



## Assessment of the analgesic potency of constant rate infusion of tramadol hydrochloride and as an adjunct to ketoprofen in laparotomized bitches

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### Abstract

In this study, the analgesic potency of constant rate infusion of tramadol hydrochloride and as adjunct to ketoprofen on laparotomy-induced pain was evaluated. Dogs were randomly assigned to 4 groups ( $n=5$ ). Groups 1, 2 and 3 received 0.5mg/kg/hr, 1.0mg/kg/hr and 2.0mg/kg/hr IV; CRI of tramadol hydrochloride respectively while group 4 which served as control received normal saline. Infusions were administered from 30 minutes before surgery and lasted for 105 minutes. All dogs underwent ventral midline laparotomy. Ketoprofen 50 mg/ml at the dose of 5mg/kg, SC was given at 1 hour post-surgery (hps) after pain assessment and on days 2 and 3 post-surgery (dps) to dogs in all the groups. Parameters determined were heart and respiratory rates, blood glucose level, pain score and body weight. Results showed that mean heart rate, respiratory rate and body weight were not differed significantly ( $p > 0.05$ ) within and among the groups. Mean blood glucose level of group 4 was significantly higher ( $p < 0.05$ ) than the other groups intra- and post-surgery. Mean blood glucose level of group 3 was significantly lower ( $p < 0.05$ ) than that of group 1 at 1 hps. Group 4 dogs also had significantly higher mean blood glucose intra-surgery and at 1 hps than their baseline value. Group 4 dogs had significantly higher ( $p < 0.05$ ) mean rank pain score than other dog groups on 0-3 dps while mean rank pain scores of groups 1 and 2 were significantly ( $p < 0.05$ ) higher than that of group 3 on 0 dps. It was concluded that tramadol HCL at constant rate infusion doses of 0.5mg/kg, 1.0mg/kg/hr and 2.0mg/kg/hr were effective at managing laparotomy-induced pain up to one hour post-surgery. As an adjunct to ketoprofen, 2.0mg/kg/hr of tramadol hydrochloride offered better analgesia than the other doses studied during the post-surgical days.

**Keywords:** Analgesia, Constant rate infusion, Ketoprofen, Laparotomy, Pain, Tramadol

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### Introduction

Pain is an aversive sensory and emotional experience representing awareness by the animal of damage or threat to the integrity of its tissues (Molony, 1997). Evaluation of acute pain in animals often relies on the effects of surgical trauma on animals. Thus, surgical procedures are known to induce different degrees of acute pain (Hansen & Hardie, 1993). Laparotomy has been shown to elicit mild to moderate degree of acute pain (Firth & Haldane, 1999).

Assessing the level of post-operative pain in animals is challenging due to lack of verbal communication. Hence, pain assessment in animals is often done subjectively (Firth & Haldane, 1999; Gaynor & Muir, 2009; Landa, 2012). The use of subjective assessment which includes behavioural and vital parameter changes

is however, prone to external influence and bias. Pain in animals can also be objectively assessed using physiological, biochemical and neuroendocrine responses (Flecknell, 1996; Middleton, 2003). Significant increases in blood glucose and serum cortisol have been used to objectively indicate the presence of pain (Lemke *et al.*, 2002). Just like in the subjective assessment, objective assessment parameters are also influenced by external factors. For instance, changes in serum cortisol may be due to factors such circadian rhythms, periodical fluctuations and other events which might interfere with cortisol increase. Therefore, it is necessary to obtain series of plasma or serum cortisol measurements (Landa, 2012).

Management of pain in animals could either be pre-emptive or post-inductive (Landa, 2012). In pre-emptive management, pain is anticipated and prevented while it is alleviated only after observation in post-inductive. Currently, several classes of drugs used in management of pain (analgesics) exist and include opioids, non-steroidal anti-inflammatory drugs (NSAIDS), steroid anti-inflammatory drugs (SAIDS) and local anaesthetics (Eze *et al.*, 2004; Hansen, 2005). Opioids are the most efficacious analgesics available for the control and management of post-operative pain in humans and animals (Stefano *et al.*, 2005). The use of opioids as pain relievers is associated with numerous side effects including bradycardia, hypotension, vomiting, defecation and excitatory effects (Page *et al.*, 2001). The advantages of tramadol hydrochloride over other opioids are its dual mechanism of action and minimal side effects (Perez *et al.*, 2014). However, tramadol has a short duration of action and therefore, its effect is short-lived in the body. Hence, there is a need for combination of tramadol with analgesics of longer duration to produce balanced analgesia of longer duration. It is more advantageous to combine different classes of analgesics to produce multimodal or balanced analgesia (Muir *et al.*, 2003). Proven benefits of multimodal analgesics include more efficient analgesia and possible dose reduction of one or more individual drugs (Lemke *et al.*, 2002). Ketoprofen is an aryl propionic acid derivative and a non-steroidal anti-inflammatory drug used in the treatment of inflammatory conditions with moderate to severe pain-relieving effect. It is a strong non-selective inhibitor of cyclooxygenase (COX) and has powerful anti-inflammatory, analgesic and antipyretic properties (Boothe, 2001). It has a long duration between 12-24 hours (Boothe, 2001).

Analgesics can be administered orally, subcutaneously, intramuscularly, intravenous bolus infusion or by constant rate infusion [CRI] (Gaynor and Muir, 2009). The use of CRI is advantageous because it eliminates the peak and trough effects that occur with intermittent dosing of drugs (Wagner *et al.*, 2002). Various drugs which have been used for constant rate infusion in humans and animals include ketamine (Wagner *et al.*, 2002; Muir *et al.*, 2003), lignocaine (Ortega & Cruz, 2011), fentanyl (Sano *et al.*, 2006), morphine (Guedes *et al.*, 2006) and hydromorphone (Kukanich & Papich, 2004). Despite the constant use of tramadol in human and veterinary medicine, there is no information available in literature establishing the CRI dose of tramadol HCL and as an adjunct to ketoprofen for the management of peri-operative pain to the best of our knowledge. Therefore, the study was designed

to assess the analgesic potency of CRI tramadol HCL using three different doses (0.5mg/kg/hr, 1.0mg/kg/hr and 2.0mg/kg/hr) and as an adjunct to ketoprofen with mid-ventral laparotomy as acute pain model in dogs.

## Materials and Methods

### Study animals

Twenty adult female Nigerian local dogs with mean  $\pm$  SEM age and weight of  $12.93 \pm 1.33$  and  $6.10 \pm 2.40$  kg respectively were randomly assigned to four groups of five dogs each used for the study. Dogs were housed in the Department of Veterinary Surgery dog kennel and acclimatized for two weeks prior to the experiment. They were fed routinely with dry dog food (Active<sup>®</sup>, Josera) and had access to clean drinking water *ad libitum*.

### Ethical clearance

The guidelines set out by the University of Nigeria Ethics Committee for Medical and Scientific Research (MSR) which among others include good, clean and hygienic housing, provision of clean water and humane handling of animals during sample collection were strictly adhered to in the experiment. These guidelines by the University of Nigeria Ethics Committee for Medical and Scientific Research to a greater extent is in conformity with the guiding principles for biomedical research involving animals as issued by the Council of International Organizations of Medical Sciences (CIOMS). Valid approvals and ethical clearance was obtained from the University of Nigeria Ethics Committee before the commencement of the experiment.

### Experimental design

Groups 1, 2 and 3 received 0.5mg/kg/hr, 1.0mg/kg/hr, 2.0mg/kg/hr IV; CRI of tramadol HCL respectively while group 4 which served as the control received normal saline infusion. CRI tramadol HCl was administered by gravity flow using an intravenous fluid bag. Dogs in the treatment groups received a combination of tramadol at their respective doses and normal saline while the control received normal saline (300mls) infusion only at fluid infusion rate of 5.0mg/kg/hr. Dogs in all the four groups underwent laparotomy.

### Drugs

Tramadol hydrochloride (Tramadol HCL<sup>®</sup>, 5%) and ketoprofen (Ketonal<sup>®</sup>, 5%) used for this study were obtained from IDA, Netherlands and Lek pharm, Slovenia respectively. Drugs used for anaesthetic induction include atropine sulphate (Pauco Atropine<sup>®</sup>, Pauco Pharmaceutical), xylazine (XYLM2<sup>®</sup>, VMD Belgium) and ketamine hydrochloride (Ketamine<sup>®</sup>, Laboratoe Pharmaceutical, India).

Gentamicin sulphate injection (Pantex-Genta 100<sup>®</sup>, Pantex Holland) was the antibiotic used.

#### Anaesthesia and surgery

Blood glucose level and body weight of each dog was obtained as baseline values. Feed but not water was withdrawn from the dogs 12 hours prior to surgery. Heart and respiratory rates prior to surgery were obtained. Dogs were then premedicated with 1% atropine sulphate at 0.02mg/kg, IM and 2% xylazine hydrochloride at 1.0mg/kg, IM. Anaesthesia was induced five minutes after premedication with 5% ketamine hydrochloride 20mg/kg, IM. The left cephalic vein of each dog was per-cutaneously catheterized with 21 G needle for administration of fluids. Following induction of anaesthesia, dogs in groups 1, 2 and 3 received a loading dose of 5 mg/kg, IV of tramadol hydrochloride and their specific treatments as stated above. All the dogs received infusions administered from 30 minutes pre-surgery for 105 minutes. Hairs at the ventral abdominal region were clipped, and the animals prepared for aseptic surgery following standard procedures described by Vaughan (1980). Mid-ventral laparotomy was performed on all dogs using a uniform 6 cm linea alba incision as described by Vaughan (1980). The mean  $\pm$  SD duration of mid-ventral laparotomy was 17.40 $\pm$ 5.42 minutes. Anaesthesia was maintained with ketamine hydrochloride (10mg/kg, IM) to ensure dogs received the required infusion volume (300mls each). Mean

recovery time was 7.60 $\pm$ 3.12 minutes post-infusion. Dogs in all the groups received ketoprofen 50mg/ml at the dose of 5mg/kg, SC at one hour post-surgery after pain assessment and on days 2 and 3 post-surgery. Gentamicin sulphate 50 mg/ml at the dose of 5mg/kg, IM was also administered for three consecutive days post-surgery.

#### Data collection

Heart and respiratory rates were assessed manually using a stethoscope at 20 minutes interval till the end of infusion. Blood glucose was assayed intra-surgery and at 1 and 24 hours post-surgery using a commercial glucose kit, Accuchek<sup>®</sup> glucose kit (Roche, Mannheim Germany). The dogs were evaluated for signs of pain on days 0 to 7 post-surgery using the University of Melbourne pain scale as shown in Table 1 and 2 below (Firth & Haldane, 1999). Pain was scored by two independent observers. The total pain score per group was the sum of behavioural and vital parameter scores. Body weight was also measured on days 0 to 7 post-surgery using the manual weighing scale.

#### Data analysis

Data generated from parametrics were subjected to one-way ANOVA using SPSS version 16 (SPSS, 2007). Means were separated at post-hoc using LSD. Pain score was analysed using non-parametric Kruskal-Wallis test. The mean ranks of pain scoring

**Table 1:** Subjective pain assessment using behavioural changes

Behavioral changes		Numerical scores		
	0	1	2	3
Activity	At rest (sleeping and semiconscious)	At rest (awake)	Restless	Rolling and thrashing
Mental status	Submissive	Overtly friendly	Wary	Aggressive
Response to palpation	No change from pre-surgery behavior		Guards/reacts when touched	Guards/reacts before touched
Posture	Lateral recumbency	Sternal recumbency; sitting or standing, head up; moving	Standing, head hanging down; Guarding or protecting affected area	Abnormal posture
vocalization	Not vocalizing	Vocalizing when touched	Intermittent vocalization	Continous vocalization

Firth & Haldane (1999)

**Table 2:** Subjective pain assessment using changes in vital parameters

Vital parameters	Numerical scores			
	1	2	3	4
Heart rate	Within pre-surgery range	20% $>$ pre-surgery value	50% $>$ pre-surgery value	100% $>$ pre-surgery value
Respiratory rate	Within pre-surgery range	20% $>$ pre-surgery value	50% $>$ pre-surgery value	100% $>$ pre-surgery value

Firth & Haldane (1999)

were presented as mean and standard deviation (Mean  $\pm$  SD). Probability values of less than 0.05 were considered significant.

## Results

Mean heart (Table 3) and respiratory (Table 4) rates did not differ significantly ( $p > 0.05$ ) within and among groups. Mean blood glucose level (Table 5) of group 4 was significantly higher ( $p < 0.05$ ) than the other groups intra-surgery and at 1 hour post-surgery (hps). At 1 hps, mean blood glucose level of group 3 was significantly lower ( $p < 0.05$ ) than that of group 1. Group 4 dogs also had significantly higher mean blood glucose intra-surgery and at 1 hps than their baseline value. Group 4 dogs had significantly higher ( $p < 0.05$ ) mean rank pain score (Table 6) than other dog groups on 0-3 days post-surgery while mean rank pain scores of groups 1 and 2 were significantly ( $p < 0.05$ ) higher than that of group 3 on day 0 post-surgery. There was no significant difference ( $p > 0.05$ ) in the mean body weight (Table 7) of all the groups post-surgery.

## Discussion

This study was designed bearing in mind that timing of analgesic intervention may have some influence on postoperative pain (Gassel *et al.*, 2005; Gilberto *et al.*, 2002). Therefore, tramadol hydrochloride was administered preemptively to the treatment groups.

The cardiovascular system responds to pain by increasing sympathetic nervous system activity, which in turn increases the heart rate (Middleton, 2003). In our study the heart and respiratory rates of the treated groups were all within the reference ranges, suggesting the safety of tramadol hydrochloride during the intra-operative period. This observation in the heart and respiratory rates

of dogs in the treated groups suggests that tramadol HCL by CRI at the doses administered was relatively safe on the cardiopulmonary system. This finding therefore agrees with earlier reports in literature which suggests tramadol as a safe opioid for the cardiovascular and respiratory systems (Mildh *et al.*, 1999; Cagnardi *et al.*, 2011; Marina *et al.*, 2014).

The higher blood glucose recorded in the control group when compared with the treatment groups showed that dogs in the control group manifested the highest degree of pain during laparotomy procedure and at one hour post-surgery. Pain is a stressor which threatens the normal homeostasis of a patient. Peripheral adaptation of the body to pain involves the transfer of energy substrates from storage sites to the blood stream to overcome the stressor (Middleton, 2003). Therefore, blood glucose, which is an energy substrate, is usually elevated in response to stressful and painful conditions, through the process of gluconeogenesis (Brook & Marshall, 2001; Saha *et al.*, 2005). Post-operative pain is usually worse in the immediate hour post-surgery (Hosking & Welchew, 1985). Therefore, an ideal drug regimen for the management of acute pain should be able to prevent or minimize pain post-operatively. The reduced blood glucose in the treated groups indicate a significant reduction in stress response to surgery (laparotomy) especially at one hour post-surgery and this is supported by studies which reported tramadol as a potent analgesic for post-operative pain (Udegbunam *et al.*, 2014; Ugwu *et al.*, 2016b). The higher blood glucose and pain score recorded in the 0.5mg/kg/hr group showed that dogs in this group experienced the highest degree of acute peri-laparotomy pain among the treatment groups. It has been suggested that the mechanism by which

**Table 3:** Mean heart rate  $\pm$  SD (bpm) of dogs treated with different doses CRI tramadol hydrochloride

Time in minutes	Group 1	Group 2	Group 3	Group 4
Baseline	109.33 $\pm$ 30.78	104.00 $\pm$ 8.31	109.33 $\pm$ 18.81	108.00 $\pm$ 8.26
20	100.67 $\pm$ 12.67	94.67 $\pm$ 18.61	94.00 $\pm$ 22.37	96.00 $\pm$ 8.26
40	102.00 $\pm$ 28.42	92.00 $\pm$ 12.31	107.00 $\pm$ 14.00	95.00 $\pm$ 4.85
60	105.67 $\pm$ 17.64	103.33 $\pm$ 24.02	98.67 $\pm$ 8.66	100.00 $\pm$ 14.20
80	105.67 $\pm$ 15.38	109.33 $\pm$ 24.24	102.33 $\pm$ 3.90	100.00 $\pm$ 12.11
100	95.00 $\pm$ 35.94	92.33 $\pm$ 06.82	86.00 $\pm$ 6.12	88.00 $\pm$ 12.25

No significant difference among group means ( $P > 0.05$ )

**Table 4:** Mean respiratory rate  $\pm$  SD (cpm) of dogs treated with different doses CRI tramadol hydrochloride

Time in minutes	Group 1	Group 2	Group 3	Group 4
Baseline	40.00 $\pm$ 0.00	43.00 $\pm$ 2.64	39.00 $\pm$ 6.56	40.33 $\pm$ 4.51
20	42.67 $\pm$ 11.85	42.67 $\pm$ 4.62	31.33 $\pm$ 13.61	38.33 $\pm$ 10.02
40	40.00 $\pm$ 11.11	40.00 $\pm$ 8.00	33.33 $\pm$ 11.55	39.00 $\pm$ 5.77
60	39.33 $\pm$ 19.31	39.33 $\pm$ 13.61	36.67 $\pm$ 7.57	41.33 $\pm$ 5.29
80	40.67 $\pm$ 8.67	36.33 $\pm$ 14.15	38.33 $\pm$ 7.64	36.67 $\pm$ 4.62
100	42.67 $\pm$ 17.48	36.67 $\pm$ 8.39	41.00 $\pm$ 3.61	37.33 $\pm$ 6.43

No significant difference among group means ( $P > 0.05$ )

**Table 5:** Mean blood glucose ± SD (g/dl) of dogs treated with different doses CRI tramadol hydrochloride

Time	Group 1	Group 2	Group 3	Group 4
Baseline	81.33± 20.78	92.00±4.58	89.33±8.62	93.67±4.16
Intra-surgery	100.3± 18.87 <sup>a</sup>	99.33±29.24 <sup>a</sup>	78.00±8.62 <sup>a</sup>	185.67±28.15 <sup>b</sup>
Post-surgery (1 hps)	90.00± 8.26 <sup>a</sup>	90.00±10.73 <sup>ab</sup>	70.00±10.68 <sup>b</sup>	194.33±43.32 <sup>c</sup>
Post-surgery (24 hps)	85.00±5.15 <sup>a</sup>	80.33±4.98 <sup>a</sup>	82.33±5.16 <sup>a</sup>	90.33±20.46 <sup>a</sup>

Different superscripts a,b,c within the row indicate significant difference among group means ( $P<0.05$ )

**Table 6:** Mean pain score ± SD of dogs treated with different doses CRI tramadol hydrochloride

Days post-surgery	Group 1	Group 2	Group 3	Group 4
Day 0	2.00±1.15 <sup>a</sup>	1.33±0.58 <sup>b</sup>	0.00±0.00 <sup>c</sup>	9.33±2.31 <sup>d</sup>
Day 1	1.67±0.58 <sup>a</sup>	1.67±1.15 <sup>a</sup>	0.67±0.58 <sup>a</sup>	9.33±2.52 <sup>b</sup>
Day 2	2.00±0.58 <sup>a</sup>	2.33±1.53 <sup>a</sup>	1.00±0.00 <sup>a</sup>	6.33±4.04 <sup>b</sup>
Day 3	1.67±0.67 <sup>a</sup>	0.33±0.58 <sup>a</sup>	0.00±0.00 <sup>a</sup>	3.33±4.93 <sup>b</sup>
Day 4	0.67±0.58 <sup>a</sup>	1.00±1.00 <sup>a</sup>	0.33±0.58 <sup>a</sup>	2.00±3.46 <sup>a</sup>
Day 5	0.33±0.58 <sup>a</sup>	0.33±0.58 <sup>a</sup>	0.00±0.00 <sup>a</sup>	0.67±0.58 <sup>a</sup>
Day 6	0.00±0.00 <sup>a</sup>	0.00±0.00 <sup>a</sup>	0.00±0.00 <sup>a</sup>	0.00±0.00 <sup>a</sup>
Day 7	0.00±0.00 <sup>a</sup>	0.00±0.00 <sup>a</sup>	0.00±0.00 <sup>a</sup>	0.00±0.00 <sup>a</sup>

Different superscripts a,b,c,d within the row indicate significant difference among group means ( $P<0.05$ )

**Table 7:** Mean body weight ± SD (kg) of dogs treated with different doses of CRI tramadol hydrochloride

Days post surgery	Group 1	Group 2	Group 3	Group 4
Day 0	6.60±0.15	6.10±0.10	6.13±0.23	6.33±0.42
Day 1	6.50±0.45	6.10±0.00	6.13±0.23	6.33±0.27
Day 2	6.56±0.06	6.13±0.06	6.17±0.29	6.50±0.36
Day 3	6.56±0.22	6.17±0.06	6.20±0.35	6.50±0.46
Day 4	6.57±0.15	6.17±0.06	6.23±0.25	6.40±0.66
Day 5	6.57±0.00	6.37±0.06	6.33±0.15	6.40±0.66
Day 6	6.59±0.18	6.40±0.17	6.43±0.12	6.37±0.61
Day 7	6.59±0.18	6.40±0.17	6.43±0.12	6.43±0.57

No significant difference among group means ( $P>0.05$ )

tramadol decreases blood glucose is via its specific role in carbohydrate metabolism to suppress gluconeogenesis and glucose mobilization to the blood (Berene & Levy, 1998; Bishop *et al.*, 2005). More so, serotonin antidepressants such as tramadol cause hypoglycaemia (Peyrière *et al.*, 2004).

The results of the pain score were also consistent with those of blood glucose. This strongly suggests that administration of tramadol hydrochloride by constant rate infusion was able to minimize intra-operative and early post-laparotomy pain. The effectiveness of tramadol hydrochloride in treating moderate pain has been reported to be comparable to that of morphine (Rossi, 2013). Tramadol hydrochloride is also a TRPV1 (transient receptor potential cation channel subfamily V member 1) receptor agonist (Marincsák *et al.*, 2008) with an inhibitory action on the 5-HT<sub>2C</sub> receptor. This inhibition could be partially responsible for its reducing effect on depressive and obsessive-compulsive symptoms in patients with pain and co-morbid neurological illnesses (Ogata *et al.*, 2004). The significant higher pain score at one hour post-surgery in the 0.5mg/kg/hr tramadol HCL treated group, followed by the

1.0mg/kg/hr group suggests a dose-dependent analgesic effect of CRI tramadol HCL. The combination of tramadol by CRI and ketoprofen also caused further reduction in blood glucose and pain scores. Although this combination has not been previously studied but this finding agrees with studies which suggested a possible synergy with the combination of parenteral tramadol and ketoprofen (Miranda *et al.*, 2009; Martins *et al.*, 2010; Miranda *et al.*, 2012; Ugwu *et al.*, 2016a, Ugwu *et al.*, 2016b). The minimal pain recorded in dogs which received 2.0mg/kg/hr of CRI tramadol hydrochloride in combination with ketoprofen also suggests a dose-dependent analgesic effect of the combination on acute pain.

The findings in the mean body weight of both treated and control dogs suggest that the treatments had no observable adverse effect on the digestive system post-surgery that could have resulted in reduced feeding. Changes in body weight have been shown to reveal the health status of an animal and hence, may be depressed after surgical procedures due to surgical stress and postoperative pain (Opara *et al.*, 2010; Flecknell and Liles, 1991).

In conclusion, the use of CRI tramadol hydrochloride at doses of 0.5mg/kg/hr, 1.0mg/kg/hr and 2.0mg/kg/hr attenuated rise in pain assessment parameters. Therefore, the graded doses were all effective in the management of peri-operative pain up to one hour

post-surgery. These treatments also produced balanced analgesia as a supplement to ketoprofen. However, CRI dose of 2.0mg/kg/hr was more effective especially as an supplement to ketoprofen as it produced better analgesia than the other two doses that were studied.

## References

- Berene MR & Levy NM (1998). *Physiology, fourth edition*, Mosby, St. Louis, Baltimore, Boston, Carlsbad, Chicago, Minneapolis, New York, London, Sydney, Tokyo. Pp 910-929.
- Bishop LM, Fody PE & Schoe HL (2005). *Clinical Chemistry Principles, Procedures Correlations, fifth edition*, Lippincott Williams and Wilkins, Philadelphia, Hong Kong. Pp 330-253.
- Boothe DM (2001). *Veterinary Pharmacology and Therapeutics, eighth edition*. Adams, HR Iowa state University Press. Amesterdam Pp 433-451.
- Brook C & Marshall N (2001). *Endocrinology*. Blackwell Science. Pp 37-47.
- Cagnardi P, Villa R, Zonca A, Gallo M, Beccaglia M, Luvoni GC, Vettorato, E, Carli, S, Fonda, D & Ravasio G (2011). Pharmacokinetics, intraoperative effect and postoperative analgesia of tramadol in cats. *Research in Veterinary Science*, **90**(3): 503-509.
- Eze CA, Nweke RI & Nwangwu NC (2004). Comparison of physiologic and analgesic effect of xylazine/ketamine, xylazine/lignocaine and lignocaine anaesthesia in WAD goats. *Nigerian Veterinary Journal*, **25**(2): 39-47.
- Firth AM & Haldane SL (1999). Development of a scale to evaluate postoperative pain in dogs. *Journal of American Veterinary Medical Association*, **214**(5): 651-659.
- Flecknell PA (1996). Guidelines for the Assessment and Management of Pain in Rodents and Rabbits: American College of Laboratory Animal Medicine. In: *Laboratory Animal Anaesthesia*, second edition. London, Academic Press. Pp 159-223.
- Flecknell PA & Liles JH (1991). The effects of surgical procedures, halothane anaesthesia, and nalbuphine on the locomotor activity and food and water consumption in rats. *Laboratory Animals*, **25**(1): 50-60.
- Gaynor JS & Muir WW (2009). *Handbook of Veterinary Pain Management*, second edition, St. Louis, MO, Mosby Elsevier. Pp 260-276.
- Gassel AD, Tobias KM, Egger CM & Rohrbach BW (2005). Comparison of oral and subcutaneous administration of buprenorphine and meloxicam for preemptive analgesia in cats undergoing ovariohysterectomy. *Journal of the American Veterinary Medical Association*, **227** (12): 1937-1944.
- Gilberto DB, Motzel SL, Bone AN, Burns CL, Zeoli AH, Lodge KE & Goode TL (2002). Use of three infusion pumps for postoperative administration of buprenorphine or morphine in dogs. *Journal of American Veterinary Medical Association*, **20**(4): 1655-1660.
- Guedes AGP, Rude EP & Rider MA (2006). Evaluation of histamine release during constant rate infusion of morphine in dogs. *Veterinary Anaesthesia and Analgesia*, **33**(1) 28-35.
- Hansen B (2005). Analgesia and sedation in the critically ill. *Journal of Veterinary Emergency and Critical Care*, **15**(4): 285-294.
- Hansen B & Hardie E (1993). Prescription and use of analgesics in dogs and cats in a veterinary teaching hospital: 258 cases (1983-1989). *Journal of American Veterinary Medical Association*, **202**(9):1485-1494.
- Hosking J & Welch E (1985). Assessment of pain. In: Post operation pain: understanding its natures and how to treat it. Faber and Faber, London. Pp 44-55.
- KuKanich B & Papich MG (2004). Pharmacokinetics of tramadol and the metabolite O-desmethyltramadol in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **27**(4): 239-246.
- Landa L (2012). Pain in domestic animals and how to assess it. *Veterinary Medicine*, **57**(4): 185-192.
- Marina CE, Rodrigo AS, Larissa BC, Marcia APK, Thais CR, Julia MM & Denise TF (2014). Comparison of preoperative tramadol and pethidine on postoperative pain in cats undergoing ovariohysterectomy. *BMC Veterinary Research*, **10**:252.
- Martins TL, Kahvegian MA, Noel-Morgan J, Leon-Román MA, Otsuki DA & Fantoni DT (2010). Comparison of the effects of tramadol, codeine, and ketoprofen alone

- or in combination on postoperative pain and on concentrations of blood glucose, serum cortisol, and serum interleukin-6 in dogs undergoing maxillectomy or mandibulectomy. *American Journal of Veterinary Research*, **71**(9): 1019-1026.
- Miranda HF, Puig MM, Prieto JC & Pinardi G (2006). Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. *Pain*, **121**(1-2): 22-28.
- Miranda HF, Puig MM, Romero MA & Prieto JC (2009). Effects of tramadol and dextketoprofen on analgesia and gastrointestinal transit in mice. *Fundamentals of Clinical Pharmacology*, **23**(1): 81-88.
- Lemke KA, Runyan CL & Horney BS (2002). Effects of preoperative administration of ketoprofen on anaesthetic requirements and signs of post operative pain in dogs undergoing elective ovariohysterectomy. *Journal of American Veterinary Medical Association*, **221**(9):1268-1275.
- Marincsák R, Tóth BI, Czifra G, Szabó T, Kovács L & Bíró T (2008). The analgesic drug, tramadol, acts as an agonist of the transient receptor potential vanilloid-1. *Anesthesia and Analgesia*, **106** (6): 1890-1896.
- Middleton C (2003). Understanding the physiological effects of unrelieved pain. *Nursing Times*, **99**(37): 28.
- Mildh LH, Leino KA & Kirvel AO (1999). Effects of tramadol and meperidine on respiration, plasma catecholamine concentrations, and hemodynamics. *Journal of Clinical Anesthesia*, **11**(4):310-316.
- Marina CE, Rodrigo AS, Larissa BC, Marcia APK, Thais CR, Julia MM & DeniseTF (2014). Comparison of preoperative tramadol and pethidine on postoperative pain in cats undergoing ovariohysterectomy. *BMC Veterinary Research*, **10**:252.
- Molony V (1997). Comments on Anand and Craig (Letter to the editor). *Pain*, **70**:293.
- Muir WM, Weise AJ & March PA (2003). Effects of morphine, lidocaine, ketamine, and morphinelidocaine-ketamine drug combination on minimum alveolar concentration in dogs anaesthetised with isoflurane. *American Journal of Veterinary Research*, **69**(9): 1155-1160.
- Ogata J, Minami K, Uezono Y, Okamoto T, Shiraishi M, Shigematsu A & Ueta Y (2004). "The inhibitory effects of tramadol on 5-hydroxytryptamine type 2C receptors expressed in Xenopus oocytes". *Anesthesia and Analgesia*, **98** (5): 1401-1406.
- Opara MN, Udevi N, Okoli IC (2010). Hematologic parameters and blood chemistry of apparently healthy West African Dwarf goats in Owerri, South Eastern, Nigeria. *New York Science Journal*, **3**(8), 68-72.
- Ortega M & Cruz I (2011). Evaluation of a constant rate infusion of lidocaine for balanced anaesthesia in dogs undergoing surgery. *Canadian Veterinary Journal*, **52** (8): 856-860.
- Page GG, Blakely WP & Ben-Eliyahu, S (2001). Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. *Pain*, **90**(1-2): 191-199.
- Perez-Urizar J, Martinez-Rider R, Torres-Roque I, Garrocho-Rangel A & Pozos-Guillen A (2014). Analgesic efficacy of lysine clonixinate plus tramadol versus tramadol in multiple doses following impacted third molar surgery. *International Journal of Oral and Maxillofacial Surgery*, **43**(3): 348-354.
- Peyrière H, Villiet M, Albert V & Creus, M (2004). Hypoglycemia related to Tramadol therapy. *Analysis of cases reported in the French Pharmacology*, **18**(2): 215-268.
- Rossi S ed. (2013). Australian Medicines Handbook, 2013 edition. The Australian Medicines Handbook Unit Trust Adelaide. Pp 653-654.
- Saha JK, Xia J, Grondin JM, Engle SK & Jakubowski JA (2005). Acute hyperglycemia induced by ketamine/xylazine anaesthesia in rats, mechanisms and implications for preclinical models. *Experimental Biology and Medicine*, **230**(10):777-784.
- Sano Y, Syuzo-Takabatake A, Nakaya T, Saito Y, Tomita S, Itohara S & Suzuki T (2006). Enhanced amyloidogenic metabolism of the amyloid beta-protein precursor in the X11L-deficient mouse brain. *Journal of Biology and Chemistry*, **281**(49): 37853-60.
- SPSS (Statistical Package for Social Sciences) Inc. Released (2007). SPSS for windows, version 16.0. Chicago.
- Stefano GB, Fricchione G, Goumon Y & Esch T (2005). Pain, immunity, opiate and opioid compounds and health. *Medical Science Monitoring*, **11**(5):47-53.
- Udegbunam RI, Onuba AC, Okorie-Kanu C, Udegbunam SO, Anyanwu MU & Ogbonna LI (2014). Effects of two doses of tramadol on pain and some biochemical parameters in rabbits post-gastrotomy. *Comparative Clinical Pathology*, doi: 10.1007/s00580-014-1983-y

- Ugwu NE, Eze CA & Udegbunam RI (2016a). Some haematological changes associated with constant rate infusion of ketoprofen and ketoprofen+tramadol combination in dogs undergoing laparotomy. In: *Proceedings of 41<sup>st</sup> Nigerian Society for Animal Production Conference*, Abeokuta, Ogun state, Nigeria. Pp 89-91.
- Ugwu NE, Udegbunam RI, Eze CA, Ofor GO, Udegbunam SO, Ogbanya KC, Nnaji TO & Onuba AC (2016b). Effects of constant rate infusion of ketoprofen and ketoprofen+tramadol combination on laparotomy-induced pain in dogs. In: *Proceedings of 52<sup>nd</sup> annual congress of the Nigerian Veterinary Medical Association*, Rivers state, Nigeria. Pp 41-49.
- Vaughan TJ (1980). The exploratory laparotomy of the *In: Veterinary Gastroenterology*. (NV Anderson, editor). Lea and Febiger, Philadelphia. Pp 108.
- Wagner AE, Walton JA, Hellyer PW, Gaynor JS & Mama KR (2002). Uses of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. *Journal of American Veterinary Medical Asociation*, **221**(1): 72-75.