Comparison of subcutaneous and transdermal administration of buprenorphine for preemptive analgesia in dogs undergoing elective ovariohysterectomy.

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Abstract

The clinical efficacy of the 70 μg/h transdermal buprenorphine patch and 20 μg/kg of subcutaneously administered buprenorphine for relieving postoperative pain was determined in 24 female healthy dogs undergoing elective ovariohysterectomy. Dogs were randomly assigned to three groups: a control group received no analgesics, a BSC group received buprenorphine subcutaneously (20 μg/kg), and a BP group received buprenorphine by 70 μg/h transdermal patch. Dogs were scored for signs of pain at 0, 2, 4, 6, 8, 10, 14, 20, 26, 32 and 38 h after extubation using the NRS and modified UMPS scales. Mean NRS and UMPS scores for dogs in the buprenorphine groups were significantly lower compared with to dogs in the control group, while differences between the two buprenorphine treatment groups were not significant. These results indicate that the analgesia produced by the 70 μg/h patch was similar to that induced by SC administration of 20 μg/kg of buprenorphine in dogs undergoing ovariohysterectomy, suggesting that the transdermal buprenorphine patch may be an useful alternative for pain management in dogs.

Keywords: Buprenorphine; Dogs; Pain; Transdermal; Subcutaneous.

Introduction

Over the last decade, pain management has gained a great importance in veterinary medicine, since pain activates the stress response and may have a negative impact on immune function (Mathews, 2000; Dobbins et al., 2002; Wagner, 2002; Meert and Vermeirsch, 2005; Shih et al., 2008). There are many analgesic drugs currently available commercially for pain alleviation. Opiates have traditionally been the most widely used analgesics to relief moderate and severe pain. They can be administered prior to surgery, to provide pre-emptive analgesia, as well as during the postoperative period using either injectable or oral formulations. Nevertheless, although oral medication is a satisfactory option during the postoperative period, there is a risk of deliberate or inadvertent self-administration by the animal's owners. In order to avoid these problems Transdermal (TD) Delivery Systems developed for human use are a good option in veterinary practice.

TD delivery of opioid analgesics offers an attractive means for maintaining analgesia during extended periods of time in veterinary patients and avoids many of the disadvantages of oral or injectable periodical administration. TD fentanyl patch systems have been used successfully in veterinary patients for the alleviation of acute post-operative pain and for chronic cancer pain in both dogs and cats (Egger et al., 1998; Kyles et al., 1998; Robertson et al., 2005; Egger et al., 2007). Nevertheless fentanyl patches are also associated with some adverse effects as sedation, disforia and respiratory and cardiovascular depression that may contraindicate its use in some veterinary patients (Egger et al., 1998).

Recently buprenorphine TD delivery system has been developed for the treatment of moderate to severe cancer-associated pain and severe pain unresponsive to nonopioid analgesics in humans beings (Evans and Easthope, 2003; Griessinger et al., 2005).

Buprenorphine is a potent, semi-synthetic opioid with mixed agonist/antagonist properties – it is a partial agonist at μ-opioid receptors (OP_3) and an antagonist at the κ-opioid receptor (OP_2) (Leander, 1988; Budd, 2002). Several studies have shown that it is an effective drug for the treatment of moderate to severe perioperative pain in dogs and cats producing minimal adverse effects (Dobbins et al., 2002; Stanway et al, 2002; Tusell et al., 2005; Slingsby et al., 2006; Shih et al., 2008). Buprenorphine is an ideal candidate for delivery via a TD patch, because it has a low molecular weight, high lipid solubility, high affinity for opioid receptors and prolonged duration of action (Cowan et al., 1977; Stinchcomb et al., 1996; Carroll, 1998; Budd, 2002). The TD delivery system for buprenorphine uses a new technology (matrix system), which incorporates the active agent within a polymer matrix that forms the adhesive layer of the patch, allowing the drug to be continuously and accurately released through the skin and into the systemic circulation by a matrix diffusion process. The buprenorphine delivery system is safer than older reservoir patch systems (fentanyl patches), because the structure of the matrix reduces the risk of 'dose-dumping' when the membrane is damaged, since the whole dose cannot be delivered suddenly (Evans and Easthope, 2003). The absence of a drug reservoir also reduces the danger associated with accidental consumption and reduces the potential for drug abuse.

Although the pharmacokinetics and thermal antinociceptive effects of the 35 μg/h buprenorphine patch have been tested in cats (Murrell et al., 2007), to the authors' knowledge, no studies have been performed to assess the analgesic effects of buprenorphine administered TD in dogs. The aim of this study was to compare the effectiveness of TD and subcutaneous (SC) administration of buprenorphine for prevention of pain in dogs undergoing elective ovariohysterectomy (OHE).

Materials and methods

Animals

Twenty-four client-owned female dogs of different breeds weighing 12.67 kg ± 1.58 kg (range 10.2-15.8 kg) were enrolled in the study. The mean age of dogs was 15 ± 11.44 months (range 9-36 months) and all of them were judged to be healthy based on physical examination, complete blood count and biochemical profile. All dogs were assessed as being free of sings of pain and they didn't receive any previous analgesic treatment. The study protocol was approved by the Ethical Commission of Animal and Human Experimentation and the Ethical Commission of the Autonomous University of Barcelona, and informed consent was obtained from each owner.

Groups

All dogs were randomly assigned to 3 groups of 8 animals each. Dogs in control group (CTRL) received no analgesics. Dogs in BSC group received buprenorphine SC (20 µg/kg [9 µg/lb]) during the pre and postoperative period. Dogs in BP group received buprenorphine by transdermal patch (70 µg/h) during the pre and postoperative period.

Experimental design

Each dog was housed in an individual room for 72 h before surgery to decrease the influence of environmental stressors on behavioral changes. The same handler was used for all dog interactions and assessments over the 3-day period. During acclimation, physiologic variables, Numerical Rating Scale (NRS) and the University of Melbourne Pain Scale (UMPS) were recorded. This established preoperative baseline objective and subjective data for each dog. Food was withheld for 12 h prior to anesthesia with free access to water. Dogs in group CTRL received no analgesics. Dogs in BSC group, received 20 µg/kg SC of

buprenorphine hydrochloride (Buprex, Schering-Plough) 30 min before anesthesia and every 6h for 38h during the postoperative period. Animals in BP group, received a 70 µg/h TD buprenorphine patch (Transtec, Grünenthal) which was applied 48 h before surgery to the left thorax of the dog and remained there during the overall period of 86 hours.

The area for patch application was prepared by clipping, gently washing with warm water, and air drying. TD buprenorphine patch was pressed firmly in place on the skin for 1 min to ensure good adhesion. After patch application, a light wrap of conformable bandage was applied (Askina, B.Braun). The bandage was changed every 24 h. Because the experiment was conducted under double-blind conditions, the left thorax of all dogs in group CTRL and BSC were also prepared as described for dogs in group BP. Likewise, dogs in groups CTRL and BP received a 0.06 mL/kg of SSF subcutaneously 30 min before anesthesia and every 6h during the study period.

Dogs were anesthetized with a single bolus of thiopental sodium (Tiobarbital braun, B.Braun) (10 mg/kg) and diazepam (Valium, Roche Farma) (0.5 mg/kg) administered through a catheter placed in the cephalic vein. The animals were intubated and anesthesia was maintained with 1.5-2% isofluorane (Forane, Abbott Laboratories) in 100 % oxygen through a Bain coaxial breathing system (150 mL/kg/min oxygen). All animals received an infusion of lactated Ringer's solution (Ringer Lactato Braun, B.Braun) at a rate of 10 mL/kg/h (4.5 mL/lb/h) during the perioperative period. Antibiotic therapy (Cefazolina Genfarma laboratorio, 20 mg/kg) was administered IV via the cephalic vein q8h. Heart rate, respiratory rate, pulse oximetry, capnography and invasive blood pressure measurement were monitored during anesthesia using a multiparametric monitor (Datex Ohmeda Cardiotap II, GE Healthcare).

Each dog was positioned in dorsal recumbency and the surgical field prepared aseptically. OHE was performed through a ventral midline approach by experimental surgeons. All surgical procedures were performed endeavoring to maintain the same duration and the same operation times. General anesthesia was discontinued when suturing of the skin was completed and oxygen was administered until extubation. Extubation was performed laryngeal reflexes were recovered.

Postoperative pain assessment was performed by one blinded assessor at 0, 2, 4, 6, 8, 10, 14, 20, 26, 32 and 38 h after extubation. Evaluation of postoperative pain was performed using the NRS and modified UMPS (Table 1). In the NRS, the observer assigns a numerical score for pain intensity. These scores range from 0 to 10 (0 represents no pain and 10 represents the worst pain possible for the procedure). In the modified UMPS, the observer assigns a numerical score for each physiologic and behavioral scoring variable. The minimum possible total pain score obtained by use of this scale was 0, while the maximum possible score was 23. The mental status was structured so that it would reflect the degree of change before and after the procedure. A baseline mental status was assessed in each dog before the procedure was performed. Then, at each fixed time, dogs were assessed again and the absolute difference between the 2 scores (baseline and after procedure) was used as the mental status score. A final score of 0 in the mental status category indicated no change in the dog's behaviour from its preprocedural state.

In our study physiological data were recorded 5 min after the assessor entered the hospitalization area and prior to palpation of the wound, in order to minimize stress due to observer's presence. The overall clinical and behavioral responses were assessed to assign the

NRS score. Activity, posture, vocalization and respiratory rate were observed prior to interacting with the dog. Respiratory rate was measured by looking to the dog's flank. Heart rate was then measured by auscultation. Finally, response to palpation of the wound area was recorded.

Statistical analysis

Data were analyzed using a statistical computer software program (SPSS version 14.0, SPSS Ibérica). The statistical tests were used to compare NRS, modified UMPS and mean scores for the components categories of modified UMPS. The results of NRS, mean of modified UMPS, physiologic data, activity, mental status, posture and vocalization were analyzed using a one-way analysis of variance (ANOVA), with fixed effects being treatment and time. When significant differences were found, a Bonferroni post hoc analysis for pairwise comparisons was performed. The Mann-Whitney U test was used to evaluate palpation data. For all analyses, values of $P < 0.05$ were considered to be significant.

Results

Mean surgery time was 32 ± 4 min (mean ± SD; range 25 – 42 min), mean anesthesia time was 41 ± 5 min (range 34 – 49 min) and mean extubation time (time between discontinued anesthesia and extubation) was 6 ± 4 min (range 2 – 15 min) for all dogs. Six dogs in BP group showed mild sedation during the first 30 – 40 hours of patch application. All patches remained in place during the entirely study period. The patches did not cause any skin irritation or pruritus.

NRS

Significant differences in the mean NRS score between groups were observed during the 0-32 h after extubation (Fig. 1). Mean NRS score for dogs in CTRL group (5.42 ± 0.38) was significantly higher ($P < 0.05$) compared to BSC (2.56 ± 0.23) and BP (2.02 ± 0.24) groups. There were no significant differences between animals treated with SC and TD buprenorphine.

Modified UMPS

Mean

Significant differences in the mean UMPS score between groups were observed during the 0-32 h after extubation (Fig. 2). Mean UMPS score for dogs in CTRL group (7.89 ± 0.44) was significantly higher ($P < 0.05$) compared to BSC (3.05 ± 0.27) and BP (2.67 ± 0.23) groups. There were no significant differences between animals treated with SC and TD buprenorphine.

Physiologic variables

Significant differences in the mean physiologic variables between groups were observed during the 0-32 hours after extubation (Table 2). Mean heart rate score for dogs in BP group (0.14 ± 0.04) was significantly lower ($P<0.05$) compared to CTRL (0.59 ± 0.09) and BSC (0.44 ± 0.08) groups. Mean respiratory rate and mean temperature scores for dogs in CTRL group (0.8 ± 0.08 and 0.57 ± 0.05 respectively) were significantly higher ($P<0.05$) compared to BSC (0.19 ± 0.06; 0.2 ± 0.04) and BP (0.32 ± 0.08; 0.33 ± 0.05) groups.

Behavioral variables

Significant differences in the mean behavioral variables between groups were observed during the 0-32 h after extubation (Fig. 3). Mean UMPS behavioral score for dogs

without analgesic treatment (CTRL) (5.76 ± 0.3) was significantly higher (P<0.05) than those obtained in BSC (2.20 ± 0.21) and BP (1.89 ± 0.18) groups.

Palpation

Mean palpation rate score for dogs in CTRL group (1.53 ± 0.1) was significantly higher ($P < 0.05$) compared to BSC (0.52 ± 0.09) and BP (0.55 ± 0.09) groups.

Activity

Mean activity rate score for dogs in CTRL group (1.17 ± 0.07) was significantly higher (P<0.05) compared to BSC (0.57 ± 0.06) and BP groups (0.48 ± 0.06). Six dogs of CTRL group, one dog of BSC group and one dog of BP group were pacing continuously during the first 10 h after extubation. From this period, all animals remained resting or sleeping and interoperating with the handler during the assessments.

Mental Status

Mean mental status rate score for dogs in CTRL group (1 ± 0.06) was significantly higher ($P < 0.05$) compared to BSC (0.22 ± 0.06) and BP (0.23 ± 0.05) groups. After surgery, dogs in BSC and BP groups remained more friendly than CTRL group, which showed protecting behavior.

Posture

Mean posture rate score for dogs in BP (0.3 ± 0.06) group was significantly lower ($P < 0.05$) compared to CTRL (0.67 ± 0.07) and BSC (0.6 ± 0.05) groups. Combinations of standing with head up or down were the most common pain postures in all groups.

Vocalization

Mean vocalization rate score for dogs in CTRL group (1.39 ± 0.1) was significantly higher ($P < 0.05$) compared to BSC (0.3 ± 0.08) and BP (0.34 ± 0.08) groups. Six dogs of CTRL group presented intermittent vocalization during the entirely experimental period and when the wound area was palpated. Dogs of BSC and BP group presented intermittent vocalization only during the first 6 h post-extubation.

Discussion

Providing effective perioperative analgesia for animals is an essential aspect of good veterinary practice. Pain is associated with prolonged stays in hospital and with greater potential for complications, including immunosuppression, delayed healing and higher morbidity (Mathews, 2000). It is therefore important to not only identify pain in animals, but also to study new analgesics therapies and administration routes, such as TD delivery systems. To the authors' knowledge this is the first study in which buprenorphine patch has been clinically evaluated in dogs. In this study SC and TD buprenorphine have shown to be equally useful for pain treatment after OHE in dogs.

In this investigation the buprenorphine SC dose was selected according to previous reports in which a 5 to 20 µg/kg dose at 6-12 h intervals were recommended for dogs (Pascoe, 2000; Wagner, 2002). For the BP group a 70 µg/h patch was selected, corresponding to the biggest buprenorphine patch commercially available, in order to evaluate the maximum analgesic effect that we can reach using these patches after OHE in dogs. The time period between patch application and surgery was selected according to the study of Andaluz et al. (2009), who observed that plasma buprenorphine concentrations increased slowly during the first 36–48 h and remained in a steady-state period during 108 h. Finally, the inclusion of a

control group (animals undergoing surgery without analgesics) allowed us to differentiate the real effectiveness of each buprenorphine treatment, since different administration routes of a same analgesic were evaluated, as well as the determination of the painful period after an elective OHE. Although this period has been established by several authors for 24 h (Hardie et al., 1997; Firth and Haldane, 1999; Fox et al., 2000; Shih et al., 2008), in our study significant differences between treated and control groups remained until 38 h post-extubation, suggesting that pain in dogs undergoing OHE remains at least for 38 h, a time period slightly higher than the 24 h described previously. The different assessment periods used for pain evaluation, 38 versus 24 h, could be liable for these results. In fact Morton et al. (2005) reported gradual amelioration of discomfort over approximately 10-14 days after soft tissue surgeries.

In the present study analgesia has been assessed by a combination of NRS and UMPS scores. Identification of a valid and reliable pain assessment method has been a concern for the effective pain management in veterinary practice (Holton et al., 2001) and different approaches for pain evaluation as analgesiometric tests, physiologic measures and pain scales have been described (Conzemius et al., 1997; Holton et al., 1998a; Holton et al., 2001; Hielm-Björkman et al., 2003; Meert and Vermeirsch, 2005; Murrell et al., 2007; Steagall et al., 2007). Of those, pain scales have been described as a reliable method to assess clinical pain (Firth and Haldane, 1999; Holton et al., 2001; Morton et al., 2005) because both analgesiometric test and physiologic measures may be altered by numerous factors as the intensity of the stimulus, the timing of trials, the species (Nolan et al., 1987; Meert and Vermeirsch, 2005; Steagall et al., 2007) and by fear, stress or the use of opioids (Conzemius et al., 1997; Hansen et al., 1997; Holton et al., 1998a; Mathews et al., 2001), respectively. Although pain measurement using subjective scoring system has been cause of debate, the

NRS was found to be the more useful system in dogs (Holton et al., 1998a). Likewise, UMPS have been used to evaluate the degree of postoperative pain in dogs (Firth and Haldane, 1999; Wagner et al., 2002; Möllenhoff et al., 2005), showing a better accuracy over subjective pain scales and the ability to weight the importance of certain behaviors or parameters (Hellyer, 2002). In the modified UMPS used in our study, pupil size and salivation were not included, as suggested by different authors (Holton et al., 1998b; Skarke et al., 2003; Polis et al., 2004; Acosta et al., 2005), since those descriptors can be influenced by multitude of factors. Moreover, physiologic and behavioral data have been evaluated separately following the recommendations of Holton et al. (2001) and Morton et al. (2005) who consider that physiological signs are nonspecific indicators of pain.

In our study no adverse effects were observed in dogs treated with buprenorphine. Nevertheless dogs in the BP group showed a slight degree of sedation between the first 30-40 h of patch application. This fact has also been observed by Murrell et al. (2007) after patch application in cats. In that study cats showed signs of sedation only during the first 6 h after patch application and the authors suggested that sedation probably occurs at buprenorphine concentrations lower than those required to induce analgesia. Differences in the characteristics of skin and the species-specific variability of opioids might explain the different sedation times observed between dogs and cats.

The effectiveness of buprenorphine for pain management after OHE in dogs has been previously described by Shih et al. (2008) who observed no differences between IM buprenorphine and SC carprofen at 2, 4, and 24 h after extubation, showing a suitable and similar degree of analgesia for these two analgesics. The lack of significant differences between the TD and SC groups observed in our study, as well as the similar absorption curve

observed after SC and IM buprenorphine administration (Gralow et al., 1995) may shown that the effectiveness of TD and SC administration of buprenorphine are similar to those described by Shih et al. (2008) for the IM route. Nevertheless our results differ from those observed in cats in which no analgesic effects were demonstrated after the application of the 35 µg/h patch (Murrell et al., 2007). The authors attribute these results to the slow and gradual increase of buprenorphine plasma concentrations, resulting in too few receptors occupied to induce analgesia, so they recommend the administration of a systemic loading dose of buprenorphine before patch application. However, the few number of animals included as well as the analgesiometric method used in the study of Murrell et al. (2007) may miss the analgesic effects observed after the administration of buprenorphine by the TD route. In fact, some authors have shown that these tests do not involve all the mechanisms responsible for clinical pain (Rougham and Flecknell, 2002) and may be altered by numerous factors (intensity of the stimulus and the timing of trials of the response) (Nolan et al., 1987; Meert and Vermeirsch, 2005; Steagall et al., 2007).

Several studies (Sadée et al., 1982; Meert and Vermeirsch, 2005; Steagall et al., 2007) have shown that analgesic response to buprenorphine varied depending on the stimulus applied, mechanical or thermal, since mechanical likely stimulus activate Aδ and C fibers, whereas the thermal stimulus mainly affects C fibers (Steagall et al., 2007). These differences in neural responses to the stimuli may account for differences in the response to the drugs administered. The discrepancy observed between different analgesiometric test as well as the fact that the effectiveness of buprenorphine for the treatment of postoperative pain has been demonstrated by different authors (Dobbins et al., 2002; Stanway et al., 2002; Shih et al., 2008) may shown the importance of clinical studies, using pain scales, to assess the efficacy of analgesic therapies in the different species.

In our study, the period in which animals showed more signs of pain included the first 5-10 h after extubation, decreasing slowly during the 20-30 h, especially in the control group. During this time period painful animals were pacing continuously showing a protecting behavior when the wound area was palpated, and vocalizing intermittently. Although these manifestations of pain have been described by others (Firth et al., 1999), the inclusion of palpation in the present study showed that, although no differences between groups were observed after 36 h post-extubation, analgesia produced by SC and TD buprenorphine appeared to be incomplete, since some treated animals continued reacting to wound palpation at the end of the study period. Nevertheless it is important to note that while behavioral variables have followed a similar pattern showing significant higher scores for the control group, the physiological variables have not shown this trend, especially heart rate that was found to be significantly lower in the BP group. This fact was probably attributed to the sedation observed in some animals of this group. According to other authors (Hansen et al., 1997; Holton et al., 1998b), physiological measures of pain have been shown to be unreliable in order to assess postoperative pain intensity, here the importance of assessing separately the physiologic and behavioral variables. Physiologic variables may be altered by the use of opioids, which frequently reduce heart rate even in the presence of pain. For these reason some authors do not recommend to include physiologic variables to assess the degree of pain (Conzemius et al., 1997; Mathews et al., 2001).

Conclusions

This study assessed the clinical analgesic efficacy of a TD matrix formulation of buprenorphine in dogs. The 70 µg/h patch induces similar analgesia to administration of 20 µg/kg buprenorphine SC in dogs undergoing OHE. The patches were well tolerated by the

dogs and did not cause any adverse effects. The results of the study suggest that TD buprenorphine patch may be an alternative for pain management in dogs. However, further clinical studies are required to determine a range of analgesic buprenorphine patch in the dog, which may provide guidelines for the most appropriate patch size to use in clinical patients.

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537

538 Table 1: Modified UMPS for assessing severity of pain in dogs that have undergone surgery.

Category	Descriptor	Score
Physiologic data		
a) Choose only one	Percentage increase in heart rate relative to preprocedural rate	
	> 20%	1
	> 50%	2
	> 100%	3
b) Choose only one	Percentage increase in respiratory rate relative to preprocedural rate	
	> 20%	1
	> 50%	2
	> 100%	3
c)	Rectal temperature exceeds reference range	1
Response to palpation		
Choose only one	No change from preprocedural behaviour	0
	Guards/reacts* when touched	2
	Guards/reacts* before touched	3
Activity		
Choose only one	At rest - sleeping	0
	- semiconscious	0
	- awake	1
	Eating	0
	Restless (pacing continuously, getting up and down)	2
	Rolling, thrashing	3
Mental status		
Choose only one	Submissive	0
	Overtly friendly	1
	Wary	2
	Aggressive	3
Posture		
a)	Guarding or protecting affected area (includes fetal position)	2
b) Choose only one	Lateral recumbency	0
	Sternal recumbency	1
	Sitting or standing, head up	1
	Standing, head hanging down	2
	Moving	1
	Abnormal posture (eg, prayer position, hunched back)	2
Vocalization†		
Choose only one	No vocalizing	0
	Vocalizing when touched	2
	Intermittent vocalization	2
	Continuous vocalization	3

* Includes turning head toward affected area; biting, licking, or scratching at the wound; snapping at the handler; or tense muscles and a protective (guarding) posture.
Does not include alert baking.

539

Table 2: Mean ± SD modified UMPS pain scores by category for each analgesic-treatment group of dogs at each observation time. CTRL = control group. BSC = buprenorphine SC group. BP = buprenorphine transdermal group. [a], significant ($P< 0.05$) difference from control group. [b], significant ($P< 0.05$) difference between subcutaneous and transdermal buprenorphine groups.

	TIME (h)										
Category	**0**	**2**	**4**	**6**	**8**	**10**	**14**	**20**	**26**	**32**	**38**
Physiologic data											
CTRL	3.3±0.3	2.8±0.6	2.6±0.7	2.8±0.6	2.5±0.5	2.1±0.4	1.7±0.4	0.9±0.3	0.75±0.3	0.5±0.1	0.25±0.1
BSC	1.9±0.6[a,b]	1.2±0.4[a]	1.2±0.7[a]	1.2±0.6[a]	1±0.6[a]	1±0.6[a]	0.7±0.4[a]	0.5±0.3[a]	0.1±0.1[a]	0.1±0.1[a,b]	0.1±0.1[b]
BP	0±0[a,b]	1.7±0.6[a]	1.7±0.7[a]	1±0.6[a]	1.1±0.5[a]	1.1±0.6[a]	0.8±0.5[a]	0.5±0.3[a]	0.1±0.1[a]	0.6±0.4[b]	0.7±0.4[a,b]
Palpation											
CTRL	1.4±1	2.4±0.5	2.4±0.5	2.1±0.9	2±0.9	1.75±1	1.5±0.9	1.5±0.9	1.5±0.9	1.5±0.9	0.75±1
BSC	0.25±0.1[a]	0.25±0.1[a,b]	1.25±0.8[a]	1±0.7[a]	1±0.7[a]	1±0.7[a]	0.5±0.4[a]	0.25±0.1[a,b]	0.25±0.1[a,b]	0±0[a]	0±0[a]
BP	0±0a	0.8±1[a,b]	0.6±0.9[a]	0.6±0.9[a]	0.6±0.9[a]	0.8±1[a]	0.6±0.9[a]	0.6±0.9[a,b]	0.6±0.9[a,b]	0.4±0.8[a]	0.4±0.8[a]
Activity											
CTRL	0.9±0.3	1.5±0.7	1.75±0.3	1.75±0.7	1.6±0.7	1.5±0.5	0.75±0.4	0.9±0.3	0.9±0.3	0.9±0.3	0.5±0.5
BSC	0.4±0.3[a,b]	0.25±0.1[a,b]	0.5±0.4[a]	0.5±0.3[a]	0.6±0.3[a]	0.5±0.3[a]	0.75±0.4[b]	0.75±0.4[b]	0.9±0.5[b]	0.9±0.5[b]	0.2±0.1
BP	0.7±0.4[b]	0.7±0.6[a,b]	0.8±0.6[a]	0.4±0.5[a]	0.7±0.4[a]	0.3±0.4[a]	0.2±0.4[a,b]	0.3±0.4[a,b]	0.4±0.5[a,b]	0.6±0.5[a,b]	0.4±0.5
Mental Status											
CTRL	0.9±0.3	1.1±0.3	1.4±0.5	1.25±0.7	1.25±0.7	1.25±0.7	1.1±0.6	0.9±0.6	0.9±0.6	0.75±0.7	0.25±0.3
BSC	0.1±0.1[a,b]	0.1±0.3[a]	0.4±0.5[a]	0.4±0.5[a]	0.4±0.5[a]	0.4±0.5[a]	0.25±0.3[a]	0±0[a]	0±0[a]	0.25±0.2[a]	0.1±0.2
BP	1±0.8[b]	0.2±0.4[a]	0.2±0.4[a]	0.1±0.3[a]	0.1±0.3[a]	0.2±0.3[a]	0.3±0.2[a]	0±0[a]	0±0[a]	0±0[a]	0±0[a]
Posture											
CTRL	0.1±0.3	0.6±0.4	1.25±0.5	1.4±0.7	0.9±0.6	0.9±0.6	0.75±0.4	0.6±0.5	0.5±0.5	0.25±0.3	0.1±0.2
BSC	0.25±0.3[b]	0.5±0.5	0.75±0.4[a]	0.5±0.5[a]	0.5±0.4[a]	0.75±0.4	0.75±0.4[b]	0.9±0.3[b]	0.9±0.3[b]	0.75±0.4[b]	0.1±0.2
BP	0.6±0.5[a,b]	0.3±0.4[a]	0.1±0.2[a]	0.5±0.7[a]	0.5±0.8a	0.4±0.6[a]	0±0[a,b]	0.1±0.3[a,b]	0.2±0.4[a,b]	0±0[a,b]	0±0
Vocalization											
CTRL	1.9±1	1.6±1	1.5±0.9	1.5±0.9	1.5±0.9	1.5±0.9	1.5±0.9	1.25±1	1.25±1	1.25±1	0.5±0.7
BSC	0.75±0.8[a,b]	0.25±0.3[a,b]	0.5±0.5[a]	0.25±0.3[a]	0.25±0.3[a]	0.5±0.4[a]	0.5±0.4[a]	0±0[a]	0.25±0.3[a]	0±0[a]	0±0[a]
BP	0±0[a,b]	1.2±0.8[a,b]	0.6±0.7[a]	0.6±0.7[a]	0.2±0.4[a]	0.2±0.3[a]	0.4±0.2[a]	0.2±0.1[a]	0.2±0.1[a]	0±0[a]	0.2±0.1

Figure Legends

Figure 1: Mean ± SD NRS scores during 38 hours after ovariohysterectomy. Control group had significantly ($P< 0.05$) higher mean NRS pain scores, between 0-32 hours, than subcutaneous and transdermal buprenorphine groups. CTRL = control group. BSC = buprenorphine SC group. BP = buprenorphine transdermal group.

Figure 2: Mean ± SD UMPS scores during 38 hours after ovariohysterectomy. Control group had significantly ($P< 0.05$) higher mean UMPS pain scores, between 0-32 hours, than subcutaneous and transdermal buprenorphine groups. CTRL = control group. BSC = buprenorphine SC group. BP = buprenorphine transdermal group.

Figure 3: Mean ± SD behavioral scoring variables during 38 hours after ovariohysterectomy. Control group had significantly ($P< 0.05$) higher mean behavioral pain scores, between 0-32 hours, than subcutaneous and transdermal buprenorphine groups. CTRL = control group. BSC = buprenorphine SC group. BP = buprenorphine transdermal group.

Figures

Figure 1

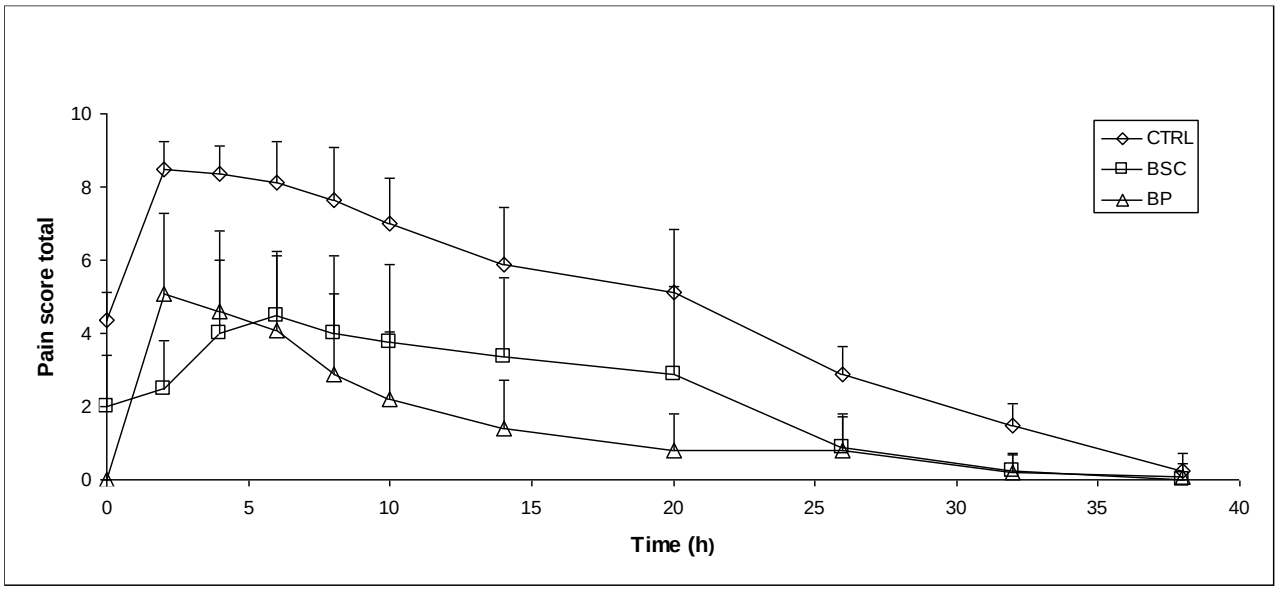
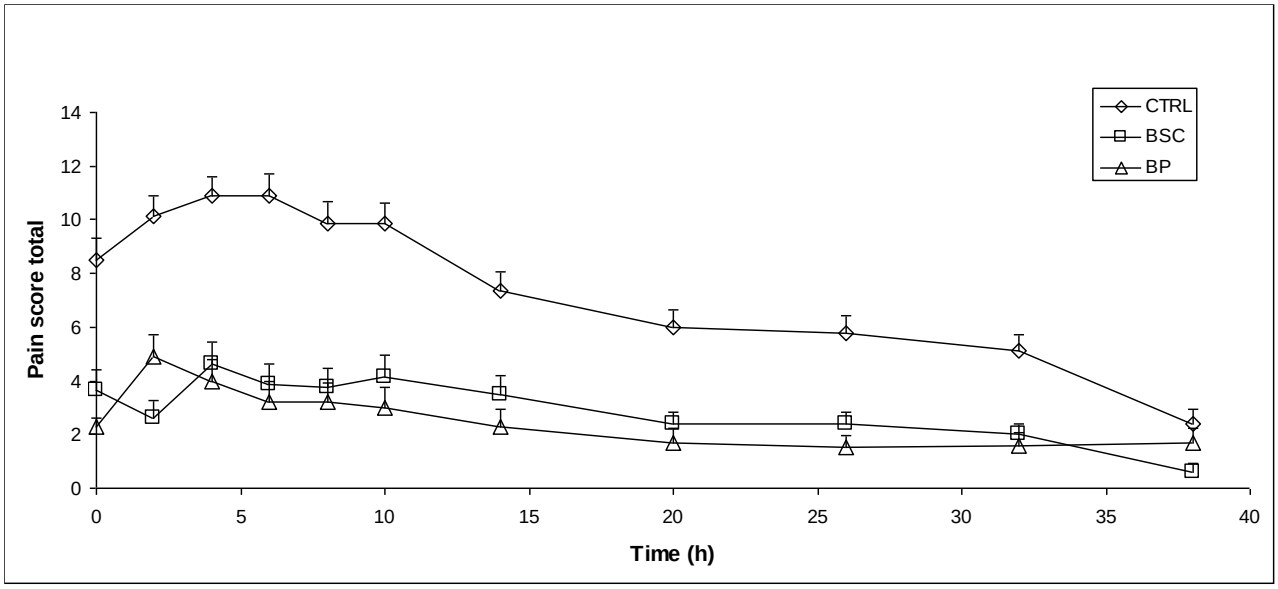
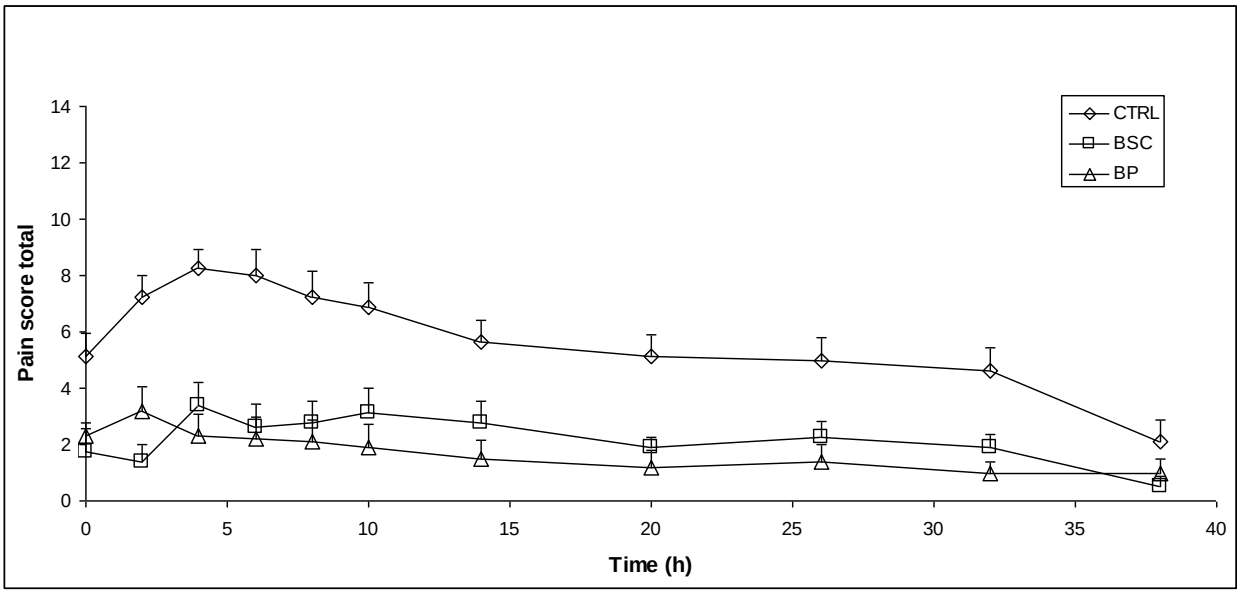


Figure 2



586 Figure 3



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