*Original Article*

# The Effect of Transdermal Fentanyl Patches on Required Isoflurane Concentration when Compared with Intramuscular Morphine during Patellar Luxation Repair in Dogs

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## *Abstract*

This clinical trial aimed to assess the intraoperative analgesic effect, based on the required minimum alveolar concentration (MAC) of isoflurane, of transdermal fentanyl when compared with intramuscular morphine in dogs undergoing patellar luxation repair. Seventeen healthy dogs with grade II or grade III of medial patellar luxation were randomly assigned to group M or group F, receiving a sham patch or a transdermal fentanyl patch (25 μg/h), respectively, applied on the skin at least 24 h prior to surgery. Three dogs had bilateral medial patellar luxation and were then enrolled in both groups, resulting in ten animals for each group. Before surgery, group M dogs were premedicated intramuscularly with 0.03 mg/kg acepromazine and 0.5 mg/kg morphine while group F dogs were premedicated intramuscularly with the same dose of acepromazine and normal saline at an equivalent volume to morphine. Anesthesia was induced intravenously with propofol and maintained with isoflurane in oxygen and assisted respiration. Anesthesia monitoring and measurement of all parameters in all dogs were conducted by the same investigator blinded to the applied patches and premedications. Vital signs, end-tidal concentration and MAC of isoflurane were monitored and recorded before making surgical incision (baseline values) and at 5-min intervals after initiation of the incision (intraoperative values). All patellar luxation were repaired by the same surgeon and techniques. Mean±SD (median) baseline and intraoperative MACs of isoflurane for group M were 1.22±0.25% (1.2%) and 1.1±0.27% (1.1%), respectively; and for group F were 1.1±0.31% (1.05%) and 1.1±0.26% (1%), respectively. Significant differences between the baseline and intraoprative isoflurane MACs within each group and between the two groups were not observed ($p$>0.05); indicating that transdermal fentanyl and intramuscular morphine have comparable intraoperative analgesic effects. In conclusion, transdermal fentanyl patches can be used for preemptive analgesia to reduce the required isoflurane concentration during surgery.


**Keywords**: analgesia, dogs, fentanyl, isoflurane, MAC, transdermal

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## Introduction

Fentanyl is a synthetic mu-opioid agonist and is most commonly used for control of perioperative pain in human and small animals because of its profound analgesic effect; approximately 100 times potency of morphine (Pascoe, 2000; FDA, 2013). Fentanyl is routinely administered by intravenous continuous rate infusion to obtain a steady plasma concentration. Besides the continuous infusion, stable plasma concentration of fentanyl can be obtained by transdermal administration (Ilkiw, 1999). High lipophilicity, low molecular weight, and potent analgesic effect of fentanyl make it ideal to be used transdermally (Grond et al., 2000). The transdermal delivery mimics continuous intravenous infusion and maintains a steady-state concentration of fentanyl in the blood for a period of more than 2 days after patch application (Gilberto et al., 2003). The transdermal delivery system allows easy drug administration, reduces the need for frequent doses, avoids venous access or frequent IM injections, allows animals to be treated as outpatients, and assures long-lasting sufficient analgesia (Wilson et al., 2006; Bellei et al., 2011).

A transdermal fentanyl patch produces a mean constant-state plasma concentration of 1.6 ng/ml in dogs (Kyles et al., 1996) and median concentration of 1.58 ng/ml in cats (Lee et al., 2000). Plasma fentanyl concentrations ranging from 0.5 to 1 ng/ml are considered analgesic in dogs (Kyles et al., 1998; Robinson et al., 1999). In contrast, a minimum plasma concentration of 0.23 ng/ml fentanyl is required to achieve analgesia in human (Egger et al., 1998; Bellei et al., 2011).

A transdermal fentanyl patch must be applied to non-damaged skin of the dorsolateral thorax which is clipped and cleaned with water in order to attain efficacy and certain action onset (Hofmeister and Egger, 2004). External heat sources could increase drug uptake and should not be applied to the patch application site. The plasma fentanyl concentration reaches the level consistent with that producing analgesia approximately 24 h in dogs and 7 h in cats after patch application which remains for a period of 72 h (Kyles et al., 1996; Hofmeister and Egger, 2004). Therefore, to be effective intraoperatively and postoperatively, transdermal fentanyl patches must be applied at least 7 and 24 h prior to surgery to cats and dogs, respectively.

An indirect and clinical method to assess analgesic potency of opioids in the intraoperative period is to determine reduction in required anesthetic concentration; either minimum alveolar concentration (MAC) or end-tidal concentration (McEwan et al., 1993; Criado and Gomez de Segura, 2003; Docquier et al., 2003; Steagall et al., 2006). The reduction in the required concentration of an anesthetic inhalant is beneficial in that it decreases adverse cardiovascular effects of the inhalant. Reduction in isoflurane MAC by continuous rate infusion (CRI) of fentanyl has been reported in humans (McEwan et al., 1993), pigs (Moon et al., 1995), dogs (Hellyer et al., 2001; Ueyama et al., 2009), rats (Criado and Gomez de Segura, 2003), and horses (Thomasy et al., 2006). End-tidal concentration of isoflurane was reduced in dogs receiving fentanyl CRI (Steagall et al., 2006). The infusion of fentanyl has also been reported to reduce MAC of enflurane in dogs (Murphy and Hug, 1982).

The intraoperative analgesic potency of transdermal fentanyl can be assessed by comparing MAC of isoflurane before and after patch placement (Yackey et al., 2004; Wilson et al., 2006). Besides the required end-tidal concentration and MAC of isoflurane, the intraoperative analgesic effect of transdermal fentanyl can be evaluated from plasma fentanyl concentration (Glerum et al., 2001; Yackey et al., 2004) and attenuated rise in biochemical markers of stress and pain; serum cortisol and blood glucose (Glerum et al., 2001). For postoperative analgesia, antinociception can be determined from plasma fentanyl concentration, serum cortisol, blood glucose, required rescue morphine, and pain scores or scales (Kyles et al., 1998; Robinson et al., 1999; Franks et al., 2000; Glerum et al., 2001; Gilberto et al., 2003; Egger et al., 2007; Bellei et al., 2011). To test efficacy of analgesics, these parameters may be compared between those measured before and after fentanyl patches are applied or compared with those measured in animals receiving other opioids with known potency such as butorphanol (Franks et al., 2000), morphine (Robinson et al., 1999; Egger et al., 2007) and oxymorphone (Kyles et al., 1998).

Uses of transdermal fentanyl patches mostly reported are for postoperative analgesia in dogs and cats (Kyles et al., 1998; Robinson et al., 1999; Franks et al., 2000; Glerum et al., 2001; Gilberto et al., 2003; Egger et al., 2007; Bellei et al., 2011). There are only few studies on the intraoperative effect of transdermal fentanyl on isoflurane MAC in research dogs and cats not undergoing surgery (Yackey et al., 2004; Wilson et al., 2006); and one study on serum cortisol and blood glucose (Glerum et al., 2001). The purpose of this study was to compare the intraoperative analgesic effect, based on required end-tidal concentration and MAC of isoflurane, of transdermally administered fentanyl with that of intramuscularly administered morphine in dogs undergoing medial patellar luxation repair.

## Materials and Methods

***Animals:*** The study protocol was approved by Chulalongkorn University Animal Care and Use Committee (Approval No. 12310043). Seventeen dogs with grades II or III of medial patellar luxation, presented at the Teaching Hospital of the Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand, were enrolled in the study after written owner consent had been obtained. All dogs were considered healthy on the basis of history, preoperative physical examination and results of complete blood count and serum chemistry study.

***Study design and anesthetic procedure:*** The 17 dogs were randomly assigned to group M (positive control) and group F (treatment) (Tables 1 and 2). Three of the

**Table 1** Sex, breed, age, weight, stifle side and medial patellar luxation (MPL) grade of dogs receiving intramuscular morphine

| Dog | Sex | Breed | Age | Weight (kg) | Stifle | MPL grade |
|---|---|---|---|---|---|---|
| M1 | M | Pomeranian | 7y | 2.4 | Left | 3 |
| M2(F6)* | M | Pomeranian | 8m | 3.7 | Right | 3 |
| M3 | F | Spitz | 8y | 7 | Right | 2 |
| M4 | M | Yorkshire Terrier | 4m | 3 | Left | 3 |
| M5 | M | Pomeranian | 4y | 3.3 | Left | 3 |
| M6(F4)* | M | Chihuahua | 1y6m | 1.1 | Right | 3 |
| M7 | M | Pomeranian | 11m | 5 | Right | 3 |
| M8 | F | Pomeranian | 4y | 4.5 | Right | 3 |
| M9(F2)* | F | Chihuahua | 1y8m | 2.6 | Left | 3 |
| M10 | F | Pomeranian/Maltese | 1y11m | 3.1 | Left | 3 |

*Dogs enrolled in both groups.

**Table 2** Sex, breed, age, weight, stifle and medial patellar luxation (MPL) grade of dogs receiving fentanyl transdermal patches

| Dog | Sex | Breed | Age | Weight(kg) | Stifle | MPL grade |
|---|---|---|---|---|---|---|
| F1 | F | Pomeranian | 4y2m | 2.5 | Left | 2 |
| F2(M9)* | F | Chihuahua | 1y | 2.3 | Right | 3 |
| F3 | M | Pomeranian | 2m | 2 | Left | 2 |
| F4(M6)* | M | Chihuahua | 1y11m | 1.2 | Left | 3 |
| F5 | M | Pomeranian | 1y9m | 5.2 | Left | 3 |
| F6(M2)* | M | Pomeranian | 1y3m | 4.2 | Left | 3 |
| F7 | F | Yorkshire Terrier | 1y | 2.5 | Right | 3 |
| F8 | F | Yorkshire Terrier | 2y | 2.9 | Right | 3 |
| F9 | F | Pug | 5m | 4.8 | Left | 3 |
| F10 | M | Pug | 6m | 6.2 | Left | 2 |

*Dogs enrolled in both groups.

17 dogs had bilateral medial patellar luxation and were then enrolled in both groups as M2 (F6), M6 (F4) and M9 (F2), resulting in ten animals for each group. Medians of dog ages were 1 year and 9.5 months for group M, and 1 year and 1.5 months for group F. Mean±SD weight of dogs in group M and group F were 3.6±1.6 (median, 3.2) and 3.4±1.6 (median, 2.7) kg, respectively.

Group M dogs received a sham patch (TEGADERM Film, 3M Health Care, USA) which did not contain any drugs while group F dogs received a 25 µg/h fentanyl patch (DUROGESIC, Janssen Pharmaceutica NV, Belgium), applied on clipped skin at the upper third of the lateral thorax at least 24 h prior to surgery. A light bandage was applied around the thorax of all dogs to prevent the patch from being dislodged and to blind the investigator to the patch applied. We used the same investigator to monitor anesthesia and measure parameters in all dogs throughout this study. Food and water were withheld at least 24 h prior to premedication. After heart rate, systolic blood pressure (VET-DOP, Blood Flow Doppler, Vmed Technology, USA), respiratory rate, and blood glucose (ONE TOUCH, SURESTEP, Hospital Test Strips, LifeScan, Inc., Johnson & Johnson Co., USA) determinations, group M dogs were premedicated with intramuscular injection of 0.03 mg/kg acepromazine maleate (COMBISTRESS,

Phenix Pharmaceuticals N.V., Belgium) and 0.5 mg/kg morphine sulfate (M & H Manufacturing Co., Ltd., Thailand).

Group F dogs were premedicated with intramuscular injection of the same dose of acepromazine and normal saline at an equivalent volume to morphine. The premedication drugs were prepared and administered by the same person who applied the patch to the dogs. Anesthesia for all dogs was induced by the investigator with intravenous injection of 2 – 4 mg/kg propofol (PROPOFOL-LIPURO 1%, B. Braun Melsungen A.G., Germany) to take effect 30 minutes after premedication. Following endotracheal intubation, anesthesia was maintained with isoflurane in oxygen and mechanically assisted respiration at 15 breaths/minute, through a Bain coaxial circuit. The animal was positioned in lateral recumbency on a hot water circulating heating pad to maintain normal body temperature. Acetated Ringer's solution was given intravenously at 10 ml/kg during the first h, then 5 ml/kg afterwards. Heart rates, respiratory rates, oxygen saturation, body temperature (DATASCOPE PASSPORT® V, Mindray D.S., USA, Inc., USA), systolic blood pressures, end-tidal concentrations and MACs of isoflurane (GAS MODULE-3, Datascope Corp., USA) were measured and recorded at 5-minute intervals. The investigator adjusted vaporizer settings of isoflurane at the lowest concentration adequate for maintaining surgical anesthesia which was based on clinical signs, including absence of palpebral reflex, absence of pedal reflex, absence of jaw tone, heart rate between 60 and 160 beats/min, and systolic blood pressure between 80 and 160 mmHg. The parameters measured at this stage of anesthesia before making surgical incision were recorded as baseline values and after initiation of the incision as intraoperative values. Blood glucose was determined intraoperatively at 30 and 60 minutes after making the incision. Anesthesia duration (time elapsed from premedication until turning off isoflurane) and surgery duration (time elapsed from the first incision until placement of the last suture) for each dog were recorded.

***Determination of isoflurane MAC:*** The DATASCOPE PASSPORT® V showed on its monitoring screen the isoflurane MAC at each point of measurement which was calculated from the end-tidal concentration of isoflurane, measured by the GAS MODULE-3, at that time divided by 1 MAC value of isoflurane (1.15) (Passport® V operating instructions, 2009). The latter value is a clinically-derived coefficient or % volume fraction of isoflurane in oxygen.

***Surgery:*** Surgical repair with the same techniques in all dogs was performed by the same surgeon throughout the study. The techniques included V-shaped wedge recession sulcoplasty, patellar and tibial antirotational suture ligaments, and fascia lata overlap. 25 mg/kg cefazolin (ZEFA M.H.®, M & H Manufacturing Co., Ltd., Thailand) was given preoperatively IV and postoperatively per oral twice daily for five days. All dogs were treated as outpatients and received 4 mg/kg oral carprofen (RIMADYL, Pfizer Inc., USA) postoperatively once daily for four days. The fentanyl patch was removed two days after surgery.

***Statistical analysis:*** Age and weight of animals, blood glucose level, anesthesia duration, surgery duration, baseline and intraoperative heart rates, blood pressures, end-tidal concentrations and MACs of isoflurane are reported as mean±SD and median. The data of the intraoperative heart rates, blood pressures, and isoflurane concentrations used for analysis were those measured while the animals were stabilized at the anesthetic depth adequate for surgery; and changes of the heart rates or blood pressures from the baseline values were less than 30%. The intraoperative heart rates, blood pressures, end-tidal concentrations and MACs of isoflurane from multiple measurements in each dog were averaged to be used for comparison. Paired t-test was used for comparing measured parameters within group while the Mann-Whitney U test was used for comparing the parameters between groups. Differences are considered significant at $p \leq 0.05$.

## *Results*

There were no significant differences ($p > 0.05$) in animal age, weight, anesthesia duration and surgery duration between group M and group F, although there were many older dogs in group M (Tables 1, 2 and 3). Means of the intraoperative heart rates, blood pressures, end-tidal concentrations and MACs of isoflurane were analyzed from 65 and 62 measurements in groups M and F, respectively. The intraoperative values of heart rates and blood pressures of dogs in both groups were not significantly different from the baseline values (Table 3). Also found were insignificant differences in heart rates and blood pressures, both baseline and intraoperative values, between the two groups. Therefore, the end-tidal concentrations and MACs of isoflurane required for the two groups were measured at the same depth of surgical anesthesia.

Mean±SD baseline and intraoperative end-tidal concentrations of isoflurane for group M were 1.4±0.29% (median, 1.4%) and 1.3±0.32% (median, 1.3%), respectively (Table 3). Mean±SD baseline and intraoperative end-tidal concentrations of isoflurane for group F were 1.29±0.40% (median, 1.35%) and 1.2±0.29% (median, 1.1%), respectively. Mean±SD baseline and intraoperative MACs of isoflurane for group M were 1.22±0.25% (median, 1.2%) and 1.1±0.27% (median, 1.1%), respectively. Mean±SD baseline and intraoperative MACs of isoflurane for group F were 1.1±0.31% (median, 1.05%) and 1.1±0.26% (median, 1%), respectively. In both groups, end-tidal concentrations of isoflurane were not significantly different from isoflurane MACs measured at the same point of time.

The intraoperative values of the required isoflurane end-tidal concentrations and MACs of the two groups were not significantly different from the

**Table 3** Anesthesia durations, surgery durations, baseline (before making surgical incision) and intraoperative (intraop) heart rates, systolic blood pressures (BP), end-tidal concentrations, and minimum alveolar concentrations (MACs) of isoflurane for dogs receiving intramuscular morphine and transdermal fentanyl.

| Group | Anesthesia duration (min) | Surgery duration (min) | Baseline heart rate (beat/min) | Intraop heart rate (beat/min) | Baseline systolic BP (mmHg) | Intraop systolic BP (mmHg) | Baseline isoflurane end-tidal conc (%) | Intraop isoflurane end-tidal conc (%) | Baseline isoflurane MAC (%) | Intraop isoflurane MAC (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Morphine | | | | | | | | | | |
| Mean±SD | 111.50±22.50 | 79.50±15 | 103±17 | 101±16 | 100±14 | 105±18 | 1.4±0.29 | 1.3±0.32 | 1.22±0.25 | 1.1±0.27 |
| Median | 105 | 80 | 107 | 100 | 100 | 105 | 1.4 | 1.3 | 1.2 | 1.1 |
| Measurements | 10 | 10 | 10 | 65 | 10 | 65 | 10 | 65 | 10 | 65 |
| Fentanyl patch | | | | | | | | | | |
| Mean±SD | 113.50±29.10 | 74±17.80 | 107±17 | 107±17 | 109±31 | 110±26 | 1.29±0.40 | 1.2±0.29 | 1.1±0.31 | 1.1±0.26 |
| Median | 112.50 | 77.50 | 101 | 106 | 101 | 100 | 1.35 | 1.1 | 1.05 | 1 |
| Measurements | 10 | 10 | 10 | 62 | 10 | 62 | 10 | 62 | 10 | 62 |

baseline values. Also found were insignificant differences in the end-tidal concentrations and MACs; both baseline and intraoperative values, between the two groups, although the required concentrations were slightly higher for group M.

Surgery caused increases in blood glucose in both groups. Mean±SD blood glucose levels measured at 30 (group M, 136±35; group F, 116±20 mg/dl) and 60 minutes (group M, 138±40; group F, 124±25 mg/dl) after making surgical incision were significantly ($p$<0.05) higher than the baseline values (group M, 91±7; group F, 95±15 mg/dl). There were no significant differences ($p$>0.05) in the baseline and the intraoperative blood glucose levels between the two groups.

## *Discussion*

This study revealed the intraoperative analgesic effect of transdermally administered fentanyl, which did not differ from the effect of intramuslarly administered morphine. There was no negative control group not receiving analgesics due to the ethical concern on animal pain. Withholding analgesics to establish an untreated control group in orthopedic patients will violate accepted standards of care (Glerum et al., 2001). We compared fentanyl with morphine; the positive control, instead of the negative control. Morphine is the prototype of opioids and is the standard drug commonly used for comparing with most analgesics (Thurmon et al., 1996). A recommended intramuscular dose of morphine for dogs is 0.5 - 1 mg/kg (Hellyer et al., 2007). From this study, there were no significant differences between the isoflurane MACs required for groups F and M, indicating that transdermal fentanyl and intramuscular morphine have comparable sparing effects on isoflurane MAC. As previously mentioned, analgesic potency of the opioid can be assessed by comparing certain parameters when using the tested opioid with those when using the analgesic with known potency. Therefore, it can be extrapolated from results of the present study that transdermal fentanyl provides intraoperative analgesia comparable to that received after intramuscular morphine. Interestingly, postoperative analgesia provided by transdermal fentanyl was reported to be similar to that achieved after epidural morphine (Robinson et al., 1999) and intramuscular morphine (Egger et al., 2007) in dogs undergoing orthopedic surgery.

There have been some reports on the isoflurane MAC for dogs not receiving any analgesics (Hellyer et al., 2001; Wilson et al., 2006; Ueyama et al., 2009). When comparing the isoflurane MACs for groups F and M with the isoflurane MACs of the previous reports, we presume that the transdermal fentanyl and intramuscular morphine have the sparing effects on isoflurane MAC. For dogs receiving propofol to induce anesthesia similar to the present study, mean ±SD of isoflurane MACs was 1.41 ±0.10% (Ueyama et al., 2009), more than means ±SD of baseline isoflurane MACs for group F dogs (1.1±0.31%) and for group M dogs (1.22±0.25%). Moreover, the mean±SD of isoflurane MACs for group F dogs was less than means±SD of isoflurane MACs previously reported for dogs masked with isoflurane to induce anesthesia (Hellyer et al., 2001, 1.80±0.21%; Wilson et al., 2006, 1.20±0.17%).

Besides MAC, the required concentration of isoflurane can be determined from the end-tidal concentration. Steagall et al. (2006) assessed the sparing-effect of fentanyl CRI on required concentration of isoflurane in dogs from the reduction in the end-tidal concentration. Isoflurane MACs in this study were calculated by the DATASCOPE PASSPORT® V from the end-tidal concentrations of isoflurane, therefore, there were no significant differences between the two concentrations at every interval. Because this study used the clinical cases, the method for determining the isoflurane MAC differed from others using research dogs not undergoing surgery (Wilson et al., 2006; Ueyama et al., 2009). Their methods involved exposing the dogs to a constant concentration of isoflurane for a fixed time, then applying an electrical stimulus to the buccal mucosa of the dog, and observing the animals for gross purposeful movement. Isoflurane concentration was reduced by 20% (if there was no movement) or increased by 10% (if the dog moved) and held constant for 15 minutes to allow inhalant equilibration. The isoflurane MAC was then determined to be the value midway between the

lowest end-tidal isoflurane concentration, at which no movement was detected and the highest concentration, at which the movement occurred.

This study used the same surgeon and surgical techniques to treat all dogs with moderate grades of medial patellar luxation, in order to minimize differences in tissue handling, tissue trauma and duration of surgery that could result in varied degrees of pain. The reason to use the same investigator monitoring anesthesia and measuring all parameters throughout this study was to minimize differences in subjective interpretation of vital signs by different investigators. The investigator was blinded to the applied patches and premedications for each dog in order to avoid assessment bias. From the findings of no significant differences in animal age, weight, anesthesia duration and surgery duration between the two groups, the variables that might influence the results were evenly distributed to both treatment groups. However, there were many older dogs in group M, but the difference in animal ages between the two groups was statistically insignificant due to the wide range of ages within both groups. Thus, ages of the dogs were presented as median values instead of mean values.

No significant differences between the baseline and intraoperative values of heart rates and blood pressures of the dogs were observed within and between the two groups. This confirmed that the end-tidal concentration and MACs of isoflurane required for the two groups were measured at the same depth of surgical anesthesia. Changes in heart rates and blood pressures were not observed in this study. In contrast, continuous IV infusion of fentanyl increased blood pressure of dogs (Ueyama et al., 2009) and transdermal fentanyl decreased heart rates of dogs 12 h after path application (Gilberto et al., 2003).

The increase in intraoperative blood glucose of the dogs in this study resulted from stress of tissue trauma from surgery rather than pain because the animals were under surgical anesthesia. The finding of the increase in blood glucose was consistent with the result of a previous study on efficacy of fentanyl patches in cats (Glerum et al. 2001). From that report, serum cortisol and blood glucose; biochemical markers of pain and stress, of cats undergoing ovariohysterectomy were higher than those of cats without surgery and the increases in cortisol and blood glucose were attenuated in cats receiving transdermal fentanyl patches. The attenuated rise in cortisol was presumably due to diminished pain or stress caused by the fentanyl patches while the attenuated rise in blood glucose is a reflection of the attenuated rise in cortisol. According to the latter statement and results of this study, blood glucose is not the suitable marker for pain assessment.

Normal body temperature of dogs must be maintained during anesthesia to decrease variation in serum concentrations of fentanyl during transdermal administration and to maximize isoflurane MAC reduction. Hypothermia during isoflurane anesthesia significantly reduced serum concentrations of fentanyl in cats and dogs receiving transdermal administration (Pettifer and Hosgood, 2003; 2004). Transdermal fentanyl significantly reduced isoflurane MAC in normothermic dogs while the isoflurane MAC-sparing effect was not apparent in hypothermic dogs. Lack of the sparing effect of the transdermal fentanyl could be the result of less uptake of fentanyl from the dermal depots during hypothermia (Wilson et al., 2006). In contrast to hypothermia, halothane anesthesia and anesthesia/ ovariohysterectomy did not change serum fentanyl concentrations of cats receiving a 25 µg/h transdermal fentanyl patch (Egger et al., 2003).

The use of the transdermal fentanyl patches for perioperative pain control offers many advantages such as convenient means of maintaining steady-state serum concentration and long-lasting analgesia. This administration method allows patients to be movable when compared with the continuous intravenous infusion, reduces costs of monitoring, avoids frequent injections and hepatic metabolism following oral administration, and lessen some side effects from injections. Moreover, the use of the patches may reduce total analgesics needed. When the fentanyl patches are used for preemptive analgesia, there is no need for other analgesics during the first two postoperative days. The postoperative analgesic effect of the transdermal fentanyl patches has been reported in dogs and cats (Kyles et al., 1998; Robinson et al., 1999; Franks et al., 2000; Glerum et al., 2001; Gilberto et al., 2003; Egger et al., 2007; Bellei et al., 2011). However, to assure that the patients had no pain, we prescribed carprofen to all dogs including those receiving the fentanyl patches because all of them went home after full recovery from anesthesia. Although the cost of the fentanyl patches is relatively high compared with injectable morphine, avoiding intermittent injections of morphine reduces personnel and material costs, and thus is more economical than the injections (Egger et al., 2007). One of the disadvantages of using the transdermal fentanyl patches is that special care is required to prevent the patients and other pets from receiving drug overdose from removing and swallowing the patches. The prevention includes uses of a collar and a thoracic wrap over the patch. Another disadvantage is that when the fentanyl patches are applied to the patients in pain or for preemptive analgesia, additional analgesics is necessary at least 7 and 24 h until adequate level of analgesia is attained in cats and dogs, respectively.

In conclusion, the results from this study and previous reports substantiate the analgesic effect of transdermal fentanyl patches which is comparable to the effect of intramuscular morphine. However, advantages and disadvantages must be considered before using the fentanyl patch in each case.

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## *References*


Bellei E, Roncada P, Pisoni L, Joechler M and Zaghini A 2011. The use of fentanyl-patch in dogs undergoing spinal surgery: plasma concentration and analgesic efficacy. J Vet Pharmacol Therap 34: 437-441.

Criado AB and Gomez de Segura IA 2003. Reduction of isoflurane MAC by fentanyl or remifentanil in rats. Vet Anaesth Analg 30(4): 250-256.

Docquier MA, Lavand'Homme P, Ledermann C, Collet V and de Kock M 2003 Can determining the minimum alveolar anesthetic concentration of volatile anesthetic be used as an objective tool to assess antinociception in animals? Anesth and Analg 97: 1003-1039.

Egger CM, Duke T, Archer J and Cribb PH 1998. Comparison of plasma fentanyl concentrations by using three transdermal fentanyl patch sizes in dogs. Vet Surg 27: 159-166.

Egger CM, Glerum LE, Allen SW and Haag KM 2003. Plasma fentanyl concentrations in awake cats and cats undergoing anesthesia and ovariohysterectomy using transdermal administration. Vet Anaesth Analg 30: 229-236.

Egger CM, Glerum L, Haag KM and Rohrbach BW 2007. Efficacy and cost-effectiveness of transdermal fentanyl patches for the relief of post-operative pain in dogs after anterior cruciate ligament and pelvic limb repair. Vet Anaesth Analg 34: 200-208.

FDA 2013. Fentanyl injection official FDA information, side effects and uses. [Online] Available: http://www.drugs.com /pro/ fentanyl-injection.html. Accessed November 29, 2013.

Franks JN, Boothe HW, Taylor L, Geller S, Carroll GL, Cracas V and Boothe DM 2000. Evaluation of transdermal fentanyl patches for analgesia in cats undergoing onychectomy. J Am Vet Med Assoc 217(7): 1013-1020.

Gilberto DB, Motzel SL and Das SR 2003. Postoperative pain management using fentanyl patch in dogs. Cont Topics Lab Anim Sci 42: 21-26.

Glerum LE, Egger CM, Allen SW and Haag M 2001. Analgesic effect of the transdermal fentanyl patch during and after feline ovariohysterectomy. Vet Surg 30(4): 351-358.

Grond S, Radbruch L and Lehmann KA 2000. Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. Clin Pharmacokinet 38: 59-89.

Hellyer PW, Mama KR, Shafford HL, Wagner AE and Kollias-Baker C 2001. Effect of diazepam and flumazenil on minimum alveolar concentration for dogs anesthetized with isoflurane or a combination of isoflurane and fentanyl. Am J Vet Res 62: 555-560.

Hellyer PW, Robertson SA and Fails AD 2007. Pain and its management. In: Lumb and Jones' Veterinary Anesthesia and Analgesia. 4th. WJ Tranquilli, JC Thurmon, and KA Grimm (eds). Blackwell Publishing: Iowa. 31-57.

Hofmeister EH and Egger CM. 2004. Transdermal fentanyl patches in small animals. J Am Anim Hosp Assoc 40: 468-478.

Ilkiw JE 1999. Balanced anesthetic techniques in dogs and cats. Clin Tech Small Anim Pract 14: 27-37.

Kyles AE, Papich M and Hardie EM 1996. Disposition of transdermally administered fentanyl in dogs. Am J Vet Res 57: 715-719.

Kyles AE, Hardie EM, Hansen BD and Papich MG 1998. Comparison of transdermal fentanyl and intramuscular oxymorphone on post-operative behavior after ovariohysterectomy in dogs. Res Vet Sci 65: 245-251.

Lee DD, Papich MG and Hardie EM 2000. Comparison of pharmacokinetics of fentanyl after intravenous and transdermal administration in cats. Am J Vet Res 61: 672-677.

McEwan AI, Smith C, Dyar O, Goodman D, Smith LR and Glass PS 1993. Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology 78: 864-869.

Moon PF, Scarlett JM, Ludders JW, Conway TA and Lamb SV 1995. Effect of fentanyl on the minimum alveolar concentration of isoflurane in swine. Anesthesiology. 83: 535-542.

Murphy MR and Hug CC 1982. The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology. 57: 485-488.

Orsini JA, Moate PJ, Kuersten K, Soma LR and Boston RC. 2006. Pharmacokinetics of fentanyl delivered transdermally in healthy adult horses – variability among horses and its clinical implications. J Vet Pharmacol Ther 29: 539-546.

Pascoe P 2000. Opioid analgesics. Vet Clin North Am Small Anim Pract 30: 757-772.

Passport® V operating instructions 2009. Gas monitoring. Datascope Passport® V operating instructions. Mindray DS, USA, Inc, USA. 11-2.

Pettifer GR and Hosgood G 2003. The effect of rectal temperature on perianesthetic serum concentrations of transdermally administered fentanyl in cats anesthetized with isoflurane. Am J Vet Res 64: 1557-1561.

Pettifer GR and Hosgood G 2004. The effect of inhalant anesthetic and body temperature on peri-anesthetic serum concentrations of transdermally administered fentanyl in dogs. Vet Anaesth Analg 31: 109-120.

Robinson TM, Kruse-Elliott KT, Markel MD, Pluhar GE, Massa K and Bjorling DE 1999. A comparison of transdermal fentanyl versus epidural morphine for analgesia in dogs

undergoing major orthopedic surgery. J Am Anim Hosp Assoc 35: 95-100.

Steagall PVM, Teixeira Neto FJ, Minto BW, Campagnol D and Correa MA 2006. Evaluation of the isoflurane sparing effects of lidocaine and fentanyl during surgery in dogs. J Am Vet Med Assoc 229: 522-527.

Thomasy SM, Steffey EP, Mama KR, Solano A and Stanley SD 2006. The effects of i.v. fentanyl administration on the minimum alveolar concentration of isoflurane in horses. Br J Anaes 97(2): 232-237.

Thurmon JC, Tranquilli WJ and Benson GJ 1996. Preanesthetics and anesthetic adjuncts. In: Lumb and Jones' Veterinary Anesthesia. 3rd ed. JC Thurmon, WJ Tranquilli and GJ Benson (eds). Williams and Wilkins: Baltimore. 183-209.

Ueyama Y, Lerche P, Eppler CM and Muir WW 2009. Effect of intravenous administration of perzinfotel, fentanyl, and a combination of both drugs on the minimum alveolar concentration of isoflurane in dogs. Am J Vet Res 70(12): 1459-1464.

Wilson D, Pettifer GR and Hosgood G 2006. Effect of transdermally administered fentanyl on minimum alveolar concentration of isoflurane in normothermic and hypothermic dogs. J Am Vet Med Assoc 228: 1042-1046.

Yackey M, Ilkiw JE, Pascoe PJ and Tripp LD 2004. Effect of transdermally administered fentanyl on the minimum alveolar concentration of isoflurane in cats. Vet Anaesth Analg 31: 183-189.

# บทคัดย่อ

## ผลของเฟนตานิลชนิดแผ่นติดผิวหนังต่อความเข้มข้นของไอโซฟลูเรนที่ต้องการเมื่อเปรียบเทียบกับมอร์ฟีนที่ฉีดเข้ากล้ามเนื้อระหว่างการแก้ไขสะบ้าเคลื่อนในสุนัข

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การศึกษาทางคลินิกนี้ประสงค์ที่จะประเมินฤทธิ์ระงับปวดในระหว่างการผ่าตัดของเฟนตานิลชนิดแผ่นติดผิวหนังเมื่อเปรียบเทียบกับมอร์ฟีนที่ฉีดเข้ากล้ามเนื้อ โดยเปรียบเทียบความเข้มข้นขั้นต่ำของยาดมสลบไอโซฟลูเรนในถุงลมปอดที่ต้องการขณะผ่าตัดแก้ไขสะบ้าเคลื่อนระดับ 2 หรือ 3 ในสุนัขที่มีสุขภาพดี 17 ตัว แบ่งสุนัขโดยการสุ่มออกเป็น กลุ่มเอ็มได้รับแผ่นติดผิวหนังที่ไม่มียา และกลุ่มเอฟได้รับเฟนตานิลชนิดแผ่นติดผิวหนังที่มีเฟนตานิล (25 มคก/ชม) สุนัข 3 ตัวมีสะบ้าเคลื่อนเข้าด้านในทั้ง 2 ขาจึงถูกจัดเข้าอยู่ในทั้ง 2 กลุ่ม สุนัขทุกตัวได้รับการติดแผ่นติดผิวหนังก่อนผ่าตัดอย่างน้อย 24 ชั่วโมง ก่อนผ่าตัดสุนัขกลุ่มเอ็มได้รับการนำสลบด้วย 0.03 มก/กก เอซโปรมาซีนและ 0.5 มก/กก มอร์ฟีนเข้ากล้ามเนื้อ ขณะที่สุนัขกลุ่มเอฟได้รับการนำสลบด้วยเอซโปรมาซีนขนาดเดียวกันกับกลุ่มเอ็มและน้ำเกลือในปริมาตรที่เทียบเท่ามอร์ฟีนเข้ากล้ามเนื้อ หลังจากนั้นชักนำสลบจนเห็นผลด้วยโปรโปฟอลฉีดเข้าหลอดเลือดดำและควบคุมระดับความลึกของการสลบด้วยไอโซฟลูเรนในออกซิเจนและการช่วยหายใจ การเฝ้าระวังการสลบและการวัดค่าต่างๆ ในสุนัขทุกตัวกระทำโดยคนเดียวกันที่ไม่ทราบชนิดของแผ่นติดผิวหนังและยาที่ใช้นำสลบ สุนัขได้รับการเฝ้าระวังสัญญาณชีพและบันทึกความเข้มข้นของไอโซฟลูเรนท้ายลมหายใจออกและความเข้มข้นขั้นต่ำของไอโซฟลูเรนในถุงลมปอดก่อนกรีดผ่าผิวหนังเป็นค่าควบคุมและหลังกรีดผ่าทุก 5 นาทีเป็นค่าระหว่างผ่าตัด สะบ้าเคลื่อนทุกรายได้รับการแก้ไขโดยผู้ผ่าตัดและวิธีเดียวกัน ค่าเฉลี่ย±ค่าเบี่ยงเบนมาตรฐาน (ค่ามัธยฐาน) ของค่าควบคุมและค่าระหว่างผ่าตัดของความเข้มข้นขั้นต่ำของไอโซฟลูเรนในถุงลมปอดสำหรับกลุ่มเอ็มมีค่าเท่ากับ 1.22±0.25% (1.2%) และ 1.1±0.27% (1.1%) ตามลำดับ และสำหรับกลุ่มเอฟมีค่าเท่ากับ 1.1±0.31% (1.05%) และ 1.1±0.26% (1%) ตามลำดับ ไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p>0.05$) ระหว่างค่าควบคุมและค่าระหว่างผ่าตัดของความเข้มข้นขั้นต่ำของไอโซฟลูเรนในถุงลมปอดในแต่ละกลุ่มและระหว่างกลุ่ม แสดงว่าการให้เฟนตานิลผ่านผิวหนังกับการให้มอร์ฟีนฉีดเข้ากล้ามเนื้อมีฤทธิ์ระงับปวดระหว่างผ่าตัดเท่าเทียมกัน โดยสรุปเฟนตานิลชนิดแผ่นติดผิวหนังสามารถใช้ก่อนมีการกระตุ้นให้เกิดความปวด เพื่อลดความเข้มข้นของไอโซฟลูเรนที่ต้องการระหว่างผ่าตัด

**คำสำคัญ**: ภาวะปราศจากความปวด สุนัข เฟนตานิล ไอโซฟลูเรน ความเข้มข้นขั้นต่ำในถุงลมปอด ผ่านผิวหนัง

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