Original Article

Comparison of Carprofen, Vedaprofen and Tepoxalin for Postoperative Analgesia and Serum PGE_2 Level in Dogs after Ovariohysterectomy

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Abstract

Comparison of analgesic efficacy of 3 non-steroidal analgesic drugs (carprofen, vedaprofen and tepoxalin) were performed in 40 dogs after ovariohysterectomy. Oral administration of placebo (sugar pill), carprofen (4.4 mg/kg/day), vedaprofen (0.5 mg/kg/day), or tepoxalin (20 mg/kg/day) for 3 days were performed in dogs recovering from ovariohysterectomy. Numerical pain scores (descriptive and composite pain scores) were measured in blinded fashion by three investigators at 0, 12, 24, 36, 48 and 60 hrs following the recovery. The average descriptive and composite pain scores of dogs treated with carprofen or tepoxalin were significantly lower than that of the control group ($p<0.05$), however, no significance difference was found between the vedaprofen-treated and control groups ($p>0.05$). Serum PGE_2 measurement at 60-hrs post-operation significantly decreased in tepoxalin-treated group, whereas no difference was detected in the carprofen- and vedaprofen-treated groups. This study indicates that both carprofen and tepoxalin are helpful for canine postoperative pain management.

Keywords: dogs, ovariohysterectomy, pain, postoperative analgesia, PGE_2

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บทคัดย่อ

การเปรียบเทียบผลระงับปวดของคาร์โปรเฟน วีดาโปรเฟน และทีพอกซาลิน และผลต่อระดับซีรัมพลอสต้าแกลนดินอีทูภายหลังการผ่าตัดทำหมันในสุนัขเพศเมีย

นริศ เต็งชัยศรี[1] พันพิชา สัตถาสาธุชนะ[1] สิริรัตน์ นิยม[1] วรรณสิทธิ์ จันทรวงศ์[2]*

การทดลองเปรียบเทียบประสิทธิภาพของยาระงับปวด 3 ชนิด คือ คาร์โปรเฟน (Carprofen) วีดาโปรเฟน (Vedaprofen) และทีพอกซาลิน (Tepoxalin) ในสุนัขที่ทำการผ่าตัดทำหมันเพศเมีย จำนวน 40 ตัว โดยให้ยาทางการกิน 4 ชนิด คือ ยาหลอก (แคปซูลบรรจุด้วยน้ำตาล) คาร์โปรเฟน (4.4 มก./กก./วัน) วีดาโปรเฟน (0.5 มก./กก./วัน) และทีพอกซาลิน (20 มก./กก./วัน) เป็นเวลา 3 วันหลังการผ่าตัด วัดระดับความเจ็บปวดเชิงปริมาณ (ระดับความเจ็บปวดโดยตรง และความเจ็บปวดแบบสมทบ) โดยใช้ผู้สังเกต 3 คน เริ่มวัดที่ชั่วโมงที่ 0, 12, 24, 36, 48 และ 60 ภายหลังจากที่สุนัขฟื้น โดยใช้เทคนิคที่ปราศจากอคติ ผลการทดลองแสดงให้เห็นว่าค่าเฉลี่ยของระดับความเจ็บปวดของสุนัขที่ได้รับยาคาร์โปรเฟนหรือทีพอกซาลินมีค่าระดับความเจ็บปวดต่ำกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ($p<0.05$) ในกลุ่มสุนัขที่ได้รับยาคาร์โปรเฟนหรือทีพอกซาลินมีค่าระดับความเจ็บปวดข้างเคียงต่ำกว่ากลุ่มควบคุม ในขณะที่กลุ่มสุนัขที่ได้รับยาวีดาโปรเฟนไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับกลุ่มควบคุม ($p>0.05$) นอกจากนี้ทำการวัดระดับพรอสต้าแกลนดินอีทูในซีรัมที่ชั่วโมงที่ 60 หลังการผ่าตัด ผลการทดลองพบว่าสุนัขกลุ่มที่ได้รับทีพอกซาลินมีระดับพรอสต้าแกลนดินอีทูในซีรั่มลดลงอย่างมีนัยสำคัญทางสถิติ ในขณะที่ไม่พบความแตกต่างของระดับพรอสต้าแกลนดินอีทูในซีรัมกลุ่มที่ได้รับคาร์โปรเฟนและวีดาโปรเฟน การศึกษาครั้งนี้บ่งชี้ว่าทั้งคาร์โปรเฟนและทีพอกซาลินมีส่วนช่วยในการลดปวดภายหลังการผ่าตัด

คำสำคัญ: สุนัข การผ่าตัดทำหมันเพศเมีย ความเจ็บปวด ความเจ็บปวดหลังการผ่าตัด พรอสต้าแกลนดินอีทู

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Introduction

Analgesics commonly used in veterinary practice include the narcotic analgesics (opioids) and nonnarcotic analgesics (non-steroidal anti-inflammatory drugs, NSAIDs). The use of narcotic drugs in Thailand is limited in veterinary practice due to the legal regulation. NSAIDs have gained popularity in both human and veterinary anesthesiology because newly developed NSAIDs have analgesic potency comparable to those opioids (Caulkett et al., 2003). More importantly, unlike opiods, NSAIDs have minimal or no effects on cardiovascular and pulmonary systems. The action of steroid anti-inflammatory drug involves the inhibition of phospholipase A2, consequently this blocks the formation of chemical mediators (prostaglandins, leukotrienes, thromboxanes, etc.) leading to peripheral sensitization and hyperalgesia (Taylor, 2003).

One mode of actions of NSAIDs in conferring analgesia is through suppression of prostaglandin (PG) synthesis via inhibition of cyclooxygenase (COX)-1 (homeostatic or constitutive) or COX-2 (inflammatory or inducible) isoenzymes, or both (Curry et al., 2005). Under normal circumstances, PG synthesis by COX-1 plays an important role in maintaining physiological functions such as cytoprotection of gastric mucosa, modulation of renal hemodynamics, and platelet aggregation (Curry et al., 2005). Following tissue injury (i.e. surgical operation) activation of COX-2 isoform plays an important role in inflammatory reactions and gives rise to the inflammatory symptoms including redness, pain, edema, fever and loss of function (Smith et al., 1996). Various NSAIDs have been developed and claimed to be more selective inhibition COX-2 over COX-1. Moreover, a recent development of dual inhibition of COX-2 and 5-lipoxygenase (LOX) leads to an inhibition of both prostaglandin and leukotrienes production downstream of arachidonic acid (AA) cascade (Charlier and Michaux, 2003).

There are various NSAIDs available in the market but the efficacy of different NSAIDs in controlling postoperative pain is dissimilar. In the

present study, we compare the analgesic effect of selective COX-2 inhibitors including carprofen (Curry et al., 2005) and vedaprofen (Hazewinkel et al., 2008) with a new COX-LOX inhibitor, tepoxalin (Curry et al., 2005). To our knowledge, there is no study done to compare the postoperative analgesic efficacy among these 3 drugs. This study was aimed to compare the analgesic efficacy of 3 commercially available NSIADs for veterinary in Thailand: carprofen, vedaprofen and tepoxaline, and to determine PGE_2 level after being treated with different NSAIDs. The side effects on gastrointestinal tract were also recorded in the present study.

Materials and Methods

The study was performed on 40 female mongrel patient dogs aging 2-8 years old undergoing elective ovariohysterectomy (OVH) at Veterinary Teaching Hospital, Kampangsean campus, Faculty of Veterinary Medicine, Kasetsart University. The dogs weighed 13.7±1.4 kg. All dogs were examined and classified as ASA 1. Food and water withholding time was 12 hrs.

Dogs were premedicated with the combination of xylazine hydrochloride (Xylaz® RVET, Bladel, Holland) 1 mg/kg and atropine sulphate (T.P. Drug Lab., Bangkok, Thailand) 0.04 mg/kg injected intramuscularly. Cephalic vein was catheterized and IV fluid (normal saline or lactated Ringer's solution) was administered at 10 ml/kg/hr until the subjects were able to rise. Anesthesia was induced with tiletamine/zolazepam (Zoletill®, Virbac, Carros, France) 5 mg/kg and was maintained by incremental administration of tiletamine/ olazepam to effect. Anesthetic depth and vital signs were recorded throughout the surgeries. The surgeries were completed by veterinary students. An average surgical time was 90±20 min. After awaking up from anesthesia, dogs were brought back to their cages for monitoring. The procedures followed guidelines set by Laboratory Animal Care Committee at Kasetsart University (Approval number ACKU 00150).

Treatment groups: Dogs were randomized into four groups of 10 animals each. The investigators were uninformed of the treatment groups throughout the study. At hour 0 (recovery is defined as ability to sit in sternal recumbency and medications were given after assessment of pain scores), 24 and 48, three treatments were given to the dogs orally: placebo as a sugar pill (group 1), carprofen (Rimadyl® Pfizer Thailand Ltd., Bangkok, Thailand) 4.4 mg/kg/day (group 2), vedaprofen (Quadrisol®, Intervet (Thailand) Ltd., Bangkok, Thailand) 0.5 mg/kg/day (group 3), and tepoxalin (Zubrin®, Shering-Plough Co. Ltd., Bangkok, Thailand) 20 mg/kg/day (group 4).

Postsurgical pain assessment: Three investigators examined all animals in the 60-hr postoperative period at interval of 0, 12, 24, 36, 48 and 60 hrs. Dogs were evaluated for heart rate, respiratory rate, superficial skin temperature and rectal temperature. Assessment of postoperative pain were performed using descriptive pain score (DPS) on a scale of 0-10 where 0 is no pain at all and 10 is the very worst pain (Mathews, 2000; Caulkett et al., 2003) and composite pain score (CPS) on a scale of 0-21, which is a sum of the scores from the seven assessments including 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) (Al-Gizawiy and Rude, 2004). The threshold for commencing a rescue analgesic procedure (morphine 0.5 mg/kg, tid) were set at either DPS above 5 or CPS above 10 at 12 hrs postoperatively and beyond. Any scores exceeding these limits would be expelled from the study but none were excluded. The presence of abnormal gastrointestinal symptoms (vomiting and diarrhea) were also recorded. A 5-scale appetite scoring system (1: inappetite, 2: decrease appetite, 3: normal appetite, 4: increase appetite, 5: voraciously appetite) was used in the present study.

Measurement of serum prostaglandin level: Blood was collected at pre-operatively after IV catheter placement and 60 hrs after recovery for assessment of the PGE_2 level by a competitive binding technique using enzyme immunoassay kits according to the manufacturer's protocol (R&D systems, Minneapolis, USA). In brief, duplication samples were incubated onto the microplate competing with a fixed amount of alkaline phosphatase-labeled PGE_2. Excess conjugate and unbound sample were washed out before adding a substrate solution to find out the bound enzyme activity. Immediately after color development, the microplate reader absorbance was read at 405 nm. The color intensity is inversely proportional to the serum PGE_2 concentration.

Data Analysis: DPS and CPS in each group were averaged. Differences of DPS and CPS between groups were analyzed using one-way analysis of variance (SPSS). The difference between two groups was compared using Dunnett's *t*-test. The comparison of pre-operative and postoperative PGE_2 was used paired-*t* test. Differences among groups were tested by one-way analysis of variance. The significance level was set at $p < 0.05$.

Results

All dogs recovered from surgeries uneventfully. The heart rate, respiratory rate, superficial skin and rectal temperature were not significantly different between groups throughout the observed post-surgical period (data not shown). Average DPSs immediately after recovery (0 hr) were not different in all groups. There was no significant difference in average DPS between carprofen group or vedaprofen group and control placebo at all intervals. Dogs received tepoxalin, however, showed significant lower DPS than that of the control (p=0.013) at 60-hrs post-operation (Figure 1). Average that of the DPSs from 12 to 60 hrs post-operation in dogs receiving carprofen and tepoxalin were statistically lower than that of the control (p=0.012 and 0.029, respectively), nevertheless, dogs received vedaprofen were not different (p=0.44) from control group (Figure 2).

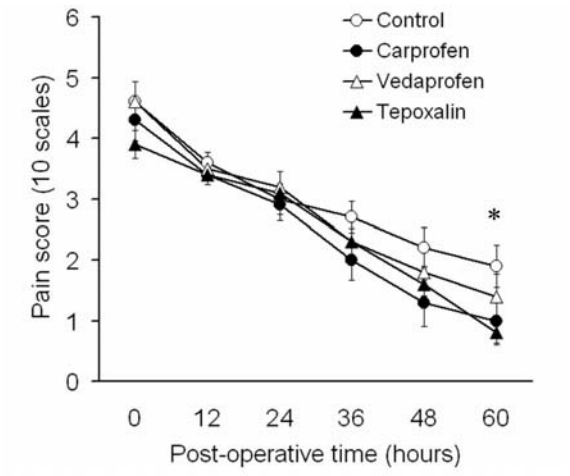

Figure 1. Average DPS in dogs after ovariohysterectomy at 0, 12, 24, 36, 48 and 60 hrs after operation. *p<0.05 control vs. tepoxalin.

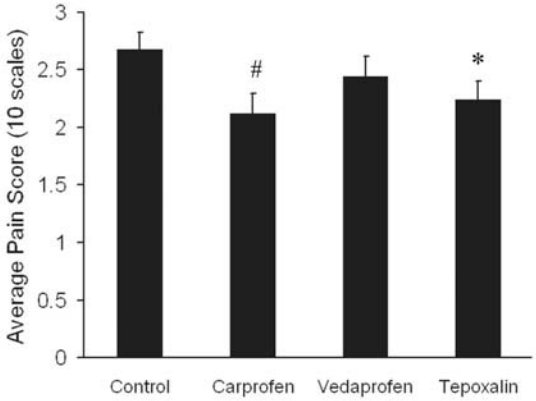

Figure 2. Average DPS from 12 to 60 hrs post-operation. *p<0.05 control vs. tepoxalin; # p<0.05 control vs. carprofen.

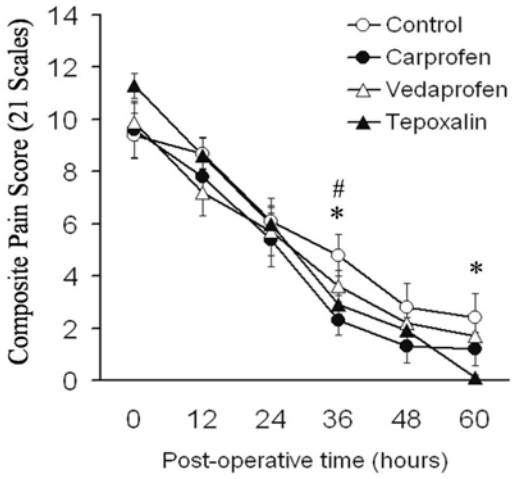

Figure 3. Composite pain scores in dogs in each group over a period of 60 hrs. *p<0.05 control vs. tepoxalin; #p<0.05 control vs. carprofen.

Average CPSs were not different among treatment groups after recovery (0 hr). Average CPSs of dogs receiving carprofen differed from those of the control group at 36 hrs (p= 0.0198; Figure 3). Dogs receiving tepoxalin also had a lower average CPSs at 36 and 60 hrs (p= 0.04 and 0.025, respectively; Figure 3). There was no significant difference in average CPS at any hour in dogs receiving vedaprofen compared to the control group (Figure 3).

Serum PGE_2 levels before operation were not considerably different between dogs receiving carprofen, vedaprofen, tepoxalin or placebo. The serum PGE_2 levels were slightly increased after operation in dogs receiving carprofen, vedaprofen, or placebo, but these increments were not statistically different from the pre-operative PGE_2 levels. Dogs receiving texpoxalin had significantly lower serum PGE_2 levels than the preoperative level and the level of all other groups (Figure 4).

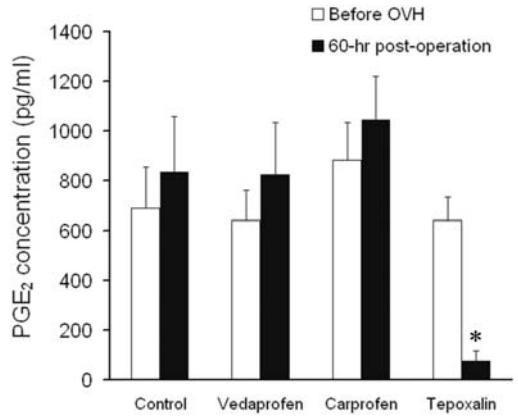

Figure 4. Serum PGE_2 concentration in dogs preoperatively and 60 hrs after ovariohysterectomy. *p<0.05 preoperation vs. 60-hour post-operation.

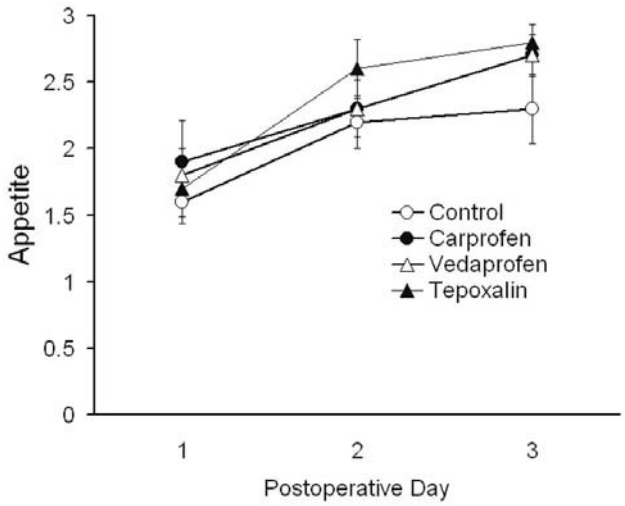

Figure 5. Appetite scores in dogs after ovariohysterectomy.

Scores for appetite recorded after OVH in the dogs receiving NSAIDs were higher than that of the control group. Although the appetite scores increased gradually, the differences were greatest on day 3 postoperatively. However, there were no statistically significant among the control and treatment groups (Figure 5). There was no diarrhea either in the control or other treatment groups. Vomiting was reported in one dog receiving carprofen and the symptom was resolved on the following day.

Discussion

Pain management in dogs and cats has become increasingly addressed as an essential component in veterinary care (Taylor, 2003). The improvement of animal welfare and higher standard of pain management are becoming well established. Although pre-emptive and multimodal analgesia are desired for better control; in Thailand, pain management post OVH in private practices routinely uses the NSAID. Hence, comparison of the efficacy of postoperative pain management of various NSAIDs available in the market offers vital for veterinary practitioners. In the present study, we tested the analgesic effects of carprofen, vedaprofen and tepoxalin on postoperative pain management after canine OVH. Our results revealed that dogs receiving carprofen, a selective COX-2 inhibitor, and tepoxalin, a COX-LOX inhibitor, had lower postoperative pain scores (both DPS and CPS). Despite a lower pain score in dogs receiving vedaprofen, a selective COX-2 inhibitor, it was not statistically significant.

NSAIDs suppress the production of prostaglandins from cyclooxygenase enzymes by blocking the access of arachidonic acid to COX active site and the suppressive effects are depended upon both type of drugs and dose chosen (Curry et al., 2005). The specificity of NSAIDs for a given COX isoform is usually reported in a ratio. A COX-2:COX-1 ratio <1.0 suggests that a specified NSAID favorably inhibits COX-2, in contrary for a COX-1:COX-2 ratio, only the ratio >1.0 preferentially inhibits for COX-2 relative to COX-1 (Al-Gizawiy and Rude, 2004). Both carprofen (Curry et al., 2005) and vedaprofen (Hazewinkel et al., 2008) are claimed to be selective COX-2 inhibitors with a comparable COX1:COX2 ratio (1.75 and 1.2 folds selective toward COX 2 for carprofen and vedaprofen, respectively) (Kay-Mugford et al., 2000). It is generally accepted that the level of PGE_2 is used to imply the level of stimulation at the peripheral nociceptors. In our study, the increased postoperative PGE_2 level was supported by the study done by Canadian researchers (Brideau et al., 2001) as they also found that carprofen was the weakest COX-2 inhibitor.

A previous study revealed that there was no significant difference in visual analogue scale (VAS) in bitches treated preemptively with vedaprofen, carprofen or ketoprofen undergoing elective ovariohystectomy (Selmi et al., 2009). In the present study, we also found similar results that both DPS and CPS were not different between bitches treated postoperatively with carprofen, vedaprofen or tepoxalin. However, both DPS and CPS of dogs treated with carprofen or tepoxalin were significant lower than that of control group suggesting a better efficacy of both drugs for postoperative pain management. In contrast to the manufacturer report, vedaprofen was shown to be a COX-1 selective inhibitor in the equine model (Lees et al., 1999). This may explain both the high post-surgical pain scores and high level of PGE_2 found in our study. Nevertheless, beneficial effects of vedaprofen were reported in cats undergoing OVH by improving the behavioral score (Lopez et al., 2007) and reduced pain scores when used in combination with tramadol (Brondani et al., 2009).

Dual COX-LOX inhibitor provides broader inhibition on prostanoid and leukotriene productions downstream of AA pathway and might carry better analgesic properties. In the present study, both carprofen and tepoxalin attenuated postoperative pain (DPS and CPS) scores. There was no significant difference of postoperative pain scores between selective COX-2 and dual COX-LOX inhibitors.

The concentration of PGE_2 production was related to the level of inflammation and the effectiveness of COX-2 inhibition. Prostaglandin E_2 production at 60-hrs post-operation was elevated. The serum PGE_2 levels in dogs receiving carprofen and vedaprofen were slightly elevated at 60 hrs after the operation but were not statistically significance. Interestingly, serum PGE_2 levels in dogs receiving tepoxalin were significantly lower than the pre-operative level and also lower than, those after other treatments. Because an inflammatory process is a necessary part of tissue healing, inhibition of inflammatory cytokines by NSAIDs may lead to many side effects on the healing process. Suppression of prostaglandin production confers the inhibitory effects on bone metabolism and formation (Kawaguchi et al., 1995). The remaining questions are the effects of tepoxalin on tissue healing and other normal homeostasis including thrombosis. We did not see any adverse effects on wound healing in dogs receiving tepoxalin.

The most commonly prescribed categories of drugs for management of pain and inflammation in people are NSAIDs (Scott and Lamb, 1999). The analgesic, antipyretic and anti-inflammatory properties of classical NSAIDs are due to their inhibitory effects on the production of pro-inflammatory PGs (via COX-2 inhibition), however, the side effects on gastrointestinal tract and kidney are due to their inhibitory effects on physiological PGs (via COX-1 inhibition) (Charlier and Michaux, 2003). The selective COX-2 inhibitors are more potent inhibitors for COX-2 than COX-1 isozymes, therefore, the effective dosage used for anti-inflammation and analgesia of selective COX-2 inhibitors should have less adverse effects compared with classical NSAIDs. Recent studies indicate that COX-2 might play a physiological role in kidney (Gambaro, 2002), healing process of GI mucosa (Parente, 2001) and prevention of cardiovascular thrombotic events (Mukherjee, 2002). A dual COX/LOX inhibitor is claimed to be over selective COX2 inhibitors due to the inhibition of leukotriene productions. Leukotrienes produced by

inflammatory cells (Charlier and Michaux, 2003) are found to be involved in pathogenesis of several inflammatory disorder and allergy diseases including rheumatoid arthritis, inflammatory bowel disease, asthma and allergic rhinitis (Lewis et al., 1990). In the present study, we did not see any difference of the effects of selective COX-2 inhibitors and COX-LOX inhibitor on appetite. Only one dog received carprofen elicited a vomiting and the symptom was resolved on the day after.

Conclusions

This study provides evidence that selective COX-2 and COX-LOX inhibitors are useful for postoperative pain management. The anti-inflammatory and analgesic properties of NSAIDs are due to the inhibition of prostanoid production. Both carprofen and tepoxalin have an important clinical implication for postoperative pain in dogs with minimal side effects.

Conflict of interest statement: Authors have no financial relationship with other people or organizations that could improperly influence the content of current study.

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