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 postsurgery (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

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), steroidal 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 ± SEM age and weight of 12.93 ± 1.33 and 6.10 ± 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®, 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®, 5%) and ketoprofen (Ketonal®, 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®, Pauco Pharmaceutical), xylazine (XYL-M2®, VMD Belgium) and ketamine hydrochloride (Ketamine®, Laborate Pharmaceutical, India).
Gentamicin sulphate injection (Pantex-Genta 100®, 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 ± SD duration of mid-ventral laparotomy was 17.40±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±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 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 seperated at post-hoc using LSD. Pain score was analysed using non-parametric Kruskal-Wallis test. The mean ranks of pain scoring

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

| Behavioral changes                  | Numerical scores |
|-------------------------------------|------------------|
| **Activity**                        |                  |
| At rest (sleeping and semi-conscious) | 0                |
| At rest (awake)                     | 1                |
| Restless                            | 2                |
| Rolling and thrashing               | 3                |
| **Mental status**                   |                  |
| Submissive                          |                  |
| Overtly friendly                    |                  |
| Wary                                |                  |
| Aggressive                          |                  |
| **Response to palpation**           |                  |
| No change from pre-surgery behavior |                  |
| Sitting or standing, head up; moving |                  |
| Standing, head hanging down; Guarding or protecting affected area |                  |
| **Posture**                         |                  |
| Lateral recumbency                  |                  |
| Lateral recumbency; sitting or standing, head up; moving |                  |
| Standing, head hanging down; Guarding or protecting affected area |                  |
| Lateral recumbency; abnormal posture|                  |
| **Vocalization**                    |                  |
| Not vocalizing                      |                  |
| Vocalizing when touched             |                  |
| Vocalizing when touched             |                  |
| Vocalizing when touched             |                  |
| Vocalizing when touched             |                  |
| **Table 2: Subjective pain assessment using changes in vital parameters**

| Vital parameters | Numerical scores |
|------------------|------------------|
|                  | 1                |
| Heart rate       |                  |
| Within pre-surgery range | 20% > pre-surgery value |
| Respiratory rate |                  |
| Within pre-surgery range | 20% > pre-surgery value |

Firth & Haldane (1999)
were presented as mean and standard deviation (Mean ± 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 ± 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±30.78 | 104.00±8.31 | 109.33±8.18 | 108.00±8.26 |
| 20               | 100.67±12.67 | 94.67±18.61 | 94.00±22.37 | 96.00±8.26 |
| 40               | 102.00±28.42 | 92.00±12.31 | 107.00±14.00 | 95.00±4.85 |
| 60               | 105.67±17.64 | 103.33±24.02 | 98.67±8.66 | 100.00±14.20 |
| 80               | 105.67±15.38 | 109.33±24.24 | 102.33±3.90 | 100.00±12.11 |
| 100              | 95.00±35.94  | 92.33±06.82  | 86.00±6.12  | 88.00±12.25  |

No significant difference among group means (P>0.05)

| Table 4: Mean respiratory rate ± 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±0.00 | 43.00±2.64 | 39.00±6.56 | 40.33±4.51 |
| 20               | 42.67±11.85 | 42.67±4.62 | 31.33±13.61 | 38.33±10.02 |
| 40               | 40.00±11.11 | 40.00±8.00 | 33.33±11.55 | 39.00±5.77 |
| 60               | 39.33±19.31 | 39.33±13.61 | 36.67±7.57 | 41.33±5.29 |
| 80               | 40.67±8.67  | 36.33±14.15 | 38.33±7.64  | 36.67±4.62  |
| 100              | 42.67±17.48 | 36.67±8.39  | 41.00±3.61  | 37.33±6.43  |

No significant difference among group means (P>0.05)
Tramadol decreases blood glucose 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-HT3c 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 synergism 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).

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            | 81.3±20.78     | 92.00±4.58     | 89.33±8.62     | 93.67±4.16     |
| Intra-surgery       | 100.3±18.87a   | 99.33±29.24a   | 78.00±8.62a    | 185.67±28.15b  |
| Post-surgery (1 hps)| 90.00±8.26a    | 90.00±10.73ab  | 70.00±10.68b   | 194.33±43.32b  |
| Post-surgery (24 hps)| 85.00±5.15a   | 80.33±4.98a    | 82.33±5.16a    | 90.33±20.46a   |

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±1.15a     | 1.33±0.58a     | 0.00±0.00a     | 9.33±2.31a     |
| Day 1             | 1.67±0.58a     | 1.67±1.15a     | 0.67±0.58a     | 9.33±2.52b     |
| Day 2             | 2.00±0.58a     | 2.33±1.53a     | 1.00±0.00a     | 6.33±2.04b     |
| Day 3             | 1.67±0.67a     | 0.33±0.58a     | 0.00±0.00a     | 3.33±2.93b     |
| Day 4             | 0.67±0.58a     | 1.00±1.00a     | 0.33±0.58a     | 2.00±3.46a     |
| Day 5             | 0.33±0.58a     | 0.33±0.58a     | 0.00±0.00a     | 0.67±0.58a     |
| Day 6             | 0.00±0.00a     | 0.00±0.00a     | 0.00±0.00a     | 0.00±0.00a     |
| Day 7             | 0.00±0.00a     | 0.00±0.00a     | 0.00±0.00a     | 0.00±0.00a     |

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 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)
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.

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