Introduction

In cats and dogs, pain is often associated with tumors, surgery, chemotherapy, radiotherapy, or chronic diseases such as osteoarthritis (Duncan and Lascelles, 2007). Pain thresholds may differ between animal species. It may even vary among individuals of the same species. Therefore, assessing pain in animals is challenging (Mich and Hellyer, 2009).

The general approach for drug use in pain management is listed in the following order: non-opioid drugs, weak opioid drugs, and potent opioid drugs (Hellyer et al., 2007). All opioids used clinically for this purpose show their analgesic effects as μ-receptor agonists (Lamont and Mathews, 2007). Opioid analgesics can be used as an intravenous bolus to achieve rapid analgesia during the postoperative period. Thus, the duration of absorption is reduced and rapid analgesia is achieved (Muir III, 2009).

Tramadol is a synthetic derivative of codeine and is classified as an opiodiergic/monoaminergic drug with weak μ-receptor agonist effects (Lamont and Mathews, 2007). Tramadol can be used to treat moderate to severe pain, such as osteoarthritis, fibromyalgia, diabetic neuropathy, neuropathic pain, and perioperative pain (Lascelles and Gaynor, 2007). This study aimed to examine the effects of tramadol on tumor-related pains and to compare its analgesic effects with morphine.

Material and Methods

Animals

The research material consisted of 20 dogs with tumors, which included different breeds and both genders, brought to the Clinic of Surgery Department, Veterinary Faculty, Ankara University. The dogs were not provided any food for 12 hours preoperation. However, they were allowed to drink water.

Anesthesia protocol

Serum biochemical analysis (blood urea nitrogen, creatinine, alkaline phosphatase, alanine transaminase, aspartate transaminase, bilirubin, albumin, total protein, and gamma-glutamyl transferase) and complete blood count were carried out for preoperative diagnostic evaluation of the dogs. Chest radiographs were taken to exclude metastatic diseases. The age, body weights, heart rates, respiratory rates, and body temperatures were recorded before the operation.

Electrocardiography electrodes were placed in the extremities, and heartbeats were monitored with the multichannel monitor (PETAS, KMA 460 R, 2009).

Comparison of the analgesic effects of morphine and tramadol after tumor surgery in dogs

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Abstract

Background: Pain thresholds may differ between animal species. It may even vary among individuals of the same species. Therefore, assessing pain in animals is challenging.

Aims: The objective of the present study was to compare the analgesic effects of tramadol with morphine.

Methods: The study was carried out on randomly selected 20 dogs with tumors in different breeds and gender. After induction of anesthesia with propofol, dogs were intubated, and anesthesia was maintained with sevoflurane. Intravenous fentanyl citrate was used for intraoperative analgesia after stabilization of the anesthesia. When the tumors were surgically removed and the operation was completed, dogs were divided into two groups to give the postoperative analgesic agent. The first 10 dogs to be investigated were identified as the morphine group and the second 10 dogs as the tramadol group. Postoperative pain scores, heart rates, respiratory rates, and body temperatures were recorded at 0, 4, 8, 12, 16, 20, and 24 hours after the operation.

Results: Pain scores were lower in the morphine group than in the tramadol group during all postoperative processes.

Conclusion: As a result, it was determined that tramadol has immediate analgesic effects than morphine; however, morphine provides better analgesia than tramadol.

Keywords: Dog, Morphine, Pain management, Tramadol, Tumor.

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Ankara, Turkey) during anesthesia. After stabilization of the anesthesia, fentanyl citrate (0.002–0.007 mg/kg, Fentanyl, Johnson and Johnson, Istanbul, Turkey) was applied as an intravenous bolus for the purpose of intraoperative analgesia. Once all surgical procedures were completed, the sevoflurane administration was discontinued, and oxygen was given to dogs to aid resuscitation.

**Analgesia protocol**

After the dogs’ swallowing reflexes had returned and extubated, we accepted this hour as 0th hour, and analgesics were applied. Ten dogs were placed in the morphine group and the other 10 dogs were placed in the tramadol group. At 4-hour intervals, 0.3 mg/kg IV morphine (Morphine HCl, Galen, Istanbul, Turkey) was administered to the morphine group, and 3 mg/kg IV tramadol (Contramal, Abdi İbrahim, Istanbul, Turkey) was administered to the tramadol group. Heart rates, respiratory rates, and body temperatures were measured at 0, 4, 8, 12, 16, 20, and 24 hours. Rectal temperature measurements were made using a digital thermometer (accuracy 0.1°C). Pain scores were evaluated and recorded using the University of Melbourne Pain Scale. Signs of behaviors such as body posture positions, vocalizations, attention to the environment and the caregiver, and appetite were also recorded. The pain score was accepted as normal for 0–9, and higher scores than 9 were accepted as an indicator of pain. In insufficient analgesia cases, 0.2 mg/kg IV morphine was administered to the morphine group, and 2 mg/kg IV tramadol was administered to the tramadol group as additional doses of analgesics. All dogs were evaluated by the same anesthetist.

**Statistical analysis**

Data normality and homogeneity of variances were evaluated using the Shapiro–Wilk test and Levene’s test, respectively. According to the results obtained, the Student’s *t*-test was used to assess the statistical significance of the difference between drug groups in terms of related variables at each time period. Significance tests were carried out in assessing the heart rates, respiratory rates, body temperatures, and pain scores of the groups. The variation of variables related to each drug group over time was assessed by analysis of variance in repeated measures. *p* < 0.05 was accepted as statistically significant.

**Ethical approval**

The research was conducted with the approval of the Ethics Committee of the University of Ankara (2009-45 211). Consent for the inclusion of the patients in the study was obtained from the dog owners.

**Results**

**Heart rates**

In both groups, heart rates at 0th hour were found higher than the preoperative values. The changes in heart rates between the preoperative and 0th hour were statistically significant (*p* < 0.05). The heart rates were observed as decreasing from the 4th hour in relation to the 0th hour (Fig. 1).

**Respiratory rates**

There were no significant differences between the groups in respiratory rates (*p* > 0.05) at all time periods (Fig. 2).

**Body temperatures**

Body temperatures were significantly decreased in both groups at 0th hour. At the 4th hour, temperatures were closer to the preoperative values at all time periods. The difference between the groups at the 0th hour was statistically significant (*p* < 0.05) (Fig. 3).

**Pain scores**

The pain scores of the morphine group are lower than the tramadol group. The mean pain scores of both groups decreased over time (*p* < 0.001). This decrease in pain scores stopped and stabilized from the 8th hour. There were no significant differences between the groups in time-based comparisons. In other words, there were no significant differences between the mean pain scores at different time periods.
pain severity of dogs using morphine or tramadol at any
time ($p > 0.05$) (Fig. 4).

**Signs of behaviors**

It was observed that the dogs in both groups were
comfortable recovering from anesthesia, and there
was no moaning, crying, or twitching. In general,
mild inappetence was observed in both groups. The
dogs in the morphine group ate from the 4th hour
and the dogs in the tramadol group ate from the 8th
hour. Any restlessness and dysphoria were not noted
in the morphine group. Restlessness was detected in
five dogs in the tramadol group. Postoperative turmoil
continued in the 8th hour for one dog and for another
up to 12 hours. Hunchback posture and shivering and
shaking motion for 24 hours were noticed in two dogs
from the tramadol group. Reluctant behaviors were
observed in the same dogs for 8 hours. It was observed
that postoperative restlessness ended in the 4th hour in
another three of five dogs.

**Discussion**

Some studies show that during the recovery from
anesthesia, heart rates in the postoperative period were
higher than the preoperative period. Heart rates decreased
during the advancing postoperative hours and closed to
the preoperative values. It was reported that these changes
can result from increased locomotor activity during
anesthesia awakening and from sympathetic stimulation
during extubation (Lucas et al., 2001; Pekcan and Koç,
2010; Cagnardi et al., 2011). In this study, postoperative
0-hour heart rate measurements were higher than the
preoperative period, while heart rate measurements
in the morphine group were found to be closer to the preoperative period. However, postoperative 4th hour heart rate values were lower than the preoperative period \((p < 0.05)\). It was thought that the increase in heart rate values at 0 hour in both groups may be due to increased locomotor activity during endotracheal extubation. Opioids are known to cause hypothermia by affecting the hypothalamic thermoregulatory system, and this effect is primarily seen in dogs (Lamont and Mathews, 2007). It was observed that tramadol did not produce hypothermia in some studies (Monteiro et al., 2009; Malek et al., 2012; Cardoso et al., 2014). In this study, body temperatures were found lower in the postoperative 0th hour compared to the preoperative period. Decreasing body temperature at the 0th hour was observed to return to its standard value at the postoperative 4th hour. These changes at postoperative 0th hour maybe as a result of the opioid effect.

It may be difficult to distinguish the difference between pain and dysphoria after trauma or surgery. Pain and dysphoria may occur simultaneously, but it is possible to distinguish the difference between pain and dysphoria with a few symptoms. The supply of pain can be determined by administering an additional or increased analgesic dose (Hellyer, 2007). Some studies revealed that the tramadol effect was shown after 3–4 hours due to the operation area and that additional doses of analgesics can be used (Martins et al., 2010; Buhari et al., 2013). It was observed that restlessness disappeared without additional dosage depending on the effectiveness of the analgesic agent in the 4th hour in three of the five restless dogs in the tramadol group. After an additional dose of tramadol was applied to two dogs whose restlessness took longer to subside, the observed perturbation ended. The calming of dogs with additional doses showed that the cause of the restlessness was pain-induced.

Tramadol studies on cats and dogs demonstrated that, despite additional analgesic dose administration, the analgesic effect of tramadol is the same or sufficient as opioids and is a suitable alternative to the other analgesics (Mastrocinque and Fantoni, 2003; Martins et al., 2010; Cagnardi et al., 2011; Kongara et al., 2012, 2013; Teixeira et al., 2013). However, in studies on the effects of oral tramadol on orthopedic pain, it has been stated that the effect of tramadol is insufficient (Davila et al., 2013; Budsberg et al., 2018; Giudice et al., 2019). In addition, acute antinociceptive studies have reported that the effect of tramadol is inadequate, and its use in pain management is controversial (Kögel et al., 2014). Nevertheless, in studies on soft tissue surgery such as thoracotomy, mastectomy, ovariohysterectomy, and tumor surgery, it is stated that tramadol has a sufficient analgesic effect (Martins et al., 2010; Teixeira et al., 2013; Karrassch et al., 2015; Read et al., 2019). There was no statistically significant difference between morphine and tramadol in terms of pain scores in this study. The pain scores in both groups were close to each other and decreased from postoperative 8th hour. This condition changed at postoperative 4th hour. However, an additional dose of analgesic was given to five dogs in the tramadol group and a reduction in pain was observed. Besides, the hunchback posture and shaking movements that continued in two dogs, despite the generous additional dose of analgesic in the tramadol group, has indicated that the analgesic effect of tramadol was insufficient. As a result, it was observed that the dogs in the morphine group were more comfortable than the dogs in the tramadol group in terms of postoperative behavioral pain assessments.
This study aimed, especially related to tumor surgery, to compare the efficacy of tramadol and morphine. When analgesic properties were evaluated, it was found that morphine was superior to tramadol, and dogs were more behaviorally comfortable in the postoperative period. In conclusion, the analgesic effectiveness of tramadol as a postoperative analgesic agent was found close to morphine but insufficient.

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Conflict of interest
There is no financial or personal conflict of interest with other persons or organizations.

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