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RESEARCH PAPER

The post-operative analgesic effects of epidurally administered morphine and transdermal fentanyl patch after ovariohysterectomy in dogs

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Abstract

Objective To investigate the analgesic and side effects of epidural morphine or a fentanyl patch after ovariohysterectomy in dogs.

Study design Prospective, randomized clinical study.

Animals Twenty female mongrel dogs undergoing ovariohysterectomy.

Methods The dogs were allocated to one of two groups: epidural morphine or transdermal fentanyl patch. Anaesthesia was induced with propofol and maintained with isoflurane. Morphine (0.1 mg kg^{-1}) was administered epidurally in the epidural morphine group and a transdermal fentanyl patch was applied 24 hours before the operation in the fentanyl patch group.

The heart rate, respiratory rate, body temperature, plasma cortisol concentration, and sedation and analgesia scores were recorded during the 24 hour post-operative period. Adverse effects such as vomiting, anorexia, skin reactions, urinary retention, and time to start licking the surgical site were also recorded. $p < 0.05$ was considered significant. Statistical analyses utilized ANOVA for repeated measures, Friedman tests, Mann–Whitney *U*-tests and independent sample *t*-tests as relevant.

Results Pain scores were lower in the epidural group than in the fentanyl group at all post-operative times. The dogs in the epidural morphine group were calm and relaxed, whereas discomfort and vocalization were recorded in the fentanyl patch group. The sedation scores were higher in the fentanyl patch group throughout the 12 hour period. Salivation and anorexia lasted longer in the fentanyl patch group than in the epidural morphine group. Plasma cortisol concentrations were high in the early post-operative period in both groups. The fentanyl patch group had higher cortisol concentrations than the epidural morphine group. Slight erythema was recorded in two dogs when the patches were removed.

Conclusion and clinical relevance Epidurally administered morphine provided better analgesia and caused fewer adverse effects than the fentanyl patch after ovariohysterectomy in dogs.

Keywords analgesia, dog, epidural morphine, extradural morphine, fentanyl patch.

Introduction

Surgical pain in dogs frequently is managed using parenteral administration of opioids during and after surgery. Fentanyl and morphine are potent mu opioid-receptor agonists often used for this purpose. Although their use usually alleviates signs of pain,

a continuous level of pain control is difficult to achieve through intramuscular (IM) or intravenous (IV) routes of administration because of waxing and waning plasma concentrations (Robinson et al. 1999; Pascoe 2000; Torske & Dyson 2000; Gilberto et al. 2003; Hofmeister & Egger 2004).

Morphine administered epidurally at the lumbosacral junction can produce analgesia as far cranially as the diaphragm; the onset of analgesia begins within 20–60 minutes and lasts up to 24 hours. Side effects include nausea, vomiting, respiratory depression, urinary retention, and pruritus (Pascoe & Dyson 1993; Torske & Dyson 2000; Troncy et al. 2002). The administration of fentanyl from a transdermal patch has become increasingly popular for the provision of analgesia, especially for human cancer patients. When used for post-operative analgesia in dogs, it is applied 24 hours before surgery, and plasma fentanyl concentrations remain stable until patch removal at 72 hours. The patch's ease of application and its price make it an excellent option for post-operative pain control (Kyles et al. 1998; Robinson et al. 1999; Welch et al. 2002; Gilberto et al. 2003; Hofmeister & Egger 2004; Lafuente et al. 2005).

Increased production of catecholamines and cortisol after anaesthesia, surgery and post-operative pain are part of the neurohumoral stress response and, despite its limitations, cortisol is widely used as an indicator of stress (Hendrix et al. 1996; Ko et al. 2000; Sibanda et al. 2006). In dogs, various analgesic techniques have been reported to suppress this surgical stress response (Hendrix et al. 1996; Grisneaux et al. 1999; Lafuente et al. 2005). It has been demonstrated that epidural morphine alleviates pain as well as the neurohumoral stress response in dogs undergoing a surgical orthopaedic procedure (Hendrix et al. 1996; Sibanda et al. 2006).

The aim of this study was to compare the analgesic and side effects of the fentanyl patch and epidural morphine after ovariohysterectomy in dogs.

Materials and methods

Twenty adult female mongrel dogs admitted for elective ovariohysterectomy at the Ankara University Faculty of Veterinary Medicine Department of Surgery were studied. The mean body mass of the dogs was 22.6 ± 2.6 kg [95% confidence interval (CI)]. The dogs were admitted to the clinics 10 days prior to surgery, in order to prevent separation anxiety and to allow them to become familiar with the handler. During this period the observer who scored the animals' pain fed and exercised the dogs twice a day. The study was approved by the local Ethics Committee. All dogs were fasted overnight prior to anaesthesia, but had free access to water. All anaesthetic procedures, epidural injections, and pain scoring were performed by the same anaesthetist.

Anaesthetic protocol

Following placement of a catheter in a cephalic vein, 20 mg kg^{-1} cephalosporin was administered. Anaesthesia was induced with 4–6 mg kg^{-1} propofol and the trachea was intubated. The dogs were placed in dorsal recumbency and connected to an anaesthetic circle system. Anaesthesia was maintained with isoflurane in oxygen, with fresh gas flows of 2 L $minute^{-1}$ and the vaporizer (Isoflurane; River Medical Engineering, Korea) set at 1–2%. All dogs underwent intermittent positive pressure ventilation (automatic ventilator; AMS Junior-620, Turkey) with a respiratory rate (f_R) of 14 breaths $minute^{-1}$ and tidal volume of 10–15 mL kg^{-1}. All dogs received an infusion of 10 mL kg^{-1} $hour^{-1}$ lactated Ringer's solution. Heart rate (HR), oxygen saturation, and invasive arterial blood pressures were measured and recorded during general anaesthesia (PETAS KMA 460R, Turkey). Deviations of more than 20% in HR and blood pressure were assumed to indicate inadequate analgesia and 2.5 μg kg^{-1} fentanyl (Fentanyl Citrate; Antigen Pharmaceuticals, Germany) was administered IV as a rescue analgesic.

Analgesic protocol

Each animal was assigned randomly to one of two pain management groups. In the fentanyl patch group, 24 hours prior to the induction of anaesthesia a 50 or 75 μg $hour^{-1}$ transdermal fentanyl patch (Duragesic; Janssen-Cilag, NJ, USA) was applied to the lateral or dorsal thorax of the dogs. A 50 μg patch was applied to dogs lighter than 20 kg and a 75 μg patch to heavier dogs. Prior to application, the area was clipped using electric clippers and cleaned with water but not scrubbed. The patch was applied onto the clipped area and then covered with a light bandage. The fentanyl patch stayed in place for 72 hours.

After being anaesthetized, the dogs in the epidural morphine group, received 0.1 mg kg^{-1} preservative- free morphine (Morphine; Galen Ilac, Turkey) diluted in a saline solution to 0.3 mL kg^{-1} and injected epidurally into the lumbosacral space through a 17 gauge Tuohy needle. Correct placement of the needle was confirmed using the hanging-drop technique or the lack-of-resistance technique, and aspiration was used prior to injection of morphine to ensure that the injection was not into a blood vessel.

All dogs underwent overohysterectomy by the same surgeon. The abdomen then was closed in a routine manner and the animals allowed to recover from anaesthesia. Ability of the animal to support its own head was considered as recovery (time 0).

Post-operative pain assessments and other observations

The parameters HR, f_R, rectal temperature (RT), agitation, sedation and pain scores were recorded pre-operatively, at 0, 30, 60, 90, 120, and 150 minutes, and 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours after recovery.

Pain was scored using a multifactorial scoring system modified from that of Grisneaux et al. (1999) and Robinson et al. (1999). The subjective and objective variables evaluated to obtain this score were vocalization, agitation, movement, HR, f_R, RT, and response to palpation beside the incision site (Appendix). A score of 0–16 was possible, with increased scores indicative of greater pain. During the observation period, analgesia was considered inadequate if the total pain score was ≥8, and morphine (0.3–0.5 mg kg^{-1}, IM) was administered as a rescue analgesic post-operatively. The level of sedation was assessed using the following scoring system: 1) agitated, 2) normal, 3) sedated, sleepy, stand up position when the handler opened the door of the cage and verbally encouraged the dog to rise, but does not want to walk, head down with semiclosed eyes, 4) lethargic, lies down, does not want to stand up, no response to the handler's voice or to palpation. To minimize variability, pain and sedation were assessed only by one person who was familiar with the pain scoring system. Due to the visible difference, the individual was aware of the treatment protocol.

Other variables noted and evaluated were; salivation, vomiting, the start of eating (the food was first offered 6 hours after recovery), and attention to the surgical site. The last two parameters were recorded at 6 hour intervals during the 48 hour period unless the dogs began eating or demonstrating self-care (cleaning and licking) of the operation site.

Peripheral venous blood was collected from dogs via a needle from the cephalic vein into a heparinized tube just prior to induction of the anaesthesia and at 0 (recovery from anaesthesia), 2, 4, 6, 12, and 24 hours for cortisol measurement. The plasma was stored in a freezer at −70 °C in duplicates until the time of assaying. The total plasma cortisol concentration was measured using a radioimmunoassay kit (Immunotech, Czech Republic). The assay was validated for canine plasma. The lowest detectable concentration of the cortisol assay was 10 nmol L^{-1}. The interassay coefficients of variation were 1.23% and 1.95%, respectively, for the plasma standards of 16 and 177 nmol L^{-1}.

Statistical analysis

Normality check of continuous variables was carried out using Shapiro Wilk test, and, according to these test results, between and within group differences in HR, f_R, temperature, and cortisol were analyzed by analysis of variance (ANOVA) for repeated measures. Pain and sedation score differences over time for each group were determined by Friedman test, while the group comparisons for particular time points were done by Mann–Whitney *U*-test. First urination and eating time comparisons between groups were tested by the nonparametric Mann–Whitney *U*-test, while the comparison of first wound licking time between groups was tested by independent sample *t*-test. The statistical analyses were performed with commercially available software (SPSS, IL, USA). Data are reported as mean ± 95% confidence interval (CI) and median and interquartile range (IQR) for parametric and non-parametric tested parameters respectively. Differences were considered significant where $p < 0.05$.

Results

Mean surgical times for the epidural morphine and transdermal fentanyl groups were 42 ± 3.9 minutes and 48 ± 7.3 minutes, respectively. No dog required rescue post-operative analgesia.

The hanging-drop technique failed in five of the 10 dogs in the epidural morphine group; therefore,

the lack-of-resistance technique was used to indicate the appropriate placement during the epidural injection.

The dogs in the epidural morphine group were calm and relaxed during the recovery period. Vocalization (in response to a calm voice) was recorded in seven dogs in the fentanyl patch group. In these seven dogs, vocalization lasted up to 30 minutes in two dogs and up to 60 minutes in five dogs. Among these seven dogs, four of them continued to whine softly for longer periods; one of them continued for 8 hours, two of them for 12 hours, and one for 24 hours.

During the recovery period, in the epidural morphine group, salivation was recorded in one dog for the first 30 minutes. Vomiting was not observed. In the fentanyl patch group, salivation lasted up to 30 minutes in three dogs, up to 60 minutes in one dog, up to 90 minutes in one dog, and up to 120 minutes in one dog. Vomiting was recorded in the two dogs in which salivation had continued the longest time.

No sedation was recorded pre-operatively in either group. However in the fentanyl patch group sedation was seen immediately in all dogs post-operatively; and lasted 10–24 hours (median 12, IQR (10–15) hours). Although the dogs recovered from anaesthesia, when in a standing position their heads were down and their eyes were semiclosed. The sedation score was higher in the fentanyl patch group than in the epidural morphine group at 4, 5, 6, 8, 10, and 12 hours. The differences were statistically significant between the two groups ($p < 0.03$) (Fig. 1).

None of the dogs in either group had pain scores >7 and the administration of additional analgesics were not required. Pain scores were significantly lower in the epidural morphine group than in the fentanyl patch group at all post-operative times ($p < 0.02$) (Fig. 2). For both groups, the highest pain scores were recorded at 0 minutes, and declined within the 12 hour observation period (Fig. 2).

Licking of the wound began after the pain score declined. Such licking occurred at mean 8.9 ± CI 2.2 hours in the epidural morphine group and 23.4 ± 5.9 hours in the fentanyl patch group, these times differing significantly ($p = 0.0008$). Dogs in the epidural morphine group began eating significantly earlier (median 6, IQR (6–18) hours) than the fentanyl patch group (24, IQR (24–24) hours) ($p = 0.0004$). The median time to first urination was 1.5, IQR (0.75–10.0) hours in the epidural morphine group and 3, IQR (1.0–14.5) hours in the fentanyl patch group ($p = 0.594$). Urinary retention was not observed.

In both groups, at time 0 minutes HR was elevated when compared to pre-operative values, but decreased within 30 minutes (Fig. 3). Mean f_R did not decrease to <19 breaths minute^{-1} in the fentanyl patch group and 22 breaths minute^{-1} in the epidural morphine group during the study

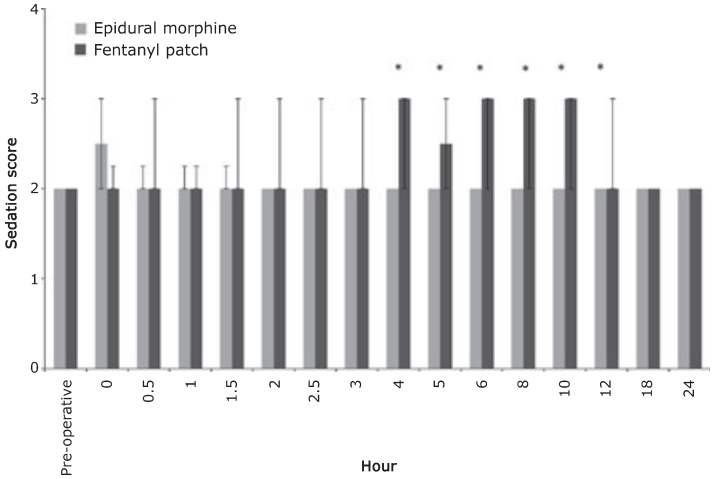

Figure 1 The sedation score (median, interquartile range) of the dogs before and during a 24 hour period following ovariohysterectomy. Analgesic treatment was either epidural morphine 0.1 mg kg^{-1} given after induction of anaesthesia ($n = 10$) or a fentanyl patch (50 or 75 μg hour^{-1}) applied 24 hours before surgery ($n = 10$). Ability of the animal to support its own head was considered as time 0. Sedation was scored on a scale of 1–4, 1 representing agitation, and 4 heavily sedated. *The two groups differed significantly ($p < 0.03$).

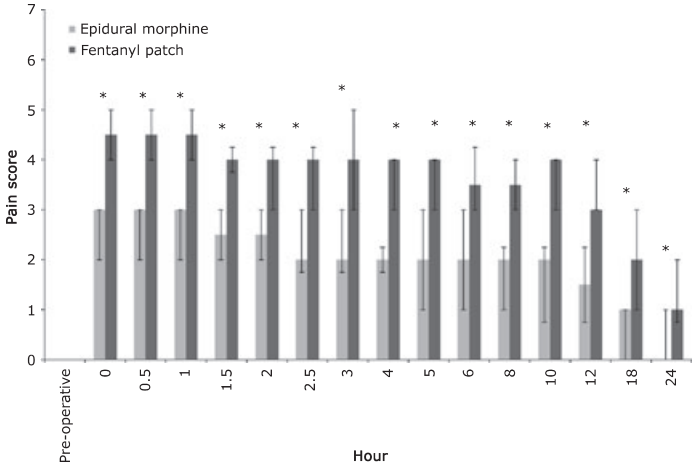

Figure 2 The pain score (median, interquartile range) of dogs before and during a 24 hour period following ovariohysterectomy. Pain was scored using a multifactorial system on a scale of 0–16: increased scores were indicative of greater pain. For group treatments – see Fig. 1. *The two groups differed significantly ($p < 0.02$).

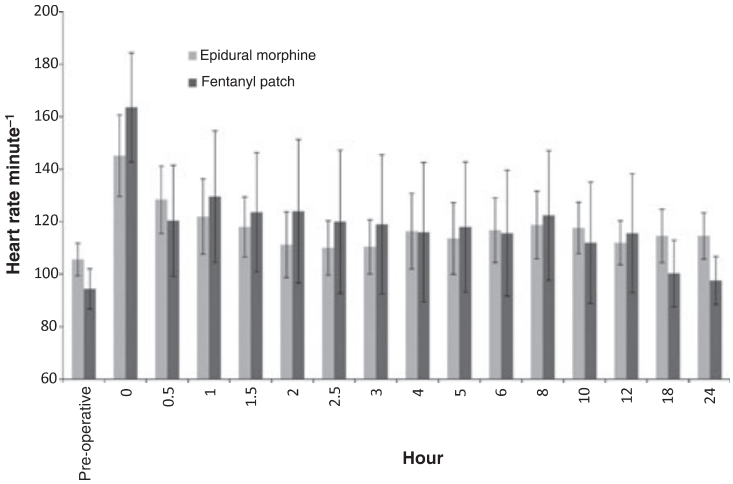

Figure 3 The heart rate (mean ± 95% confidence interval) of dogs before and during a 24 hour period following ovariohysterectomy. For group treatments – see Fig. 1. The heart rates in the two groups did not differ significantly.

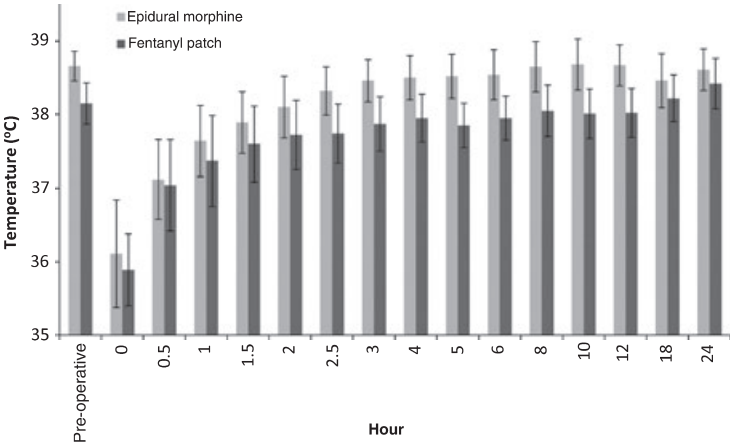

Figure 4 The temperature (mean ± 95% confidence interval) of dogs before and during a 24 hour period following ovariohysterectomy. For group treatments – see Fig. 1. The rectal temperatures in the two groups did not differ significantly.

period. HR and f_R were not statistically significant between the two groups.

The rectal temperature was significantly lower than pre-operative baseline values at 0 minutes in both groups (Fig. 4). Rectal temperatures recorded had returned to within the reference range (37.8–39.2 °C) after mean 1.6 ± CI 1.0 hours in the epidural morphine group and 6.3 ± 5.1 hours in

the fentanyl patch group. Mean rectal temperature in the fentanyl patch group was lower than that of the epidural morphine group at all post-operative times, but the difference was not statistically significant ($p = 0.053$).

Two dogs in the fentanyl patch group had a slight irritation (erythema) at the application site at the end of the third day which resolved spontaneously within 24 hours. There was no evidence of discomfort or skin reaction associated with the patches in any other dog.

Mean cortisol concentrations pre-operatively were 29.5 ± 7.8 nmol L^{-1} in the epidural morphine group and 50 ± 18.2 nmol L^{-1} in the fentanyl patch group, which was within the reference range (0–138 nmol L^{-1}) (Hendrix et al. 1996). Maximum cortisol concentrations were recorded at time 0 minutes; concentrations then decreased to values within the reference range by 6 hours in the epidural morphine group and by 12 hours in the fentanyl patch group, and to pre-operative values by 24 hours. Cortisol concentrations were significantly higher ($p = 0.003$) in the fentanyl patch group than in the morphine group for 12 hours post-operatively (Fig. 5).

Discussion

It is difficult to assess pain in animals because of lack of verbal communication between the animal and the handler. Pain scoring systems have been developed in an attempt to interpret physiological changes which may be related to pain such as HR, f_R, body temperature, blood pressure, and subjective variables such as movement, appearance, salivation, vomiting, appetite, mental state, vocalization, and interest shown to the handler (Firth & Haldane 1999; Mathews 2000; Pascoe 2000; Dobromylskyj et al. 2001; Lafuente et al. 2005). Some researchers (Conzemius et al. 1997; Holton et al. 1998, 2001), emphasize that the physiological variables can be altered by fear, stress, anxiety, and degree of anaesthesia and therefore are not good indicators of pain. In our study, the dogs were allowed to familiarize with the new environment for at least 10 days, and that this was effective in reducing stress was supported by the pre-operative cortisol measurement. As a result, all changes that occurred after the surgery were likely to relate to the anaesthesia, surgery, pain, and side effects of transdermal fentanyl or epidural morphine. Thus we decided to use a multimodal pain scoring system similar to other studies (Firth & Haldane 1999; Grisneaux et al. 1999; Pacharinsak et al. 2003; Lafuente et al. 2005). The 10-day familiarization period also provided the handler, who assessed the pain scores, with the opportunity to become familiar with each individual dog's normal behaviour and thus identify the subjective pain associated alterations more easily. To the authors' knowledge, there is no other published report involving pain scoring where such a prolonged period of familiarization has been employed.

The Tuohy needle is designed specifically for epidural puncture. It allows identification of the ligamentum flavum and the close fitting stylet prevents plugging of the needle tip and failure to recognize the loss of resistance (Novello & Corletto 2006). In our study, the hanging-drop technique

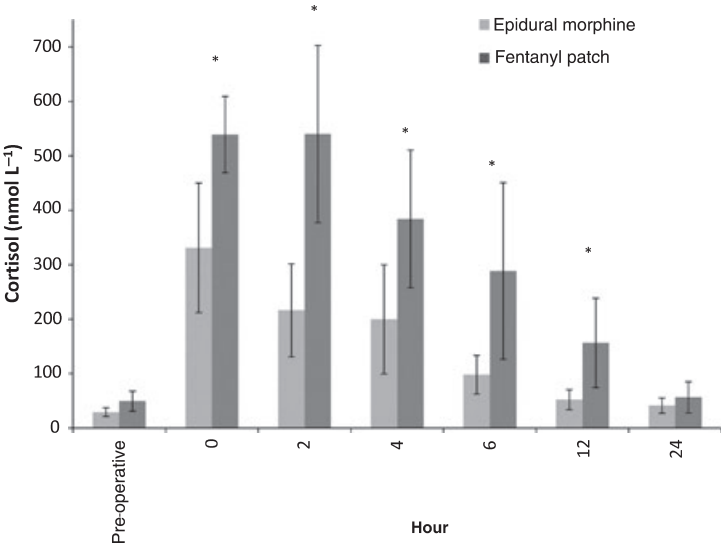

Figure 5 The cortisol concentration (mean ± 95% confidence interval) of dogs before and during a 24 hour period following ovariohysterectomy. For group treatments – see Fig. 1. *The two groups differed significantly ($p < 0.03$).

failed in five of the 10 dogs given epidural morphine. Although the 'pop' was felt, the saline in the hub of the Tuohy needle was not drawn into the epidural space. Removing the stylet before the epidural space causes the tissue to enter the needle and obstruct the needle tip and the correct placement was verified by the lack-of-resistance technique, which, in this study, we found more useful than the hanging-drop technique.

Some authors (Gilberto et al. 2003; Lafuente et al. 2005) have reported anorexia and nausea as side effects of fentanyl. Six of the 10 dogs in the fentanyl patch group continued to salivate during the post-operative period and two of them vomited. It is possible that the cause of the salivation was nausea. Dogs in the epidural morphine group began eating significantly earlier than those in the fentanyl patch group and vomiting was not observed.

Gilberto et al. (2003) reported mild hypothermia after fentanyl patch application within 12 hours pre-operatively, but this was not recorded pre-operatively in our study. The lowest rectal temperature recorded was at 0 minutes, and is presumed to have resulted from anaesthesia and from heat loss from the open abdomen (Ko et al. 2000). Although the fentanyl patch group had lower mean rectal temperature than the epidural morphine group at all post-operative times, by 30 minutes post-operatively rectal temperature had risen to acceptable values and no treatment was applied.

Some researchers (Robinson et al. 1999; Gilberto et al. 2003; Hofmeister & Egger 2004) have reported respiratory depression, as assessed by respiratory rate, both after epidural administration of morphine and after fentanyl patch application. In contrast, other researchers evaluated arterial blood gases and reported that neither fentanyl patches nor epidural morphine induced hypoventilation (Welch et al. 2002; Acosta et al. 2005). In our study, although respiratory function was not thoroughly investigated, f_R never decreased below the reference range of 18–34 breaths minute^{-1} in either group during the study period.

A reported adverse effect both of transdermal fentanyl and of epidural morphine has been bradycardia (Gilberto et al. 2003; Hofmeister & Egger 2004). In this current study, HR was never <60 beats minute^{-1}. HRs in both groups were slightly higher at 0 minutes than at the other times, possibly associated with increased sympathetic response as the dogs recovered from anaesthesia, as reported previously (Hendrix et al. 1996; Firth & Haldane 1999; Lucas et al. 2001).

With regard to the sedation score, there were disparities between previously reported findings and the results of our study. Gilberto et al. (2003) stated that the sedation began 12 hours after the fentanyl patch application pre-operatively and continued until the patches were removed, whereas in our study no sedation was recorded pre-operatively. Robinson et al. (1999) compared transdermal fentanyl and epidural morphine after major orthopedic operations and recorded higher sedation scores in the epidural morphine group than in the fentanyl patch group. In contrast, in our study, although the dogs were awake, animals in the fentanyl patch group were sedated, after the handler opened the door of the cage and verbally encouraged the dogs to rise, they would stand but not walk, were sleepy when in the standing position, and had semiclosed eyes throughout the 12 hour period. Conversely, the dogs in the epidural morphine group were calm and relaxed during the observation period.

In this current study, the serum fentanyl concentrations were not determined. Other studies have reported that plasma concentrations of fentanyl were very variable after patch application (Egger et al. 1998; Robinson et al. 1999; Welch et al. 2002; Gilberto et al. 2003). None of these studies compared the correlations between the plasma fentanyl level and associated side effects like vocalization, anxiety, and sedation. Gilberto et al. (2003) used two different doses of fentanyl during abdominal operations and recorded high pain scores in the early post-operative period (0–8 hours). Kyles et al. (1998) compared transdermal fentanyl with oxymorphone after ovariohysterectomy and documented higher pain scores in dogs receiving transdermal fentanyl in the early post-operative period (0–6 hours). In our study the pain scores in the fentanyl patch group were higher than those in the epidural morphine group in the 12 hour period post-operatively. We thought that the reason for the high pain score was vocalization, as it was one of the criteria that we used in our pain-scoring scale. Gilberto et al. (2003) used transdermal fentanyl in dogs and recorded vocalization or whining both pre-operatively and post-operatively. However they suggested that the vocalization after the fentanyl patch application may not reflect an actual pain response, but be caused by fentanyl induced anxiety. In our study, the vocalization continued for 12 hours post-operatively, and it could be that this

resulted in falsely high scores. On the contrary, neither vocalization nor whining were recorded in the epidural morphine group and the dogs were calm and relaxed during the study period.

Slight irritation of the skin at the application site, of the fentanyl patch has been reported in some studies (Egger et al. 1998; Riviere & Papich 2001) but not in others (Welch et al. 2002). In the present study, two dogs had slight irritation at the application site at the end of the third day. Nothing was observed clinically before the patch was removed and healing occurred within 24 hours.

Licking, grooming, and wound care began after the pain score declined and this was earlier in the epidural morphine group than in the fentanyl patch group. As pain wanes, interest in the surroundings, self care, and wound care increases. Practically, this may mean that collars or bandages become important when the pain begins to decrease and may not be necessary in the early post-operative period.

Factors such as fear and anxiety and surgery, trauma, or pain may cause an endocrine response in catabolic hormones such as cortisol (Hendrix et al. 1996; Thurmon et al. 1996; Grisneaux et al. 1999; Ko et al. 2000). That the pre-operative cortisol values were within the reference range suggests that pre-operative stress was minimal. Maximum cortisol concentrations were recorded during the period of recovery from the anaesthesia and this increase was lower in the epidural morphine group than in the fentanyl patch group. Although the evaluation of the cortisol concentration is important for determining physiologic status or the neurohumoral stress response in dogs, routine measurement of cortisol is impractical in clinical practice (Firth & Haldane 1999; Grisneaux et al. 1999).

Fentanyl patches are used commonly to provide analgesia after surgery in dogs because they are relatively simple to use, provide analgesia at a reasonable cost, and result in few complications. The patches have high potential for abuse and have severe restrictions when in human medical use. Significant reserves of fentanyl may remain in transdermal patches even after several days of use (Egger et al. 1998; Robinson et al. 1999; Gilberto et al. 2003; Hofmeister & Egger 2004). Schmiedt & Bjorling (2007) reported accidental transmucosal and oral absorption 38 hours after application in a dog. In our study, the site of application of the patch was covered with a light bandage to prevent its ingestion by the animals and no such complications occurred.

According to the findings in our study, epidural morphine provided better analgesia and fewer adverse effects than the fentanyl patch in dogs and may be preferred to the fentanyl patch after ovariohysterectomies. Both pain scores and cortisol concentrations were higher and remained so for a longer period in the fentanyl patch group than in the epidural morphine group. Regardless of the reason, this suggests that the fentanyl patch has limited use for early post-operative analgesia.

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Appendix

Criteria used for scoring post-operative pain in dogs after ovariohysterectomy (modified from Grisneaux et al. 1999; Robinson et al. 1999).

Variables	Criteria	Score
Heart rate	<10% above pre-operative rate	0
	11–30% above pre-operative rate	1
	31–50% above pre-operative rate	2
	>50% above pre-operative rate	3
Respiratory rate	<10% above pre-operative rate	0
	10–20% above pre-operative rate	1
	21–30% above pre-operative rate	2
	>30% above pre-operative rate	3
Vocalization	Quiet	0
	Vocalizing, response to calm voice	1
	Vocalizing, no response to calm voice	2
Agitation	Asleep or calm	0
	Mild agitation	1
	Moderate agitation	2
	Severe agitation/hysterical	3
Movement	None	0
	Frequent position changes	1
	Thrashing	2
Response to manipulation	No response	0
	Minimal response, tries to move away	1
	Turns head toward side, slight vocalization	2
	Apparent intention to bite	3

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