



# Comparison of post-operative analgesic efficacy of tolfenamic acid and robenacoxib in ovariohysterectomized cats

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**ABSTRACT.** The objective of this study was to evaluate the efficacy of a non-selective COX inhibitor (tolfenamic acid) and a selective COX-2 inhibitor (robenacoxib) for post-operative pain control in cats. Thirty cats undergoing ovariohysterectomy were randomly divided into three groups: the control (placebo) group, the tolfenamic acid (4 mg/kg/day) group, and the robenacoxib (1 mg/kg/day) group. Non-steroidal anti-inflammatory drugs (NSAIDs) were administered orally 2 hr before anesthesia induction and 24 and 48 hr post-operation. Buccal mucosal bleeding times (BMBTs) were assessed prior to anesthesia induction. Colorado pain scores and composite pain scores were evaluated in a blinded fashion before induction and 2, 8, 24, 30 and 48 hr post-operation. The Colorado pain scores of cats receiving robenacoxib were significantly lower than those of cats in the control group at 30 ( $P=0.0126$ ) and 48 ( $P=0.0439$ ) hr post-operation. The composite pain scores of cats from the robenacoxib group were lower than those of cats in the control group at 30 ( $P=0.0299$ ) and 48 ( $P=0.0103$ ) hr post-operation. The Colorado pain scores of cats receiving tolfenamic acid were significantly lower than those of cats in the control group at 30 hr ( $P=0.0186$ ) post-operation. The composite pain scores in cats in the tolfenamic acid group were lower than the scores of cats in the control group at 24 ( $P=0.0403$ ) and 48 ( $P=0.0413$ ) hr post-operation. BMBTs remained within normal limits in all groups. Both tolfenamic acid and robenacoxib are useful for post-operative pain control in cats.

**KEY WORDS:** analgesia, cat, non-steroidal anti-inflammatory drug, pain

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Postoperative pain control has been proven to reduce pain, minimize undesired complications, and accelerate the recovery of cats undergoing surgery. The efficacy of analgesic drugs has been evaluated in cats undergoing ovariohysterectomy [1, 4, 27, 30, 33]. Various analgesic agents have been used to ameliorate pain in cats, including opioids and non-steroidal anti-inflammatory drugs (NSAIDs) [1, 4, 19, 30, 32]. NSAIDs target pain mediators in the peripheral and central nervous system [7].

Inflammation is the body's defense mechanism against tissue infections and injuries. The cyclooxygenase (COX) enzyme system plays a key role in the transformation of arachidonic acid to prostaglandins, which activates the inflammatory response [7, 20, 21]. COX has two isoforms: COX-1 and COX-2. COX-1 is expressed in normal tissue throughout the body and has the effect of preserving normal gastrointestinal mucosa, maintaining homeostasis, and regulating renal blood flow. COX-2 is highly expressed when inflammation occurs and is a major source of prostaglandins formation [7, 20, 21]. NSAIDs are classified by their inhibitory effect, which is expressed as a COX-1/COX-2 ratio (20). Nonspecific COX inhibitors have a COX-1/COX-2 ratio below 1.0, whereas selective and specific COX-2 inhibitors have COX-1/COX-2 ratios between 1.0 and 100 and above 100, respectively. Nonselective COX inhibitors can damage the gastrointestinal mucosa and disrupt homeostasis, which may cause ulcerated gastric mucosa and delay blood clotting time [26]. Selective and specific COX-2 inhibitors are superior to nonselective COX inhibitors, which reduce the undesired side effects of COX-1 inhibition.

Tolfenamic acid is a commonly used nonselective COX inhibitor in cats [12]. It has a COX-1/COX-2 ratio of 16 in dogs [22], but the COX-1/COX-2 ratio of tolfenamic acid in cats has not been reported. Tolfenamic acid has been suggested to be a COX-1 inhibitor in cats [14, 34]. Robenacoxib is a selective COX-2 inhibitor with a COX-1/COX-2 ratio of 66.9 to 171 in cats [10, 11, 13, 17, 24, 25]. Several studies have evaluated the efficacy of tolfenamic acid and robenacoxib [4, 11, 12, 24, 25, 27, 29]. However, studies have not compared the efficacy of tolfenamic acid and robenacoxib in cats. Both Colorado pain scores and composite pain scale scores has been used for pain assessment in cats [5, 6, 33]. However, the comparison between Colorado pain scores

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and composite pain scores remains elusive. Therefore, the objectives of this study were (1) to evaluate the analgesic effects of tolfenamic acid and robenacoxib in cats, (2) to determine the correlation between Colorado pain scores and composite pain scores, (3) to evaluate the effects of tolfenamic acid and robenacoxib on buccal mucosal bleeding times (BMBTs) in cats before surgery, and (4) to investigate the side effects of tolfenamic acid and robenacoxib in cats undergoing ovariohysterectomy.

## MATERIALS AND METHODS

### *Animals*

Female domestic shorthair cats ( $n=30$ ) were enrolled and underwent ovariohysterectomy with the owner's consent. The study protocol conformed to the Guide for the Care and Use of Laboratory Animals of Kasetsart University (#OACKU00458). A veterinarian performed a physical and blood examination of the cats before their operation. All enrolled cats were clinically healthy adult females. The average (mean  $\pm$  standard deviation (SD)) age and weight of all cats were  $3.0 \pm 1.27$  years old and  $3.6 \pm 0.48$  kg, respectively. Prior to the procedure, all cats were admitted to the hospital for at least 20 hr. Food and water were restricted for 12 hr before the operation.

All cats were blindly randomized into three groups (control group, tolfenamic acid group, and robenacoxib group), with 10 cats per group. The control group received the placebo, a made-in-house sugar pill. The tolfenamic acid group received 4 mg/kg/day of tolfenamic acid (Tolfedine®, Vetoquinol, Queensland, Australia), and the robenacoxib group received 1 mg/kg/day of robenacoxib (Onsior®, Novartis Animal Health, Greensboro, NC, U.S.A.).

### *Anesthesia and surgery*

All cats in three groups were first given their respective treatments orally 2 hr before anesthesia induction. The placebo and medicines were given again at 24 and 48 hr post-operation. It should be noted that the placebo and treatments were given after recording the pain scores to avoid unintentional effects on pain monitoring. Except for the difference in analgesic drug administered, all cats were treated in the same manner.

All cats underwent the same anesthetic protocol. Using an intravenous catheter placed into the cephalic vein, intravenous fluids (0.9% normal saline solution) were administered to all cats. Anesthesia was induced with propofol (Anepol® injection, Hana Pharmaceutical Co., Ltd., Seoul, South Korea; 4–6 mg/kg, intravenously) without premedication. The anesthesia was then maintained with isoflurane (Attane™, Piramal Critical Care, Inc., Bethlehem, PA, U.S.A.), and oxygen was delivered in a semi-open rebreathing system. The isoflurane, which has hypnosis analgesic effects and relaxes muscles to reduce pain during anesthesia [9, 23], was initially set at 2%, approximately 1.25 minimal alveolar concentration (MAC) during the operation. The depth of anesthesia in each cat was evaluated from eye positioning, reflexes (palpebral and pedal reflexes) and body movement during surgery. In cats with light anesthesia, the concentration of isoflurane was then increased up to 2.5% (approximately 1.5 time MAC) of which should provide adequate depth of anesthesia in most cats. Enrofloxacin (Baytril®, Bayer Health Care LLC, Shawnee, KS, U.S.A.; 5 mg/kg/day) was administered as a prophylactic antibiotic by subcutaneous injection.

Before the operation, the BMBT was evaluated for all cats. A commercially available disposable surgical blade (Feather® surgical blade, stainless steel, Feather Safety Razor Co., Ltd., Osaka, Japan) was stabbed into the non-vascular and non-lesion buccal mucosa area. The stabbed lesion was  $10 \times 1$  mm (long and deep). Blood from the incision was blotted using filter paper (Fisherbrand™ qualitative-grade filter paper, Thermo Fisher Scientific, Waltham, MA, U.S.A.) held near the incision without disturbing the incision site or clot formation. The clotting time was recorded with a stopwatch to determine the time between when the incision was made to when no more blood was absorbed by the filter paper [2]. Ovariohysterectomy was performed using a ventral midline approach involving a small incision (approximately 1 cm long) by a surgeon that had several years of experience in damage control surgery. Average surgical time was  $15 \pm 5$  min.

### *Post-surgical assessment*

After surgery, animals were moved to post-operative room for extubation and continuous monitoring. Each cat was provided with private cage accommodated with litter box, food, and water. Post-operative pain assessment of all cats were recorded by the same blinded investigator in the 72-hr postoperative period at intervals of baseline (2 hr prior to induction), 2, 8, 24, 30, 48 and 72 hr. Assessment of postoperative pain was performed using Colorado pain scale scores of 0–4 [8, 18]. A score of 0 is no pain at all. A score of 1 is mild pain, where the cat appears slightly unsettled. A score of 2 is mild to moderate pain in which the cat presents with isolation and is less responsive to its surroundings. A score of 3 is moderate pain; the cat presents with constant crying or hissing and may bite or chew at the wound. A score of 4 is the worst and represents the most severe pain; the cat is unresponsive or unaware of its surroundings. Composite pain scores on a scale of 0–21 also were assessed in the present study [5, 6], where 0 is normal and 21 is the worst pain. The composite pain score is the sum of the scores from 7 indexes: temperament (0–4); appearance (0–3); body posture (0–2); unprovoked behavior (0–3); interactive behavior (0–4); movement (0–2); and vocalization (0–3) [18].

The threshold for commencing a rescue analgesic procedure was set at either a Colorado pain scale score above 2.5 or a composite pain score above 12 immediately after surgery and beyond, using morphine (M&H manufacturing Co., Ltd., Bangkok, Thailand; 0.3 mg/kg, IM) as a rescue analgesic drug. Cats with pain scores above these limits were to be immediately given a rescue analgesic drug and excluded from the study. The presence of any adverse effects, such as lethargy, somnolence, anorexia, vomiting, diarrhea, melena, constipation, hyperactivity, and skin reaction, also was recorded for each time point [15, 28].

Blood was collected before each operation as a baseline and 72 hr after surgery to evaluate complete blood count, blood urea

nitrogen (BUN), creatinine, alanine aminotransferase (ALT), alkaline phosphatase (ALK), total protein, albumin, and globulin.

### Statistical analysis

Each data set was tested for normality using the Shapiro-Wilk test. Mean  $\pm$  SD and median [range] were calculated for parametric and non-parametric data sets, respectively. The differences in age, body weight, and body temperature of all cats were determined using a one-way ANOVA.

The Colorado pain scores, composite pain scores, and BMBTs in each group were analyzed using a Kruskal Wallis test. The difference between each group was compared with Dunnett's *t*-test. The correlation between Colorado pain score and composite pain score was evaluated using Spearman's correlation test. The adverse effects in the treatment groups were compared to the control group using Fisher's exact test. All statistical analyses were performed using commercially available software packages (JMP<sup>®</sup> Pro 11, SAS Institute Inc., Cary, NC, U.S.A. and GraphPad PRISM<sup>®</sup> 6.0, GraphPad Software, Inc., La Jolla, CA, U.S.A.). The level of significance was considered to be  $P < 0.05$ .

## RESULTS

The mean  $\pm$  SD of age for cats in the control, tolfenamic acid, and robenacoxib groups was  $2.7 \pm 0.82$ ,  $3.7 \pm 1.49$  and  $3.9 \pm 1.20$  years, respectively. The mean  $\pm$  SD of weight for cats in the control, tolfenamic acid and robenacoxib groups was  $3.60 \pm 0.61$ ,  $3.58 \pm 0.56$  and  $3.57 \pm 0.53$  kg, respectively. There was no significant difference in age and body weight of cats among the three groups ( $P=0.0751$  and  $0.9902$ , respectively). The average (mean  $\pm$  SD) body temperature baseline for cats in the control ( $37.7 \pm 0.5^\circ\text{C}$ ), tolfenamic acid ( $37.8 \pm 0.6^\circ\text{C}$ ), and robenacoxib groups ( $37.1 \pm 0.7^\circ\text{C}$ ) was significantly different ( $P=0.0302$ ). There was no significant difference in the average body temperature in the cats among all three groups at 24 hr ( $P=0.7106$ ), 48 hr ( $P=0.8030$ ) and 72 hr ( $P=0.5326$ ) post-operation.

None of the cats expressed a Colorado pain scale score above 2.5 or a composite pain score above 12; therefore, no cat was excluded from the experiment. The median [range] baseline of Colorado pain scores among the control (0.25 [0–1.5]), tolfenamic acid (0 [0–1]) and robenacoxib (0 [0–2]) groups did not differ significantly ( $P=0.5971$ ; Fig. 1). The median [range] baseline of composite pain scores among the control (2.5 [0–6]), tolfenamic acid (1 [0–7]) and robenacoxib (0 [0–7]) groups also was not significantly different ( $P=0.5278$ ; Fig. 2).

The median [range] Colorado pain scale score at 2, 8, 24, 30 and 48 hr for the control group was 0.75 [0–2.5], 1.25 [0–2], 0.625 [0–1.5], 0.5 [0–1.5] and 0.625 [0–1], respectively. The median [range] Colorado pain scale score at 2, 8, 24, 30 and 48 hr for the tolfenamic acid group was 0.25 [0–2], 0 [0–2.5], 0 [0–1.5], 0 [0–1] and 0 [0–1], respectively. The median [range] Colorado pain score at 2, 8, 24, 30 and 48 hr for the robenacoxib group was 0.25 [0–2], 0.25 [0–2], 0 [0–1], 0 [0–0.5] and 0 [0–0.5], respectively.

There was no statistically significant difference in the Colorado pain scale scores among the three groups at 2, 8 and 24 hr ( $P=0.5424$ ,  $0.2559$  and  $0.3404$ ; Fig. 1). However, there was a statistically significant difference in the Colorado pain scale scores at 30 ( $P=0.0047$ ) and 48 hr ( $P=0.0207$ ). At 30 hr, the Colorado pain score in the control group was higher than in the tolfenamic acid ( $P=0.0186$ ) and robenacoxib ( $P=0.0126$ ) groups. The Colorado pain scale score in the control group was higher than in the robenacoxib group at 48 hr ( $P=0.0439$ ).

The median [range] composite pain score at 2, 8, 24, 30 and 48 hr for the control, group was 4.5 [2–12], 3.5 [1–7], 4 [0–7], 3.5 [0–6] and 2.5 [0–5], respectively. The median [range] composite pain score at 2, 8, 24, 30 and 48 hr for the tolfenamic acid group was 3.5 [1–9], 0.5 [0–7], 0 [0–7], 0 [0–6] and 0 [0–5], respectively. The median [range] composite pain score at 2, 8, 24, 30 and 48 hr for the robenacoxib group was 1 [0–10], 1 [0–9], 0 [0–5], 0 [0–3] and 0 [0–2], respectively.

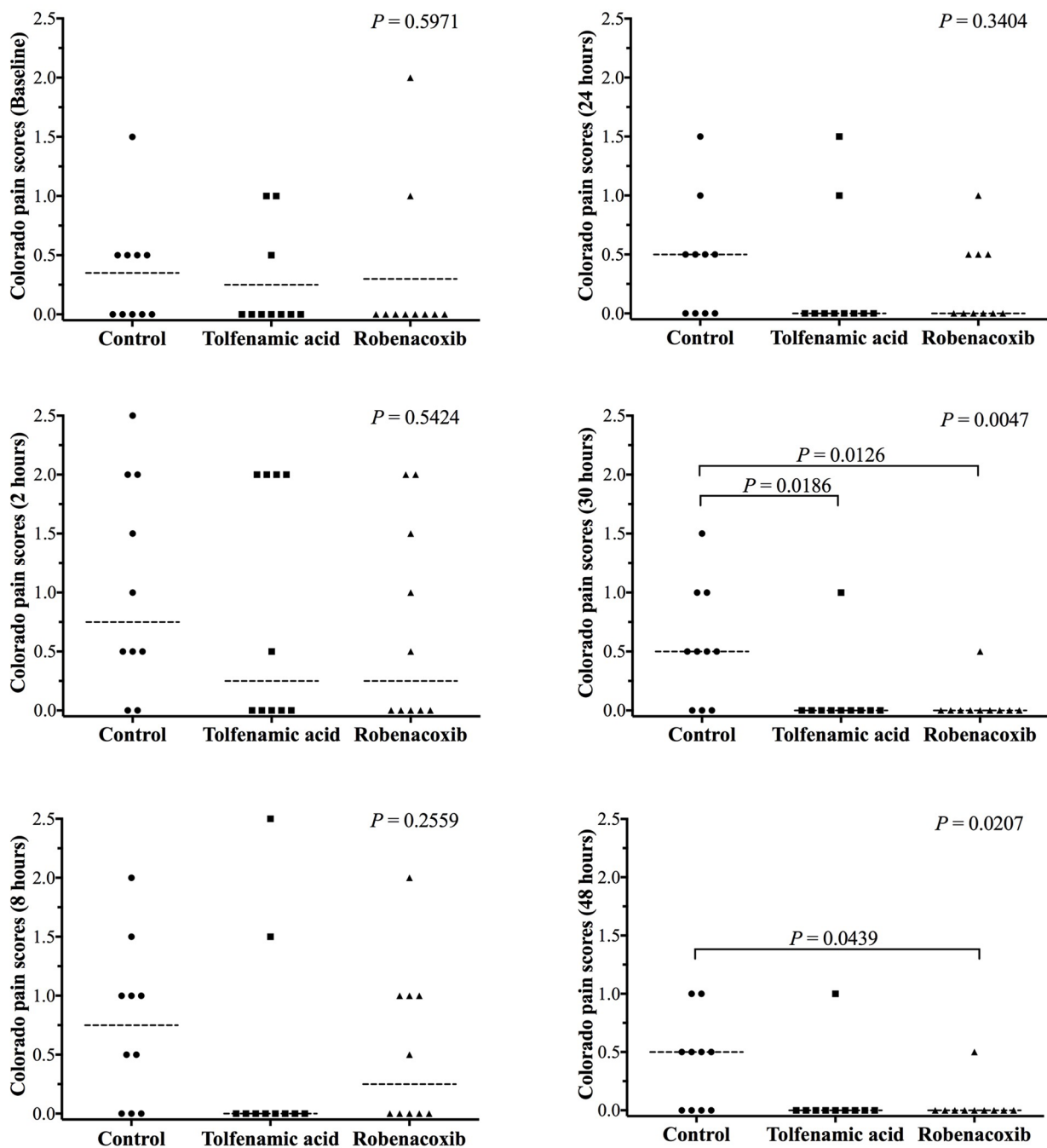
There was no statistically significant difference in the composite pain scores at 2 and 8 hr for the control, tolfenamic acid, and robenacoxib groups ( $P=0.4257$  and  $0.1634$ ; Fig. 2). The composite pain scores were significantly different at 24, 30 and 48 hr ( $P=0.0289$ ,  $0.0182$ ,  $0.0064$ ). At 24 hr, the composite pain score in the control group was higher than in the tolfenamic acid group ( $P=0.0403$ ). The composite pain score in the robenacoxib group was lower than in the control group at 30 hr ( $P=0.0299$ ). The composite pain score in the control group was higher than in the tolfenamic acid and robenacoxib groups at 48 hr ( $P=0.0413$  and  $0.0103$ ).

Spearman's correlation test revealed a significantly strong correlation between Colorado pain score and composite pain score ( $\rho=0.8288$ ,  $P < 0.0001$ ; Fig. 3). The median [range] of pre-operative BMBT among the control (37.5 [15–120] sec), tolfenamic acid (55 [15–180] sec) and robenacoxib (51 [25–150] sec) groups was not significantly different ( $P=0.4843$ ; Fig. 4).

There was no report of lethargy, somnolence, vomiting, diarrhea, melena, constipation, hyperactivity, or skin reaction in the three study groups. However, the presence of anorexia was reported at 8-hr postoperation in 4 cats within the control group, 2 cats within the tolfenamic acid group, and 3 cats within the robenacoxib group. There was no significant difference in the presence of anorexia among the groups ( $P=0.879$ ). The complete blood count and blood chemistry profiles for all cats were within normal limits.

## DISCUSSION

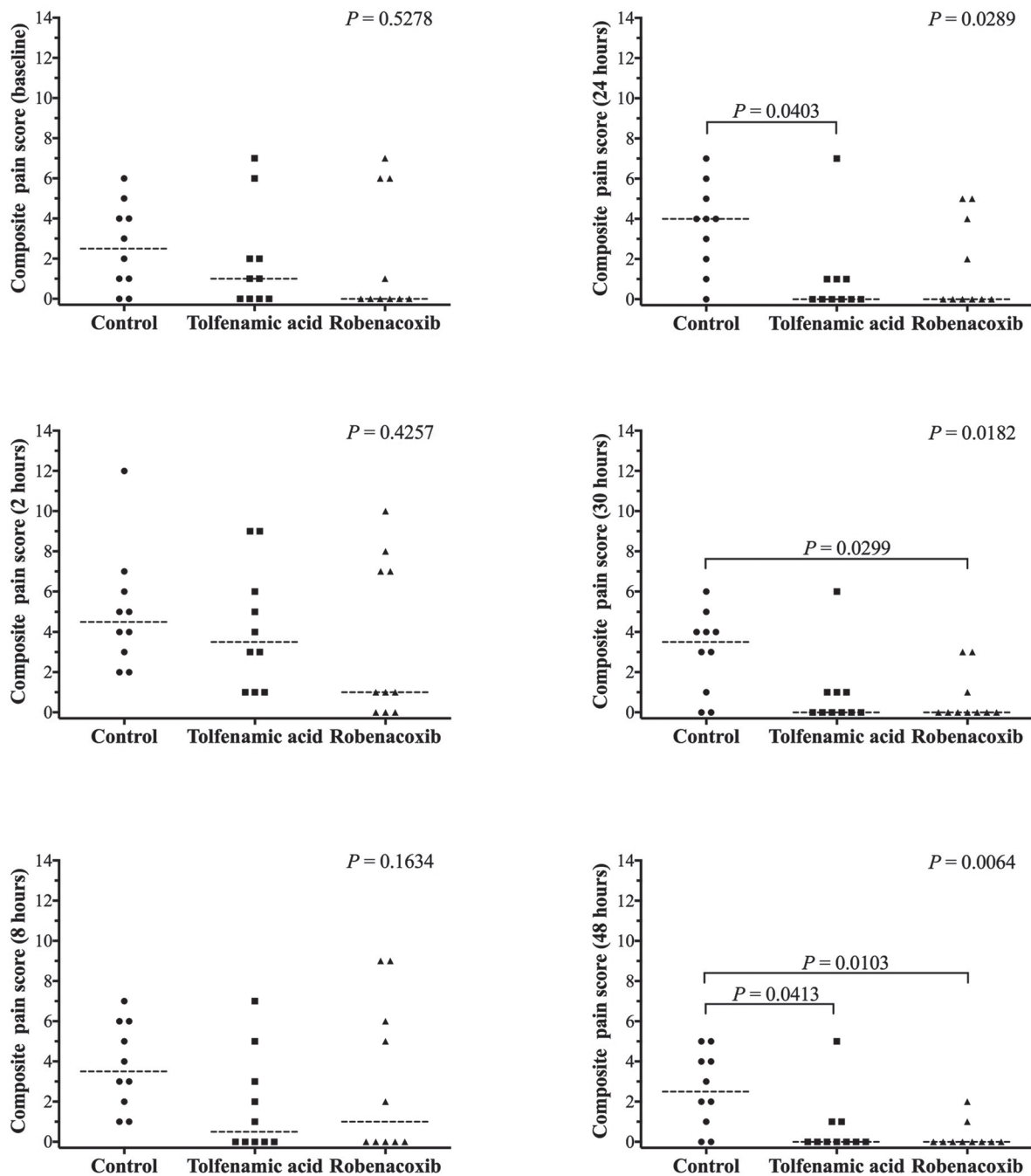
Non-steroidal anti-inflammatory drugs (NSAIDs) are helpful for post-operative pain control in animals. NSAIDs inhibit the formation of prostanoids by the enzyme cyclooxygenase (COX), which consists of two isoforms: COX-1 and COX-2. Nonetheless, the efficacy of non-selective COX inhibitors (e.g., tolfenamic acid) and selective COX-2 inhibitors (e.g., robenacoxib) for post-operative pain control in cats has not been previously evaluated. The present study found that preoperative administration



**Fig. 1.** Scatter plot showing the Colorado pain scores in the control, tolfenamic acid, and robenacoxib groups at baseline (2 hr prior to operation) and 2, 8, 24, 30 and 48 hr post-operation. The dashed lines represent the median Colorado pain score for each group of cats.

of either tolfenamic acid (4 mg/kg/day) or robenacoxib (1 mg/kg/day) in cats resulted in lower post-operative pain scores (both Colorado pain scale scores and composite pain scores) than those in the control group only after 24 hr post-operation. There was no significant difference in post-operative pain scores between cats receiving tolfenamic acid and those receiving robenacoxib. The BMBTs were comparable among the control, tolfenamic acid, and robenacoxib groups. There was no presence of side effect except anorexia in all cat groups.

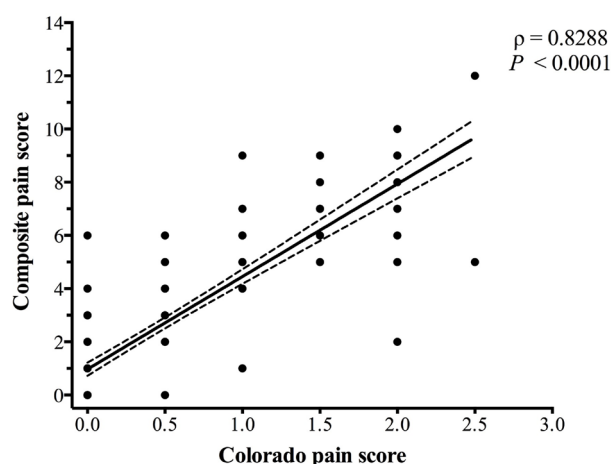
Tolfenamic acid is among the conventional non-selective COX inhibitors commonly used in Thailand [12]. Non-selective NSAIDs inhibit both COX-1 and COX-2, leading to reduce inflammation due to the inhibition of prostaglandin production [20, 30]. However, gastrointestinal and renal side effects are commonly reported with non-selective NSAIDs because prostaglandins released from COX-1 play a crucial role in normal physiological functions [20]. In the present study, cats that received tolfenamic acid had less post-operative pain than those in the control group.



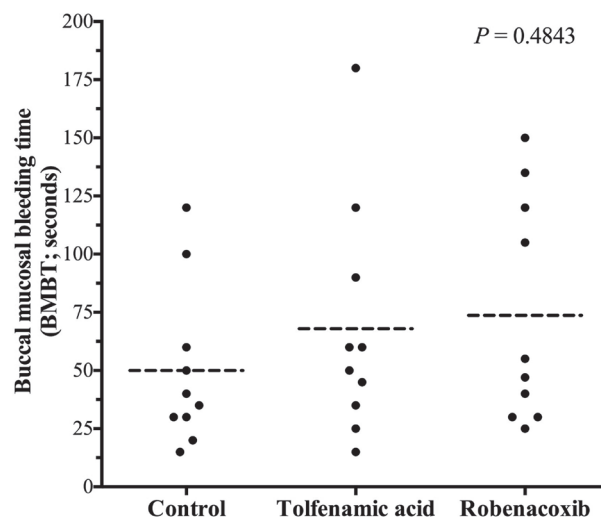
**Fig. 2.** Scatter plot showing the composite pain scores in the control, tolfenamic acid, and robenacoxib groups at baseline (2 hr prior to operation) and 2, 8, 24, 30 and 48 hr post-operation. The dashed lines represent the median composite pain score for each group of cats.

Robenacoxib, a newer FDA-approved selective COX-2 inhibitor, is generally considered safe for use in cats [13, 16, 17]. Selective NSAIDs target the COX-2 enzyme, an inducible inflammatory enzyme for inflammation and pain [13]. In the present study, cats that received robenacoxib had significantly reduced post-operative pain after ovariohysterectomy compared to those in the control group. Interestingly, firocoxib, a selective COX-2 inhibitor similar to robenacoxib, has been shown to be effective for post-operative pain control in cats [18]. In the present study, the efficacy of a non-selective COX inhibitor (tolfenamic acid) and a selective COX-2 inhibitor (robenacoxib) for post-operative pain control in cats was compared. Robenacoxib has been previously evaluated for post-operative pain analgesia in cats with no significant difference compared to non-selective COX inhibitors, including meloxicam [30] and ketoprofen [10]. Interestingly, tolfenamic acid and meloxicam provide similar post-operative pain analgesia in cats undergoing ovariohysterectomy [4]. In this study, a significant difference could not be detected for post-operative pain control between tolfenamic acid and robenacoxib. This may be due to the fact that inducible COX-2 was effectively inhibited





**Fig. 3.** Scatter plot showing the relationship between Colorado pain score and composite pain score for all cats in this study. Spearman's correlation test revealed a significantly strong correlation between Colorado pain score and composite pain score ( $\rho=0.8288$ ,  $P<0.0001$ ). The dashed lines show the 95% confidence interval (0.7881–0.8669).



**Fig. 4.** Scatter plot showing the buccal mucosal bleeding time (BMBT) in the control, tolfenamic acid and robenacoxib groups at perioperative time. There was no statistically significant difference between the three groups ( $P=0.4843$ ). The dashed lines represent the median BMBT for each group of cats.

by either 4 mg/kg of tolfenamic acid or 1 mg/kg of robenacoxib, suggesting that both drugs could be considered effective painkillers for acute pain in cats.

Prostaglandins was produced after surgery due to tissue damage causing pain and fever. COX-1 and COX2 both have been identified in the brain and spinal cord and are involved in inflammation, pain perception, and hyperalgesia [3]. Interestingly, upregulation of COX-1 mRNA (Ballou *et al.*, 2000) and protein immunoreactivity [35] have been shown after surgery at the spinal cord level. These findings an important role of COX-1 inhibition for post-operative pain control by inhibiting pain processing and sensitization at the spinal cord level similar to those in mouse [3] and rat [35] models. In the present study, there was no difference between post-operative pain scores in ovariohysterectomized cats comparing between non-selective COX inhibitor, tolfenamic acid, and selective COX-2 inhibitor, robenacoxib. Thus, our findings suggested that both non-selective and selective COX inhibitor provide comparable efficacy for post-operative pain control in cats undergoing ovariohysterectomy. Nonetheless, difference in post-operative pain scores among control, tolfenamic acid, or robenacoxib were identified only 24 hr post-operation. These results suggested that post-operative pain management with NSAIDs alone is suboptimal. Other analgesics beside NSAIDs should be employed to provide optimal pain management especially in the early post-operation.

Surgery including ovariohysterectomy can lead to mild and moderate post-operative pain. In the present study, the low pain score was observed in the control (had no analgesic medication). A variation of postoperative pain score after ovariohysterectomy may be due to a subjective nature of pain assessment in animals as well as a subtle behavior change to pain in cats [18]. In the present study, we employed an experience surgeon with a small incision approach may also help cats experience far less discomfort as shown in pain score [18]. Interestingly, the strong correlation between Colorado pain score and composite pain score ( $\rho=0.8288$ ,  $P<0.0001$ ; Fig. 3) was revealed. Our finding indicated that one point increment of Colorado pain score approximately equals to four points increment of composite pain score. In addition, animal stress and anxiety during recovery have more influence on composite pain score than Colorado pain score since animal temperaments and behaviors are incorporated into the composite pain score.

Bleeding risk is among the various complications commonly associated with the use of NSAIDs [14]. Aspirin and other NSAIDs may interfere with primary platelet activation, resulting in prolonged bleeding time [14]. In the present study, administration of tolfenamic acid or robenacoxib did not affect the BMBT before the operation. The results of this study suggest that both tolfenamic acid and robenacoxib are safe to use in cats with physically healthy and normal blood profiles. The effects of tolfenamic acid and robenacoxib in cats with bleeding disorders are beyond the scope of the present study. Similar to our study, previous research has found that tolfenamic acid [12] and robenacoxib [13] have no effect on renal function, hematological profiles, or biochemical profiles in healthy cats. Nonetheless, care should be taken to administer NSAIDs to cats with thrombocytopenia or anemia, or to those receiving anticoagulants, as NSAIDs may prolong coagulation time.

Long-term use of NSAIDs may result in various side effects, including gastric ulcer, renal failure, acute hepatitis, and myocardial infarction [14]. In our study, the short-term application of tolfenamic acid and robenacoxib resulted in minimal side effects. Anorexia was the only short-term side effect identified in the present study and appeared in all groups. Both tolfenamic acid [12] and robenacoxib [29] have reportedly been used safely for 2 weeks. However, limited data support the prolonged use of

tolfenamic acids. More studies should be done to compare the efficacy as well as the side effects of the long-term use of tolfenamic acid and robenacoxib in cats with chronic pain.

One limitation of the present study was the subjective nature of the methods and the influence of animal behavior [18]. Objective pain measurement, including mechanical nociceptive threshold testing, has been applied to provide a non-subjective pain evaluation in cats. Even so, behavioral observation remains the optimal method for clinical pain evaluation in cats [31, 32]. The present study used both Colorado pain scale scores and composite pain scores for the independent evaluation of post-operative pain in cats. The Colorado pain scores and composite pain scores were positively correlated (Fig. 3); thus, cats with a high pain score as identified by the Colorado pain scale were likely to have a high composite pain score.

In conclusion, oral administration of either tolfenamic acid or robenacoxib significantly reduced post-operative pain at 24, 30 and 48 hr after surgery in cats undergoing ovariohysterectomy with minimal side effects. Future research should be investigated for long-term side effects of chronic NSAIDs use.

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