secretions were seen in eight dogs. Moderate panting was observed in four dogs where panting started in two of them after seven minutes of

Table 3: Effect of Nalbuphine HCl on the vital signs at different evaluation times.

Times	Heart rate (beats/min)	Blood pressure (mmHg)			Respiratory rate (breaths/min)	Spo_2 (%)	Body temperature (°C)
		Systolic	Diastolic	Mean			
Baseline	81±0.58	131±0.58	76±1.15	94±1.15	19.25±1.1	98±0.58	39.40±0.53
Start time	79.33±0.33	130.83±0.44	75±0.58	93±0.58	17.50±2.78	98±0.58	39.15±0.39
15 min	77±1.15	130.83±0.58	74.83±1.36	93±1.00	22.50±3.12	98.33±0.33	39.02±0.34
30 min	77±1.73	128.50±1.44	73.33±1.33	91.33±0.88	23.50±2.53	98±0.58	38.82±0.29
45 min	76.33±1.45	127.83±1.92	72.67±1.20	90.67±1.20	20.75±4.33	97.33±0.33	38.75±0.30
60 min	68±0.58*	124±2.31	71.67±0.88	88.67±1.45	19.25±2.14	97.33±0.88	38.72±0.26
75 min	75.67±2.96	129.50±1.44	73±2.08	91.33±1.33	16±0.91	98±0.58	38.67±0.25
90 min	76.33±2.90	130.17±1.48	73.67±1.20	91.67±0.88	16.5±1.19	98.67±0.33	38.72±0.26

Table 4: Effect of Fentanyl citrate on the vital signs at different evaluation times.

Times	Heart rate (beats/min)	Blood pressure (mmHg)			Respiratory rate (breaths/min)	Spo_2 (%)	Body temperature (°C)
		Systolic	Diastolic	Mean			
Baseline	72.67±2.90	136±1.15	82±1.15	100±1.15	17.75±1.55	98.33±0.33	38.97±0.14
Start time	72±4.04	142.50±1.50	88±0.58	106±0.58	28±1.08*	98.67±0.33	38.75±0.14
15 min	60.67±3.71*	154±0.58*	101.33±0.88*	118.67±2.03*	30.75±3.06*	97.67±1.33	38.37±0.23
30 min	58.33±4.05*	149±1.73*	97.17±2.17*	114.33±0.88*	31.75±3.99*	97±1.15	38.10±0.27
45 min	62.67±4.09*	148.67±2.33*	96±1.73*	113.33±0.33*	28.75±3.04*	98.33±0.67	38.10±0.27
60 min	70±4.62	142.17±1.69	87.33±2.03	105.67±2.60	20±0.81	98.33±0.88	38±0.30
75 min	71±3.60	139.33±0.88	85±0.58	102.67±3.18	19.25±1.03	98.67±0.33	38±0.30
90 min	71.33±3.53	138.67±1.45	83.67±0.33	101.67±0.33	18±1.47	98.67±0.33	38.10±0.27

Values are presented as Means±SE. *: Significant changes at P<0.05

Table 5: Effect of Tramadol HCl on the vital signs at different evaluation times.

Times	Heart rate (beats/min)	Blood pressure (mmHg)			Respiratory rate (breaths/min)	Spo_2 (%)	Body temperature (°C)
		Systolic	Diastolic	Mean			
Baseline	70.33±1.20	133±2.89	81.33±.88	98.50±0.29	18.33±0.88	98±0.58	39.1±0.23
Start time	61±1.73*	114±2.31*	64.67±1.45*	80±1.15*	16.33±0.88	98.67±0.33	38.47±0.12
15 min	58.33±1.45*	110.67±2.31*	61±1.00*	77±2.31*	17.33±1.33	98.67±0.33	38.53±0.12
30 min	56±2.08*	109.67±2.31*	60±1.15*	76±1.15*	17.67±1.20	98±1.00	38.57±0.13
45 min	56.67±1.86*	115.7 ±2.31*	66±1.73*	82±0.58*	16.67±1.20	98.67±0.33	38.56±0.13
60 min	55.33±2.18*	114.3±2.31*	65±1.00*	81±0.58*	15.67±0.33	98.67±0.33	38.56±0.12
75 min	56.66±1.85*	117.6±2.31*	68±0.58*	84±0.58*	15.33±0.88	97.67±1.33	38.50±0.17
90 min	57±0.58*	116.33±2.31*	66±1.53*	82±1.15*	15±0.58	97±1.53	38.57±0.07

Values are presented as Means±SE. *: Significant changes at P<0.05

Table 6: Effect of Meloxicam on the vital signs at different evaluation times.

Times	Heart rate (beats/min)	Blood pressure (mmHg)			Respiratory rate (breaths/min)	Spo_2 (%)	Body temperature (°C)
		Systolic	Diastolic	Mean			
Baseline	72.50±5.27	137±1.73	82.50±1.44	100.33±1.45	19.75±1.25	98±0.71	38.87±0.25
Start time	74.50±4.72	147.58±1.97*	101.92±3.10*	116.67±1.76*	22.50±0.29	97.25±0.85	38.37±0.15
15 min	76.5±5.12	148.17±1.96*	102±2.89*	117±1.53*	26.75±1.97*	97.75±0.25	38.37±0.14
30 min	76±5.7	150.33±2.60*	104±2.31*	119.33±1.33*	27.25±2.32*	98.50±0.29	38.32±0.13
45 min	77.75±5.04	149.50±2.29*	102.25±3.32*	117.67±1.76*	23.75±1.65	98.25±0.25	38.27±0.18
60 min	77.25±4.99	147±1.73*	97±1.73*	113.33±1.76*	23.50±1.50	98.75±0.25	38.32±0.19
75 min	77.75±4.4	146.33±0.33*	96±2.31*	112.33±2.60*	22.75±1.11	97.75±0.25	38.62±0.07
90 min	76±5.48	146±0.58*	95.33±2.33*	112±2.31*	23.75±1.65	98.25±0.48	38.37±0.14

Values are presented as Means±SE. *: Significant changes at P<0.05

injection (start time) and disappeared after 15 minutes and panting began in the other two dogs after five minutes and disappeared after 45 minutes. Severe panting appeared after two minutes of administration and disappeared after 45 minutes in four dogs. Irregular breathing pattern was observed after 15 minutes in only two dogs.

Effects on vital signs

The effects of the four tested analgesics on vital signs at different evaluation times are collected in Tables 3-6.

Nalbuphine HCl induced significant decrease in heart rate only at 60 minute recording time with insignificant changes in the other recording times. There were no significant changes in other parameters at all recording times.

Fentanyl citrate induced a significant decrease in heart rate at 15, 30 and 45 minutes with insignificant changes in other observation periods. Significant increase in systolic, diastolic and mean blood pressure was recorded from 15 minute observation period up to 45 minute. Significant increase in respiratory rate was recorded from the start time up to 45 minute observation period but no significant changes in SPO_2 and temperature were recorded at any recording time.

Tramadol HCl induced significant decrease in heart rate along the entire observation periods. Systolic, diastolic and mean blood pressure also showed a significant decrease at all recording times. No significant changes in respiratory rate, SPO_2 and temperature were reported at any observation period.

Meloxicam injection induced insignificant increase in heart rate from the start time up to 90 minute observation period. Systolic, diastolic and mean blood pressure showed a significant increase at all recording times. Significant increase in respiratory rate was demonstrated at 15 and 30 minute recording times with insignificant changes in other periods. No significant changes in body temperature and SPO_2 were recorded along the entire observation period.

Hematological effects

The effects of the four tested analgesics on the hemogram at different evaluation times are collected in Tables 7-10.

Nalbuphine HCl induced insignificant decrease in red blood cell parameters (RBCs count, PCV% and Hb concentration) along the entire recording times except at 15 minute observation period where a significant decrease was demonstrated. Significant increase in TLC was recorded at 30, 45, 75 and 90 minute periods. No significant changes

Table 7: Effect of Nalbuphine HCl on the hemogram at different evaluation times.

Times	RBCs (×10⁶/µl)	PCV (%)	Hb (gm/dl)	WBCs (×10³/µl)	Neutrophil (×10³/µl)	Eosinophil (×10³/µl)	Lymphocyte (×10³/µl)	Mononcyte (×10³/µl)	Platelets (×10³/µl)
Baseline	6.81±0.20	40.88±1.21	13.63±0.40	19.77±1.39	14.75±0.41	0.14±0.01	4.55±0.15	0.26±0.01	290±0.58
Start time	6.23±0.12	37.40±0.70	12.47±0.24	22.44±1.99	16.67±0.54	0.20±0.01	5.12±0.77	0.38±0.03	268.51±0.86*
15 min	5.96±0.01*	35.73±0.03*	11.91±0.01*	20.95±1.82	15.20±0.29	0.22±0.02	5.03±0.07	0.42±0.03	244.15±1.07*
30 min	6.54±0.11	39.23±0.68	13.08±0.23	24.59±0.89*	17.30±0.69	0.21±0.01	6.64±0.33*	0.36±0.03	255.10±0.93*
45 min	6.22±0.07	37.33±0.43	12.44±0.14	27.03±0.26*	19.72±2.86	0.14±0.01	6.85± 0.23*	0.27±0.02	266.90±0.81*
60 min	6.20±0.14	37.23±0.83	12.42±0.27	22.31±2.17	16.44±0.92	0.24±0.03	5.11±0.44	0.45±0.05	278.70±0.94*
75 min	6.49±0.09	38.90±0.53	12.98±0.17	23.87±0.93*	17.17±0.65	0.21±0.01	6.03±0.50	0.40±0.04	289.9±0.73
90 min	6.21±0.06	37.23±0.38	12.42±0.13	25.25±0.25*	16.63±0.38	0.27±0.04	7.76±0.23*	0.52±0.06	288.74±0.37

Values are presented as Means±SE. *: Significant changes at P<0.05

Table 8: Effect of Fentanyl citrate on the hemogram at different evaluation times.

Times	RBCs (×10⁶/µl)	PCV (%)	Hb (gm/dl)	WBCs (×10³/µl)	Neutrophil (×10³/µl)	Eosinophil (×10³/µl)	Lymphocyte (×10³/µl)	Mononcyte (×10³/µl)	Platelets (×10³/µl)
Baseline	6.19±0.35	37.13±2.13	12.38±0.71	18.73±0.96	11.39±0.19	0.83±0.06	4.90±0.51	1.53±0.14	186.67±1.20
Start time	5.94±0.47	35.60±2.80	11.86±0.93	19.97±1.42	12.26±0.62	0.84±0.07	5.26±0.32	1.55±0.16	188.75±1.20
15 min	5.79±0.58	34.73±3.45	11.58±1.15	31.12±0.59*	20.13±0.12*	0.87±0.07	8.44±0.56*	1.61±0.21	214.81±1.33*
30 min	5.84±0.13	35.07±0.79	11.69±0.26	27.24±0.34*	17.56±0.89*	0.84±0.06	7.23±0.67*	1.55±0.15	199.39±1.06*
45 min	6.03±0.10	36.17±0.62	12.06±0.21	20.38±0.52	12.56±0.81	0.85±0.07	5.33±0.34	1.58±0.19	232.17±1.24*
60 min	6.03±0.06	36.18±0.36	12.06±0.12	20.04±0.94	12.29±0.65	0.84±0.06	5.29±0.35	1.56±0.15	227.25±0.80*
75 min	6.07±0.09	36.43±0.51	12.14±0.17	28.69±0.95*	18.90±0.96*	0.83±0.06	7.34±0.59*	1.53±0.15	223.19±0.99*
90 min	6.13±0.21	36.80±1.27	12.27±0.42	28.55±0.33*	18.74±0.89*	0.88±0.07	7.24±0.59*	1.62±0.19	201.23±1.51*

Values are presented as Means±SE. *: Significant changes at P<0.05

Table 9: Effect of Tramadol HCl on the hemogram at different evaluation times.

Times	RBCs (×10⁶/µl)	PCV (%)	Hb (gm/dl)	WBCs (×10³/µl)	Neutrophil (×10³/µl)	Eosinophil (×10³/µl)	Lymphocyte (×10³/µl)	Mononcyte (×10³/µl)	Platelets (×10³/µl)
Baseline	5.87±0.26	35.20±1.55	11.74±0.52	21.63±0.03	14.34±0.34	0.84±0.06	4.83±0.40	1.57±0.12	147.50±1.44
Start time	5.94±0.09	35.62±0.52	11.88±0.18	21.41±0.44	14.25±0.43	0.83±0.03	4.72±0.37	1.56±0.07	156.02±1.33*
15 min	5.77±0.31	34.62±1.89	11.54±0.63	17.03±0.57*	11.67±0.44*	0.79±0.06	3.03±0.58	1.47±0.07	158.09±0.63*
30 min	5.64±0.02	33.87±0.14	11.29±0.04	16.08±0.32*	11.17±0.10*	0.77±0.06	2.66±0.23	1.43±0.04	154.96±0.39*
45 min	5.50±0.35	33±2.11	11.002±0.70	15.98±0.30*	10.10±0.08*	0.84±0.07	3.43±0.19	1.56±0.12	152.55±0.33*
60 min	5.59±0.41	33.51±2.48	11.17±0.83	14.88±0.44*	9.08±0.06*	0.83±0.07	3.39±0.09	1.52±0.09	152.17±0.27*
75 min	5.67±0.24	34.02±1.44	11.35±0.48	15.07±0.67*	9.33±0.12*	0.81±0.05	3.46±0.16	1.51±0.09	161.97±0.42*
90 min	5.53±0.33	33.30±1.05	11.05±0.49	17.13±0.09*	11.78±0.44*	0.78±0.07	3.06±0.07	1.45±0.04	164.81±0.77*

Values are presented as Means±SE. *: Significant changes at P<0.05

Table 10: Effect of Meloxicam on the hemogram at different evaluation times.

Times	RBCs (×10⁶/µl)	PCV (%)	Hb (gm/dl)	WBCs (×10³/µl)	Neutrophil (×10³/µl)	Eosinophil (×10³/µl)	Lymphocyte (×10³/µl)	Mononcyte (×10³/µl)	Platelets (×10³/µl)
Baseline	6.70±0.10	40.20±0.63	13.40±0.21	22.25±1.30	14.57±0.03	0.07±0.01	7.46±0.49	0.13 ±0.01	171.00±1.15
Start time	6.56±0.26	39.34±1.55	13.11±0.52	20.59±0.31	14.78±0.24	0.05±0.01	5.64±0.77	0.10±0.01	175.73±1.27*
15 min	6.04±0.13	36.27±0.82	12.09±0.28	20.69±0.29	14.86±0.32	0.05±0.01	5.64±0.78	0.10±0.01	262.94±1.29*
30 min	6.24±0.11	37.45±0.66	12.48±0.22	20.51±0.24	14.69±0.15	0.05±0.02	5.63±0.76	0.10±0.01	201.94±0.59*
45 min	5.68±0.05*	34.10±0.29*	11.37±0.09*	20.56±0.24	14.79±0.25	0.06±0.01	5.57±0.71	0.10±0.01	179.69±0.66*
60 min	5.61±0.08*	33.65±0.49*	11.22±0.16*	20.30±0.26	14.59±0.05	0.06±0.01	5.54±0.67	0.11±0.01	178.55±0.20*
75 min	5.68±0.24*	34.10±1.44*	11.37±0.48*	20.63±0.38	14.93±0.39	0.06±0.01	5.50±0.64	0.11±0.01	173.39±1.16
90 min	5.52±0.02*	33.13±0.09*	11.04±0.03*	20.57±0.75	14.89±0.36	0.05±0.01	5.48±0.61	0.10±0.01	174.12±0.45

Values are presented as Means±SE. *: Significant changes at P<0.05

were recorded in neutrophil, eosinophil and monocyte counts along all recording times except eosinophil count at 45 minute period, it returned to base line data. Lymphocyte count showed a significant increase at 30, 45 and 90 minute periods with insignificant increase at other times. Blood platelets showed a significant decrease from the start time up to 60 minute recording time with insignificant changes in other recording periods.

Fentanyl citrate had insignificant effects on RBCs, PCV and Hb values. It induced a significant increase in TLC, neutrophil and lymphocyte counts only at 15, 30, 75 and 90 minute periods. Monocyte and eosinophil counts showed insignificant changes along the whole observation period except at 75 minute where they returned to baseline data. Blood platelets revealed significant increase at all recording times except at the start time where insignificant increase was noticed.

Tramadol HCl induced insignificant changes in RBCs, PCV and Hb values at all observation times. TLC and neutrophil counts showed a significant decrease from 15 minute up to 90 minute recording time. Eosinophil, lymphocyte and monocyte counts showed insignificant changes at all observation periods except that eosinophil was remained at basal data at 45 minute period. Blood platelets showed a significant increase along the entire recording times.

Meloxicam induced insignificant decrease in RBCs, PCV and Hb values from the start time up to 30 minute recording time followed by a significant decrease up to 90 minute period. No significant changes were recorded in TLC, neutrophil, eosinophil, lymphocyte and monocyte counts at any time along entire observation period. Blood platelets exhibited a significant increase from the start time up to 60 minute observation period followed by insignificant increase at other times.

Effects on serum biochemical parameters

The effects of the four tested analgesics on serum biochemical parameters at different evaluation times are collected in Tables 11-14.

Nalbuphine HCl induced significant decreased in TP at 15, 30, 75 and 90 minute periods with no significant change in serum albumin levels at any recording time. Serum glucose level significantly increased at 15, 30 and 90 minute observation periods with insignificant changes at other recording times. Blood urea nitrogen and creatinine showed no significant alterations along the entire observation period. The study of creatinine

Table 11: Effect of Nalbuphine HCl on the serum biochemical parameters at different evaluation times.

Times	TP (g/dl)	Albumin (g/dl)	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	ALT (units/ml)	AST (units/ml)
Baseline	6.12±0.18	2.98±0.02	77.30±0.69	63.26±1.88	0.63±0.08	49.89±4.83	45.24±1.44
Start time	5.67±0.67	3.78±0.22	80.62±2.91	59.08±3.76	0.63±0.05	49.95±4.55	45.33±3.62
15 min	4.61±0.12*	3.73±0.27	83.70±2.22*	60.32±0.97	0.62±0.07	50.89±3.69	43.73±0.52
30 min	4.14±0.44*	3.52±0.18	90.95±0.69*	59.51±2.01	0.63±0.05	51.09±2.96	44.35±0.74
45 min	5.63±0.06	3.42±0.11	80.20±2.16	60.87±1.81	0.66±0.05	49.47±5.42	48.03±0.67
60 min	5.43±0.79	3.53±0.26	80.11±3.29	58.62±0.69	0.63±0.06	48.33±0.88	45.61±0.26
75 min	4.90±0.06*	3.56±0.23	81.18±2.49	62.93±2.07	0.64±0.06	49.65±5.35	49.32±1.51*
90 min	4.64±0.15*	3.37±0.15	87.88±0.89*	60.25±4.47	0.62±0.05	49.85±5.18	46.80±1.02

Values are presented as Means±SE. *: Significant changes at P<0.05

Table 12: Effect of Fentanyl citrate on the serum biochemical parameters at different evaluation times.

Times	TP (g/dl)	Albumin (g/dl)	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	ALT (units/ml)	AST (units/ml)
Baseline	4.46±0.18	2.89±0.50	73.20±0.89	52.00±1.15	0.89±0.05	47.82±1.14	34.79±0.37
Start time	3.88±0.52	2.84±0.49	78.25±0.45	49.10±2.94	0.70±0.05	47.42±2.11	36.24±1.18
15 min	4.32±0.30	2.74±0.14	76.06±0.86	44.23±2.40*	0.70±0.05	48.66±0.93	37.07±0.94
30 min	4.10±0.37	2.59±0.35	75.61±0.87	47.12±1.60	0.66±0.03*	46.83±2.27	34.95±0.60
45 min	3.41±0.41	2.70±0.17	75.17±2.61	44.76±0.44*	0.70±0.05	45.87±2.16	35.38±0.03
60 min	4.28±0.34	2.71±0.20	77.68±2.74	45.47±0.29*	0.64±0.02*	47.58±2.25	35.63±0.74
75 min	4.24±0.07	2.62±0.37	75.44±0.99	47.95±3.14	0.89±0.05	47.05±1.86	35.26±0.89
90 min	4.08±0.46	2.81±0.48	75.33±1.20	51.43±0.96	0.87±0.04	46.53±1.47	34.89±0.28

Values are presented as Means±SE. *: Significant changes at P<0.05

Table 13: Effect of Tramadol HCl on the serum biochemical parameters at different evaluation times.

Times	TP (g/dl)	Albumin (g/dl)	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	ALT (units/ml)	AST (units/ml)
Baseline	6.44±0.06	3.05±0.17	86.86±1.08	67.50±1.44	0.68±0.01	45.12±1.07	35.07±0.99
Start time	6.94±0.06	2.83±0.03	86.30±0.56	83.20±2.33*	0.68±0.02	45.69±0.39	34.67±0.04
15 min	6.65±0.23	2.76±0.11	84.81±1.67	81.20±2.02*	0.69±0.02	43.32±0.59	34.89±0.14
30 min	6.42±0.29	3.08±0.14	86.08±1.82	78.03±0.91*	0.68±0.02	43.26±0.24	36.33±0.23
45 min	6.24±0.11	3.20±0.11	83.87±1.72	78.16±0.86*	0.69±0.01	43.35±0.12	33.94±1.79
60 min	6.15±0.54	3.16±0.01	82.80±1.03	81.13±1.43*	0.69±0.02	43.71±0.64	37.13±0.47
75 min	7.02±0.44	3.62±0.53	85.62±0.96	83.99±0.14*	0.69±0.01	43.38±0.46	33.92±0.95
90 min	6.45±0.03	3.40±0.01	86.53±0.75	79.70±2.09	0.68±0.01	44.13±0.33	33.91±0.25

Values are presented as Means±SE. *: Significant changes at P<0.05

Table 14: Effect of Meloxicam on the serum biochemical parameters at different evaluation times.

Times	TP (g/dl)	Albumin (g/dl)	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	ALT (units/ml)	AST (units/ml)
Baseline	6.32±0.07	2.68±0.05	92.14±1.18	56.00±1.15	0.59±0.02	56.64±5.85	43.52±0.41
Start time	6.22±0.06.	2.93±0.01	89.03±0.62	58.95±0.21	0.60±0.05	55.76±3.00	42.96±1.15
15 min	5.83±0.51	2.94±0.54	88.94±0.86	55.78±3.15	0.60±0.01	55.75±5.37	45.21±1.30
30 min	6.05±0.04	2.77±0.19	89.80±0.76	53.02±2.29	0.59±0.02	55.85±2.28	46.19±0.57
45 min	5.69±0.12	2.75±0.02	92.03±0.68	54.28±2.47	0.60±0.02	55.96±5.15	45.92±0.48
60 min	6.17±0.13	2.75±0.11	84.42±0.39*	54.50±0.76	0.59±0.02	55.33±3.76	45.08±0.85
75 min	6.03±0.53	2.75±0.06	91.54±1.13	53.63±0.68	0.63±0.03	55.75±6.13	44.90±0.89
90 min	5.92±0.52	3.02±0.56	83.10±0.69*	53.29±3.05	0.60±0.03	55.81±6.15	46.03±1.29

Values are presented as Means±SE. *: Significant changes at P<0.05

clearance revealed insignificant changes (baseline clearance 0.03±0.01 compared to 0.02±0.05 after Nalbuphine HCl administration). Serum ALT showed insignificant increase from the start time up to 30 minute followed by insignificant decrease at other recording times. Serum AST activity showed a significant increase only at 75 minute evaluation time.

Fentanyl citrate induced insignificant decrease in serum levels of TP and albumin at all recording times. Blood glucose level showed insignificant increase along the entire observation period. Serum urea levels revealed a significant decrease at 15, 45 and 60 minutes with insignificant changes at other periods. Creatinine levels showed a significant decrease at 30 and 60 minutes only. The study of creatinine clearance revealed no changes (baseline clearance 0.05±0.03 compared to 0.05±0.02 following Fentanyl citrate administration). Insignificant changes in ALT and AST values were demonstrated along entire observation period.

Tramadol HCl induced insignificant changes in TP, albumin and serum glucose levels at all recording times. Serum urea levels were significantly increased from the start time up to 75 minute period. Creatinine showed no significant changes along the entire observation period. The study of creatinine clearance revealed insignificant changes (baseline clearance 0.03±0.02 compared to 0.04±0.03 following Tramadol HCl administration). Serum ALT and AST activities exhibited no significant changes at any recording time.

Meloxicam induced no significant changes in serum levels of TP, albumin, urea, creatinine, creatinine clearance (base line clearance 0.05±0.02 compared to 0.02±0.04 following Meloxicam administration) and serum enzymatic activities of ALT and AST along the whole experiment. Serum glucose levels significantly decreased at 60 and 90 minute evaluation periods with insignificant decrease at other recording times.

In the present study, four commonly used analgesic agents were evaluated separately. Compared to Nalbuphine HCl, Fentanyl citrate and Tramadol HCl, Meloxicam revealed better analgesia with insignificant deleterious effects recommending it for analgesia in dogs.

Nalbuphine HCl was used at a dose of (0.5mg/kg), this dose produced mild analgesia in dogs. This finding agrees with the findings of previous studies (Benson, 2002; Lamont and Mathews, 2007). In the present study, the evaluation of Nalbuphine HCl was started 10 minutes

post injection according to Murphy and Hug (1982) where they demonstrated a significant reduction of enflurane MAC (8%) 10 minutes following intravenous injection of Nalbuphine HCl at a dose of 0.5mg/kg. Cardiovascular parameters showed no significant changes following Nalbuphine HCl administration. Similar findings were recorded by earlier workers (Sawyer et al., 1982). Additionally, respiratory rate and SPO_2 showed insignificant changes which match with the minimal respiratory depression previously reported (Heavner and Cooper, 2008). These results were clarified through Nalbuphine HCl opioid receptor-binding affinities (Lamont and Mathews, 2007).

Neither nausea nor vomiting was recorded in any of the studied dogs following Nalbuphine HCl injection. These findings agree with those reported by (Dyson, 2002) who clarified that, less profound opioids rarely cause vomiting.

Intravenous administration of Nalbuphine HCl had no significant effects on red blood cell parameters along most of observation periods except at 15 minutes where significant decrease in RBCs, PCV and Hb values was demonstrated. On contrary, Mathews et al. (2001) reported that, preoperative administration of butorphanol (agonist-antagonist opioid) in dogs undergoing abdominal surgery induced a significant decrease in the mean values of PCV only 24 hours after surgery compared with the baseline value.

Nalbuphine HCl administration had no effect on the liver function which was evidenced by absence of significant changes in serum ALT activity along the whole experimental period. Consistently, Mathews et al. (2001) found similar finding between baseline values and values at 24 or 48 hours after surgery for dogs receiving butorphanol to control postoperative pain.

Following Fentanyl citrate injection, mild sedation state was recorded that agrees with Branson et al. (2001) who mentioned that opioid analgesics induce central nervous system depression in dogs.

The start time for Fentanyl citrate was 7 minutes post injection according to Hall et al. (2001a) because Fentanyl citrate becomes effective within 4-7 minutes following intravenous injection in dogs.

No response to skin pricks was achieved in eight dogs at 15 and 30 minute observation periods following Fentanyl citrate administration which could be explained in terms of analgesic potency of such drug according to Hellyer et al. (2001) who recorded that Fentanyl citrate is a synthetic μ-opioid agonist with an analgesic potency that is 75 to 125 times the potency of morphine.

Highest analgesic score was obtained 22 minutes post Fentanyl citrate injection (at 15 minute observation period from the start of evaluation (7 minutes post administration). These results disagree with Stoelting (1999) and Gutstein and Akil (2001) who found that the peak analgesic effect of Fentanyl citrate occurs in about 5 minutes. From the obtained results Fentanyl citrate action lasted about 45 min that agrees with Hall et al. (2001b).

Significant bradycardia was demonstrated following Fentanyl citrate administration. This finding disagrees with those reported by Arndt et al. (1984) and Grimm et al. (2005) who reported no changes in heart rate following a cumulative dose of Fentanyl citrate up to 7.5 μg/kg in conscious dogs. Loeb et al. (1984) explained Fentanyl citrate induced bradycardia by suppression of sympathetic tone, a direct negative chronotopic effect on the sinoatrial node and local potentiation of vagal tone.

The recorded increase in blood pressure following Fentanyl citrate injection agrees with the findings of Hendrix et al. (1995). Additionally, the resultant hypertension could be attributed to an increased systemic vascular resistance (Keating, 2013).

Following Fentanyl citrate administration, tachypnea was observed from the start time up to 45 minute observation period. These findings are in agreement with those reported by Arndt et al. (1984). Also following Fentanyl citrate injection, temperature showed insignificant decrease and this reduction was explained by reduction in basal metabolic rate and heat loss via the respiratory system, especially in panting animals (Wagner, 2002). Similar to the findings of Haskins (2013), defecation and panting occurred in the studied dogs after Fentanyl citrate injection. Panting could be attributed to the effect of Fentanyl citrate on thermoregulatory center (Wagner, 2002; Haskins, 2013).

Fentanyl citrate administration was associated with a significant increase in TLC, neutrophil and lymphocyte counts. Similar findings were recorded by Fox (2014) after transdermal Fentanyl citrate solution in dogs. Biochemical changes following Fentanyl citrate administration included significant decrease in serum urea levels at 15, 45 and 60 minutes and in serum creatinine levels at 30 and 60 minutes. These effects could be attributed to the associated marked elevation in arterial blood pressure with subsequent increase in renal blood flow and glomerular filtration rate. No changes were demonstrated in creatinine clearance. These findings disagree with those reported by Castiglia et al. (1997) who declared that creatinine clearance was significantly decreased by Fentanyl citrate administration. This difference could be attributed to the higher dose

of Fentanyl citrate (0.05 mg/kg) used by Castiglia et al. (1997) compared with the dose (5µg/kg) evaluated in our work.

Tramadol HCl administration was not associated with any observable sedation. This agrees with Natalini et al. (2007). However, this finding disagrees with those reported by Mastrocinque and Fantoni (2003) who recorded that tramadol HCl (2 mg /kg, IV) had sedative effects comparable with morphine (0.2 mg /kg, IV) in dogs.

The start time for evaluation of tramadol was 45 minutes post injection according to Seddighi et al. (2009) who demonstrated a significant reduction in sevoflurane MAC at 45 minutes from its administration. Mild analgesia was obtained following Tramadol HCl administration. Consistently, Wu et al. (2001) and Mastrocinque and Fantoni (2003) noticed limited analgesia in dogs. This may make Tramadol HCl less effective analgesic in dogs than in people.

Significant decrease in blood pressure following Tramadol HCl administration could be attributed to the associated significant bradycardia. These findings disagree with that reported by Itami et al. (2011) who demonstrated that administration of Tramadol HCl (4mg/kg, IV) produces a transient and mild increase in arterial blood pressure which lasts for up to15 minutes with a vasoconstriction effect which may be useful for overcoming the vasodilatation in sevoflurane anesthetized dogs.

Reduction in respiratory rate following Tramadol HCl injection was insignificant because Tramadol HCl is a weak µ-opioid agonist (Duthie, 1998). Similar results were obtained by Houmes et al. (1992).

Tramadol HCl injection was associated with insignificant changes in SPO_2. Similarly, Mastrocinque and Fantoni (2003) reported the same finding. No vomiting was demonstrated following Tramadol HCl administration. This agrees with the findings obtained by Natalini et al. (2007) who added that the apparent lack of emetic action of Tramadol HCl in dogs may be useful clinically in occasions where vomit should be avoided and yet giving opioids are needed.

Regarding the hemogram, Tramadol HCl had no influences on red blood cell parameters. Similar findings were demonstrated by Costa et al. (2013). The serum urea levels were markedly elevated following Tramadol HCl administration but renal dysfunction was not expected because serum creatinine concentrations showed no significant changes. This was further supported by the results of creatinine clearance which showed no significant alterations after Tramadol HCl administration. Possible explanation for the increase in serum urea levels is the significant reduction in arterial blood pressure with a consequence decrease in renal blood flow, glomerular filtration rate and tubular excretion of urea. On contrary, Mcmillan et al. (2008) recorded no significant changes in blood biochemical parameters in dogs intravenously injected with Tramadol HCl at doses of 1, 2, and 4 mg/kg.

Following Meloxicam injection, no sedation was demonstrated in any of the studied dogs. On contrary, moderate analgesia was noticed in six of ten studied dogs with mild analgesia in others. The analgesic effect of NSAID was explained by Lamont and Mathews (2007) via inhibition of COX-1 and COX-2 activity with subsequent prevention of prostaglandin synthesis.

Meloxicam evaluation started one hour post injection to allow the drug to become effective according to Lemke and Creighton (2010). The current study revealed that Meloxicam provided greater analgesia than Nalbuphine HCl, Fentanyl citrate and Tramadol HCl. This agrees with Caulkett et al. (2003) who demonstrated that some NSAIDs are more effective than opioids for relief of pain in dogs.

Increased blood pressure following Meloxicam administration could be attributed to renal blood flow and fluid retention imbalance (Radi, 2009). On contrary, Caulkett et al. (2003) recorded three of Meloxicam treated dogs experienced a drop in systolic pressure to 75–80 mmHg.

Neither vomiting nor diarrhea was observed in any of the studied dogs following Meloxicam injection. Similar results were obtained by Luna et al. (2007) and Baba et al. (2012). Therefore, this study concluded that Meloxicam could be safe NSAID in regard to gastrointestinal tract.

As regards hemogram, intravenous administration of Meloxicam resulted in significant reduction in RBCs, PCV and Hb values from 45 up to 90 minute period. These findings could be explained by hemodilution as a result of increased blood pressure and fluid retention imbalance (Radi, 2009). On the other hand, Mathews et al. (2001) mentioned that, preoperative administration of Meloxicam in dogs showed no significant changes in PCV.

Meloxicam had no effect on serum biochemistry variables evaluated in this study. Similar results were demonstrated by Luna et al. (2007) following long-term oral administration of Meloxicam at a dose of 0.1mg/kg. Additionally, Laredo et al. (2004) reported no significant differences between the plasma concentrations of urea and creatinine before and 24 hours after surgical intervention in dogs received Meloxicam preoperatively. These findings

could be attributed to the low effect of Meloxicam on glomerular filtration that was indicated by insignificant alteration in creatinine clearance. Consistently, Bostrom et al. (2006) showed that glomerular filtration rate measured by scintigraphy was not modified by administration of Meloxicam in dogs.

CONCLUSIONS AND RECOMMENDATIONS

Meloxicam is more safe and effective analgesic than Nalbuphine HCl, Fentanyl citrate and Tramadol HCl in dogs. Therefore, Meloxicam is recommended for pain control in dogs due to its better analgesia and insignificant deleterious effects.

NOVELTY STATEMENT

This study compared four analgesic drugs in dogs and revealed that Meloxicam is better analgesic than Nalbuphine HCl, Fentanyl citrate and Tramadol HCl.

AUTHOR'S CONTRIBUTION

All authors contributed equally.

Conflict of interest

The authors have declared no conflict of interest.

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