Journal of Veterinary Science & Technology

Kindu et al., J Vet Sci Technol 2018, 9:2
DOI: 10.4172/2157-7579.1000547

Research Article Open Access

# Preemptive Analgesic Effects of Tramadol for Ovariohysterectomy in Bitches

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**Rec date:** August 02, 2016; **Acc date:** May 30, 2018; **Pub date:** May 31, 2018



## Abstract

An experimental study was conducted on 12 healthy bitches presented to University of Gondar Veterinary Clinic for Ovariohysterectomy to evaluate the preemptive analgesic efficacy of tramadol to relieve postoperative pain. The bitches were randomly assigned to experimental group I and II. Anesthesia was achieved by administration of atropine (0.04 mg/kg BW, SC) and immediately followed with xylazine-ketamine combination, (1.0 mg/kg+10 mg/kg BW, IM). When the bitch is attaining lateral recumbency, diazepam (0.5 mg/kg, BW, IV) was given. Maintenance of anesthesia was achieved by giving Ketamine (5.0 mg/kg, IV) for the bitches that showed movement during surgery. Tramadol (2.0 mg/kg, BW, IV) was administered only in group I bitches immediately after induction of anesthesia. The physiological parameters and pain scoring using Glasgow Composite Measure Pain Scale (GCMPS) and Categorized Numerical Rating Scale (CNRS) were assessed at different stages of analgesia. There was a significant ($p<0.05$) reduction in the rectal temperature, respiratory rate and heart rate at postoperative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. Postoperative pain assessment by GCMPS as well as CNRS revealed reduction in pain at postoperative 0, 30, 60, and 90 minutes in group I bitches as compared to group II due to the inclusion of tramadol in group I which favored better postoperative analgesic effect. No complications were encountered in any of the bitches in the present study revealing that the anesthetic and analgesic protocol employed was safe. However further longterm studies are needed to compare the efficacy of tramadol for various surgeries.

**Keywords:** Bitch; Ovariohysterectomy; Postoperative pain; Preemptive analgesia; Tramadol

## Introduction

Elective ovariohysterectomy is the most frequently common surgical procedure performed in companion animal practice [1] and the Center for Veterinary Medicine of the United States Food and Drug Administration considers Ovariohysterectomy (OHE) to cause moderate pain, making it suitable for clinical studies of analgesia [2].

According to the classification of pain as proposed by Ready [3], pain occuring in the postoperative period is classified as acute and is characterized by disagreeable emotional and sensory experiences arising from tissue lesions. The ability to communicate verbally and physically helps to identify pain in humans. In the case of non verbal animals, pain is a sort of behavioral reaction to an aversive sensory experience associated with actual or potential tissue damage [4].

Postoperative pain can result in many undesirable effects such as a decrease in food intake, exacerbated protein catabolism, depression of respiratory function, cardiac dysrhythmias, central hypersensitivity to noxious stimuli and chronic pain [5]. All these changes delay recovery [6]. Postoperative pain also increases the rate of postoperative infection, sepsis and delaying wound healing [7].

Routinely, post-operative pain is managed in animals and humans by giving analgesics during or immediately after surgery [8]. However, the use of analgesics before surgery (pre-emptive analgesia) to minimize post-operative pain has generated a lot of interests in the past few decades [9]. This practice prevents the occurrence of nociceptive input and minimizes or prevents any memory of pain in the central nervous system (CNS), thus resulting in lower analgesic consumption [10].

Analgesia is achieved by interrupting the nociceptive processes such as transduction, transmission, modulation and perception at one or more points between the peripheral nociceptors and the cerebral cortex [11]. Opioids are among the best therapeutic tools to control pain because they are highly selective and reasonably safe. Side effects, mainly respiratory depression, can be reversed by the administration of an opioid antagonist or agonist-antagonist agent [12]. Opioids produce analgesia through their action on specific mu(μ), kappa and delta opioid receptors found in the nervous system and various tissues. Opioids, especially μ -agonists, provide the most effective pain control [13].

Tramadol is both a weak opioid agonist with selectivity for the μ-receptor and a weak inhibitor of the reuptake of noradrenaline and 5-hydroxytryptamine (5-HT). This dual mechanism of action may be attributed to the two enantiomers of racemic tramadol. The (+) enantiomer has a higher affinity for the μ-receptor and is a more effective inhibitor of 5-HT reuptake, whereas the (–) enantiomer is a more effective inhibitor of noradrenaline reuptake and increases its release by auto receptor activation. Since endogenous noradrenaline and 5-HT are involved in central pain modulation, these properties may thus enhance the analgesic effects of tramadol produced by its opioid binding activity [14]. This binary mechanism of action of tramadol may explain the reduced potential for abuse as well as less significant respiratory depression and other adverse effects typically attributed to traditional opioids [15]. Therefore, the objective of this study is to evaluate the preemptive analgesic effects of tramadol for

ovariohysterectomy in bitches and to assess the level of pain by pain score scales and physiological parameters.

## Materials and Methods

The study was conducted on bitches that were brought to University of Gondar Veterinary Clinic for elective ovariohysterectomy (OHE) were used. By routine screening, twelve apparently healthy bitches of approximately same age and body weight were selected for ovariohysterectomy for measuring the effect of tramadol. The bitches which were in diestrus period were only selected for the study. All the selected bitches were assigned into two groups as group I (tramadol group) and group II (control group) using a complete randomized design comprising of six bitches each. OHE was performed in all the bitches through ventral midline approach as per the standard surgical procedure [16].

### Preoperative preparation of bitches

The bitches in both groups were withheld from water and food for 6 and 12 hours, respectively before surgery. The cephalic vein was catheterized using a 23 Gauge, 0.75 inch, butterfly catheter, after surgical preparation of the site and secured with adhesive tape around the leg for administration of anesthetic and analgesic drugs and maintenance of anesthesia.

### Anesthetic protocol

The OHE was done employing the following injectable general anesthetic protocol in all the animals of both groups (Table 1).

| Group | Induction of anaesthesia | Maintenance by incremental dose |
|---|---|---|
| Group 1 and 2 | a. Atropine 0.04 mg/kg/sec | Ketamine 5.0 mg/kg, IV |
| | b. Immediately followed with Xylazine 1 mg/kg+Ketamine 10.0 mg/kg IM | |
| | c. After attaining lateral recumbency Diazepam 0.5 mg/kg, IV | |

**Table 1:** Anesthetic protocol for both groups of bitches.

### Predicaments and anesthetics employed

**Atropine sulphate:** It is used as antisialagogue and to block the acetylcholine action. Atropine acted on heart by blocking vagal effect on receptors, which resulted in tachycardia. Injection of Atropine sulphate (ATN-MB, Martin & Brown-Bioscience, Baddi, India) 0.5 mg/ml was used for premedication in the present study for all the bitches.

**Xylazine hydrochloride:** It was the most commonly administered sedative-analgesic in canine and in these species; it has been proven as a safe anesthetic adjunct of ketamine hydrochloride to induce short periods of surgical anesthesia which improve visceral analgesia and muscle relaxation. Injection of Xylaxin®, (Indian Immunologicals ltd., India) 20 mg/ml was used for premedication in the present study for all the bitches.

**Ketamine hydrochloride:** It was a dissociative anesthetic which causes dissociation of thalamocortic and limbic system producing a characteristic cataleptic state with profound peripheral analgesia and altered consciousness. It had a rapid onset of action, with maximal effect occurring in approximately one minute. Injection of Ketamax®, (Troikaa pharmaceutical ltd, India) 50 mg/ml was used in the present study as an anesthetic induction agent in all the bitches.

**Diazepam:** It was a benzodiazepine derivative had calming, muscle relaxing and anticonvulsant effect. It is used as a pre-anesthetic to relieve skeletal muscle spasm. The anxiolytic and skeletal muscle relaxing effects are as a result of increased availability of inhibitory neurotransmitter glycine. Sedation and anticonvulsant activity are mediated by GABA. Injection of Calmpose®, (Sun pharmaceutical ltd., India) 5 mg/ml was used in the present study as an agent to relieve skeletal muscle spasm in all the bitches.

### Intravenous preemptive analgesia

Immediately after induction of anesthesia, animals in Group I were given tramadol 2.0 mg/kg body weight intravenously. The total required dose was diluted in distilled water to a volume of 10 ml and administered over a period of 3 min. This is in accordance with Mastrocinque and Fantoni [17] in a study compared tramadol at dose rate of 2 mg/kg with morphine at dose rate of 0.2 mg/kg after both agents were diluted in saline solution to a volume of 10 mL and administered intravenously over 3 minutes for the control of post-operative pain following OHE and found tramadol produced analgesia equivalent to morphine. Injection of Tramrod®, (Supelmax drugs and pharmaceuticals ltd., India) 50 mg/ml was used in the present study as a preemptive analgesic agent in the bitches of group I.

### Maintenance of anesthesia

In all the bitches, maintenance of general anesthesia was carried out with incremental injections of ketamine hydrochloride at dose rate of 5.0 mg/kg body weight intravenously.

### Surgical site preparation

The operating table was cleaned by 70 percent alcohol and all sterilized materials used for the surgery was ready and the bitch was placed in dorsal recumbency for midline approach and surgical site at the ventral abdomen from the xiphoid to the pubis was shaved and aseptically prepared with 7.5 percent povidone iodine scrub solution and animals was appropriately positioned on the operating table and ready for surgery.

### Surgical procedure of ovariohysterectomy

**Midline surgical approach:** A midline abdominal incision was made on the skin approximately 1 cm caudal to the umbilicus and extended about 5 cm caudally. The subcutaneous tissue was lifted with Allis tissue forceps and was cut down with scissor. Linea alba was lifted with Allis tissue forceps and a small stab incision was given with upward direction of cutting edge of scalpel. Scissor was inserted into the small stab incision and the linea alba was opened equal to the size of skin incision. Then right uterine horn was exteriorized by index finger. A small hemostat was placed across the proper ligament to aid in the caudal retraction of ovary.

The suspensory ligament was broken. The ovarian arteriovenous complex was identified and by using artery forceps an opening was made in the mesovarian immediately caudal to the ovarian arteriovenous complex in an area clear of vessels and fat. The first

clamp was placed immediately proximal to the ovary, the second approximately 5.0 mm proximal to the first and the third across the proper ligament and the ovarian arteriovenous complex was transected between the middle clamp and the ovary. A circumferential ligature using 2/0 polydioxonone was loosely placed around the proximal clamp and was tightened as the clamp was removed so that way it got tightened in the groove of crushed tissue created by clamp. The ligated ovarian arteriovenous complex was grasped in the thumb forceps and the middle clamp was removed and inspected for bleeding before leaving it back into the abdominal cavity. Then, right uterine horn was followed distally to the bifurcation and left uterine horn was located and was followed proximally to the right ovarian arteriovenous complex.

The same method of ligation and transaction was used for the left ovarian arteriovenous complex as was performed on left side. A window was made in broad ligament adjacent to the uterine artery and vein, vessels were ligated with 2/0 polydioxonone and broad ligament was grasped and torn. The uterine body and cervix was exteriorized and clamps were applied immediately proximal to the cervix. The uterine body was held and ligated with circumferential sutures using 2/0 polydioxonone. The clamp was removed and uterine stump was evaluated for bleeding and then replaced in the abdomen. Then abdominal incision was closed. Linea alba and subcutaneous tissues was closed with 2/0 polydioxonone using simple interrupted and simple continuous suture patterns, respectively. The skin was closed with cotton thread using cruciate mattress suture pattern. Antiseptic was applied to the suture line and bandaged. The bitches are shifted from Operation Theater to outside after ensuring recovery from anesthesia.

### Quality of recovery

The quality of anesthetic recovery was assessed and graded as smooth-If no excitement was noticed during recovery and rough if excitement was noticed during recovery.

### Post-surgical management

The suture line was dressed and bandaged and 20% oxytetracycline was given. Bitches were kept in owner's house after surgery. The general attitude, appetite, defecation, urination and subjective evaluation of incisional healing was done. After healing of skin incision wound, sutures were removed on 7th PO day in all the animals.

### Parameters studied

**Physiological parameters:** In group I and II, rectal temperature, respiratory rate and heart rate were recorded at 30 minute before premedication (as a baseline) and at postoperative 0 (onset of recovery) 30, 60, 90 minutes and 24 hour after surgery. Rectal temperature in degree Celsius (°C) was measured using a clinical thermometer and the heart rate in beats per minute and the respiratory rate in breaths per minute using a stethoscope.

**Pain assessment parameters:** Pain was assessed according to the GCMPS for dogs, a practical and recognized way of evaluating postoperative pain [18] and CNRS as described by Hellyer et al. [19]. Pain scoring was recorded in both groups at 30 minute before premedication (as baseline) and at postoperative 0 (onset of recovery), 30, 60 and 90 minutes and 24 hours after surgery using Glasgow composite measure pain scale (GCMPS) and Categorized Numerical Rating Scale (CNRS).

### Statistical analysis

Statistical analysis was performed using the SPSS program (IBM® SPSS software Inc. version 20, New York, USA). The results are expressed as the means ± SD. The physiological parameters and pain scores were compared using an independent t-test between the groups. A p-value of less than 0.05 was considered to be statistically significant.

## Results

The study was conducted in twelve healthy bitches and there was no significant difference ($p<0.05$) in age and body weight between the two groups. The average age and body weight (mean ± SD) in both groups of bitches selected for the study were 2.17 ± 0.98 and 2.17 ± 0.75 years and 15.33 ± 0.82 and 14.33 ± 0.82 kg in group I and II respectively. There was no significant difference ($p<0.05$) both in duration of surgery (51.00 ± 7.75 min, 46.00 ± 4.24 min) and duration of anesthesia (76.67 ± 18.80 min, 62.17 ± 6.08 min) in group I and II bitches respectively. With holding of feed and water for 12 and 6 h, respectively prior to premedication and induction of anesthesia was found satisfactory to prevent any complication events during anesthesia in both groups. The cephalic vein was catheterized using 23G, 0.75 inch, butterfly catheter was suitable and accidental dislodgement of needle was not encountered in any of the animals in both groups during the trial.

### Premedication and induction of anesthesia

The dose and route of administration of atropine sulphate at dose rate of 0.04 mg/kg body weight subcutaneously and after a lapse of 5 minute xylazine hydrochloride 1 mg/kg plus ketamine 10 mg/kg body weight intramuscularly and after attaining lateral recumbency diazepam 0.5 mg/kg body weight intravenously employed in the study was found to be effective and provided adequate sedation and facilitated smooth induction of anesthesia in both groups of the bitches.

### Preemptive analgesia

Tramadol administered in group I bitches intravenously at dose rate of 2.0 mg/kg body weight had no adverse effects related to its administration.

### Parameters

#### Physiological parameters

***Rectal temperature:*** The mean ± SD rectal temperature recorded at 30 minutes before premedication and at postoperative 0, 30, 60, 90 minutes and 24 hour after surgery were 39.33 ± 0.82, 35.83 ± 0.41, 36.33 ± 0.52, 37.17 ± 0.41 ± 37.33 ± 0.52, 38.67 ± 0.82°C in group I and 38.67 ± 0.52, 37.00 ± 0.63, 37.83 ± 0.73, 38.17 ± 0.41, 38.17 ± 0.41, 38.5 ± 0.55°C in group II bitches respectively (Figure 1).

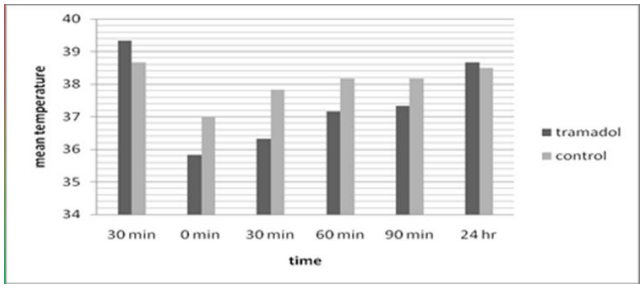


**Figure 1**: Mean temperature recorded during different stages of analgesia with in tramadol and control group.

There was a statistically significant (P<0.05) reduction in the rectal temperature at postoperative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. However there was no significant difference (p>0.05) at 30 minutes before premedication and 24 hours after surgery between the two groups.

***Respiratory rate:*** The mean ± SD respiratory rate per min recorded at 30 minute before premedication and at postoperative 0, 30, 60 and 90 minutes and 24 hour after surgery were 29.33 ± 4.13, 16.33 ± 3.88, 17.67 ± 3.45, 22.33 ± 3.20, 28.67 ± 4.13, 32.67 ± 4.50 breaths per min in group I and 29.67 ± 5.28, 22.67 ± 2.07, 25.00 ± 3.03, 26.67 ± 3.01, 33.00 ± 2.76, 35.00 ± 2.10 breaths per min in group II bitches respectively (Figure 2).

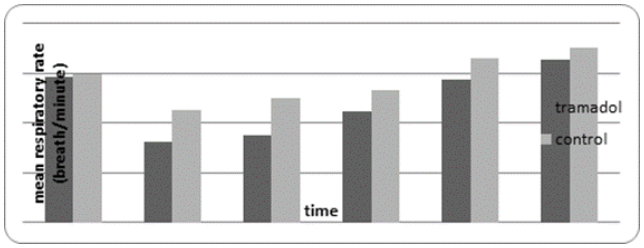


**Figure 2**: Mean respiratory rate recorded during different stages of analgesia with in tramadol and control group.

There was a statistically significant (P<0.05) reduction in the respiratory rate at postoperative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. However there was no significant difference (p>0.05) at 30 minutes before premedication and 24 hours after surgery between the two groups.

***Heart rate:*** The mean ± SD heart rate per min recorded at 30 minute before premedication and at postoperative 0, 30, 60, 90 minutes and 24 hour after surgery were 121.67 ± 6.12, 99.33 ± 4.84, 102.83 ± 6.46, 112.00 ± 5.81, 116.00 ± 9.03, 130.67 ± 3.93 beats per min in group I and 123.67 ± 5.72, 114.00 ± 7.38, 118.67 ± 6.89, 120.67 ± 4.50, 127.67 ± 2.66, 131.67 ± 3.20 beats per min in group II bitches respectively (Figure 3).

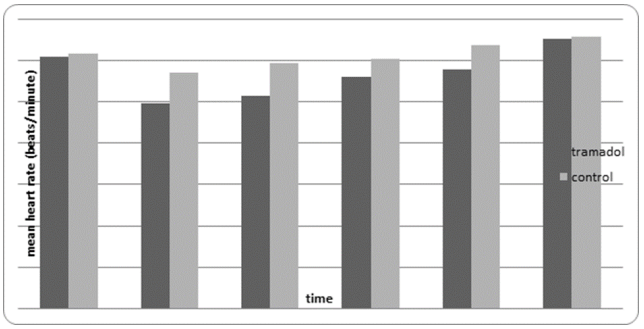


**Figure 3**: Mean heart rate recorded during different stages of analgesia with in tramadol and control group.

There was statistically a significant (P<0.05) decrease in the mean heart rate at postoperative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. However there was no significant difference (p>0.05) at 30 minutes before premedication and 24 hour after surgery between the two groups.

**Pain scores**

***Glasgow composite measure pain scale:*** The (mean ± SD) GCMPS score 30 minutes before premedication and at postoperative 0, 30, 60, 90 minutes and 24 hours after surgery were 0.00, 1.17 ± 0.75, 1.83 ± 0.41, 2.67 ± 0.82, 3.00 ± 0.63, 3.50 ± 1.05 and 0.00, 4.33 ± 0.82, 5.83 ± 1.34, 5.17 ± 1.72, 4.67 ± 1.51, 4.33 ± 0.82 in group I and group II respectively (Figure 4).

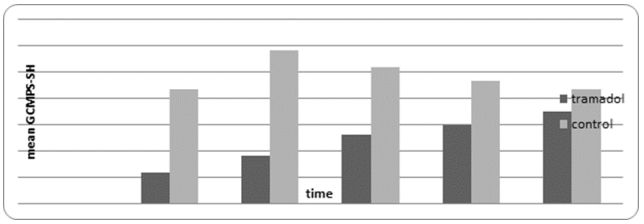


**Figure 4**: Mean pain score recorded by Glasgow Composite Measure Pain scale during different stages of analgesia between groups I & II.

There was statistically a significant (P<0.05) decreased in the GCMPS score at postoperative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. However there was no statistically significant (P>0.05) difference in the GCMPS score at 30 min before premedication and 24 hour after surgery between the two groups.

**Categorized numerical rating scale:** The mean ± SD CNRS score at 30 minutes before premedication and at postoperative 0, 30, 60 and 90 minutes and 24 hours after surgery were 0.00, 0.67 ± 0.82, 1.50 ± 0.55, 1.83 ± 0.75, 2.33 ± 1.03, 3.50 ± 0.84 and 0.00, 2.67 ± 0.82, 3.17 ± 2.23, 3.83 ± 2.04, 4.17 ± 1.94, 6.17 ± 0.98 in group I and group II bitches respectively (Figure 5).

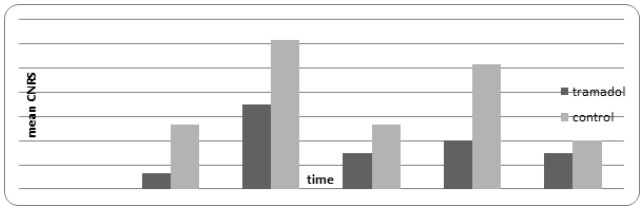


**Figure 5**: Mean pain score recorded by categorized numerical rating scale during different stages of analgesia between groups I & II.

There was statistically a significant (P<0.05) decreased in the CNRS score at postoperative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. However there was no statistically significant (P>0.05) difference in the CNRS score at 30 minutes before premedication and 24 hour after surgery between the two groups.

## Discussion

The clinical analgesic study conducted in two groups of twelve healthy bitches selected with approximately similar age and body weight of the present study was found suitable to obtain more consistent data and facilitated statistical comparison.

The withholding of feed and water for 6 and 12 hours respectively prior to induction of anesthesia was found suitable and prevented vomiting and hyper salivation in all the bitches. Similar observations were recorded by Credie et al. [20] and concur with the procedure employed by Senthil Kumar et al. [21] who reported withholding feed and water for 6 and 12 hours respectively before induction of anesthesia.

Administration of atropine sulphate and xylazine hydrochloride in all the animals as premedication employed in the study was found to be effective, satisfactory and provided adequate sedation and facilitated smooth induction. This concurs with the observations of Parikh et al. who reported that xylazine hydrochloride premedication was effective and provided adequate sedation, muscle relaxation and favored smooth induction in bitches [22].

Ketamine hydrochloride used in the study maintained anesthesia satisfactorily in all bitches. This concurs with used incremental injection of ketamine hydrochloride for maintenance anesthesia in dogs during surgery [23].

In the present study there was decrease in the mean rectal temperature in group I bitches as compared to group II at postoperative 0, 30, 60 and 90 minutes. The differences recorded during the study could be attributed to preemptive analgesia employed. This agrees with the idea mentioned, [24] such that tramadol inhibits neuronal reuptake of nor-epinephrine and 5-hydroxytryptamine facilitates 5-hydroxytryptamine release and activates μ opioid receptors and each of these actions is likely to influence thermoregulatory control and result subnormal temperature.

The result in this study indicated that there was statistically significant decrease (p<0.05) in respiratory rate at postoperative 0, 30, 60 and 90 minutes in group I as compared to group II and this could be attributed to the inclusion of tramadol. Tramadol were reported to cause significant dose dependent respiratory depression mediated through receptors leading to a direct depressant effect on brain stem respiratory centers [25]. Tramadol reduce the sensitivity of the respiratory Centre to carbon dioxide. This may result in decreased tidal volume and decreased respiratory rate [26]. The results in this paper agree with Teppema et al. that in anesthetized cats, 1-4 mg/kg of tramadol caused a dose-dependent depressant effect on ventilator control [27].

Tramadol was reported as a weak inhibitor for the reuptake of noradrenaline and serotonin and possess weak μ receptor activity on respiratory centers. It is also observed that respiratory depression after administration of tramadol which concurs with the present study. It was attributed to its lipophilicity, rapid absorption and rapid distribution to the brain through epidural vein. However, Holton et al. reported no correlation between respiratory rate and pain in dogs [28].

In this study there was statistically a decline in heart rate at post-operative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. This is supported by Lee [29] as he reported that tramadol has caused mild cardiovascular depression in bitches. On contrary Natalini et al. [30] reported no significant changes in cardiopulmonary function after administration of tramadol in bitches.

The mean pain scores of bitches measured by GCMPS and CNRS were lower in bitches received tramadol than those not received tramadol at postoperative 0, 30, 60 and 90 minutes. This could be attributed to the reduction of pain resulted from the tramadol due to the block of rostral transmission of nociceptive impulses by binding of spinal opioids receptors as well as prevention of impulses at nerve fibers and endings by the drug. This idea supported by a study conducted on children undergoing inguinal surgery which was given tramadol at 1 mg/kg and 2 mg/kg before the beginning of surgery which reported that in the first 2 hours, the intensity of pain was lower [31].

In general, it was considered that preemptive analgesia was more effective for control of postoperative pain. The main reasons for such recognition were based on the theories that preoperative medication could block the nociceptive input, increase threshold for nociception and decrease nociceptor receptor activation before the incisional injuries [32].

## Conclusion

This study compares the preemptive analgesic efficacy of tramadol in healthy bitches undergoing ovariohysterectomy and asses the changes in physiological parameters at different stage of analgesia. In the study both anesthetic protocols used provided adequate sedation, muscle relaxation, and a smooth and rapid induction in both groups of bitches. There was a statistically significant reduction in the rectal temperature, respiratory rate and heart rate at postoperative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. But there was no significant difference at 30 min before premedication and 24 hours after surgery between the two groups. A statistically significant decreased was observed in both GCMPS and CNRS score at postoperative 0, 30, 60 and 90 minutes in group I bitches as compared to group II. However there was no significant difference (p>0.05) at 30 minute before premedication and 24 hour after surgery between the two groups. Postoperative pain assessment by GCMPS as well as CNRS revealed reduction in pain in group I bitches as compared to group II. On evaluation of analgesic effects, the inclusion of tramadol preemptively had given better analgesia for postoperative pain in ovariohysterectomized bitches. However there was a limited research done in this topic.

From the above conclusions the following recommendations are forwarded:

- Preemptive administration of tramadol should be used to control postoperative pain in ovariohysterectomized bitches.
- Long term studies are needed to evaluate the efficacy of tramadol for various surgeries
- Different types of pain scale measurements should be used to know the level of pain the animal is faced.
- The dose and duration of analgesic effect of tramadol in bitches should be studied.

## Acknowledgements

We would like to express our great heartfelt gratitude to Professor N. Rajendran and Professor V. Ramaswamy for their guidance, whole hearted advice, provisions of valuable materials and devotion of their time for reading and correcting this paper. We would also like to say thank you for Dr. Ashenafi assefa for his help and advice during the period of our research. Lastly, we extend our appreciation to Gondar University who support us financially and provide material for success of this manuscript.

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