RESEARCH ARTICLE

Comparison of the Analagesic Efficacy of Transdermally Applied Buprenorphine and Ketoprofen for Postoperative Abdominal Pain in Dogs

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Abstract

Transdermal drug delivery (TDD) is defined as the non-invasive delivery of medications through the skin surface. The present study was planned to evaluate the efficacy of transdermal drug delivery system to alleviate the post-operative pain after abdominal surgery. Twelve clinical cases of dogs presented to the Department of Veterinary Surgery and Radiology, at VCC of the College, Mhow were selected for the study and divided into two groups. In group I (n=6) ketoprofen transdermal patch and in group II (n=6) buprenorphine transdermal patch was applied to the skin. The Glasgow Composite Measure Pain Scale was used to assess the pain pre-operatively (1 h before surgery), complete post recovery, 24, 48 and 72 h post operatively. The mean total pain score was maximum in ketoprofen group than the buprenorphine group. Serum glucose and serum cortisol values increased significantly ($P<0.05$) in the animals of both the groups however, this increase was minimum in buprenorphine group at complete post recovery. Based on above study, it is concluded that buprenorphine transdermal patch was considered more effective for controlling the visceral pain in comparison to ketoprofen transdermal patch in dogs undergoing abdominal surgery.

Key words: Abdominal surgery, Buprenorphine, Composite Measure Pain Scale (GCMPS), Glasgow, Ketoprofen, Transdermal patch.

Ind J Vet Sci and Biotech (2023): 10.48165/ijvsbt.19.2.14

Introduction

Pain diminishes animal well-being substantially due to its aversive nature. Successful prevention, recognition and treatment of pain are integral to ensuring welfare of the Veterinary patient. Surgical pain can impair post-operative recovery, resulting in inappetence, self-injury and immune suppression that increases risk of infection (Dawson *et al*., 2017). If surgical pain is left untreated, animals become depressed, lethargic, withdrawn, sleep deprived and eventually immobile. Transdermal drug delivery is defined as the non-invasive delivery of medications through the skin surface. When applied to skin, these patches can deliver an analgesic drug at a predetermined rate across the dermis to achieve either a local or systemic effect. Patches offer advantages over conventional parenteral or oral routes. Delivery of the drug via a simple and painless application in transdermal route (Bajaj *et al*., 2011). Ketoprofen is the propionic acid of NSAIDs and has analgesic and antipyretic effect (Verma *et al*., 2016). Buprenorphine is a partial agonist at μ receptors and an antagonist at κ receptors in the CNS and peripheral tissues and binds to both receptors with high affinity. Effects on analgesia appear to occur as a result of μ-agonist activity. The advantages of buprenorphine as an analgesic in dogs include its long duration of action, tendency not to induce vomiting and negligible cardiovascular effects in healthy animals (Andaluz *et al*., 2009). The present study was planned to compare the efficacy of ketoprofen and buprenorphine transdermal patch to control the post-surgical pain in dogs.

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How to cite this article: Singh, T., Jain, R., Dangi, R., Shukla, B. P., & Shrivastava, N. (2023). Comparison of the Analagesic Efficacy of Transdermally Applied Buprenorphine and Ketoprofen for Postoperative Abdominal Pain in Dogs. Ind J Vet Sci and Biotech. 19(2), 74-77.

Source of support: Nil

Conflict of interest: None

Submitted: 17/11/2022 **Accepted:** 30/12/2022 **Published:** 10/03/2023

Materials and Methods

The study was conducted on 12 clinical cases of dogs operated for abdominal/visceral surgery. All the animals were divided in two groups (I and II) and each group had 6 dogs. In group I, Ketoprofen transdermal patch containing 20 mg per 70 cm^2 was applied immediately at dorsal part of neck or back after the completion of surgery and was repeated at every 24 h for 2 -3 days depending on pain. In this group meloxicam

@ 0.2-0.3 mg/kg b.wt. was also administered ½ h before the surgical intervention on first day. In group II Buprenorphine transdermal patch containing 5 mg per 6.25 cm^2 was used. All the dogs were anaesthetized by using combination of inj. Atropine sulphate @ 0.02-0.04 mg/kg b.wt., inj. Xylazine hydrochloride @ 1-2 mg/kg b. wt. and inj. Ketamine @ 5-10 mg/kg b. wt. for surgery. For application of analgesic patch, hairs were clipped at dorsal part of neck region or back, cleaned with water and dried. Transdermal patch was pressed firmly at the site for complete contact and was protected by paper tape, especially around the edges. After giving general anaesthesia dogs were operated for abdominal surgery. The behavioural and biochemical parameters were studied preoperatively (1 h before surgery), complete post recovery, 24, 48 and 72 h post operatively. Behavioural parameters were studied by using Glasgow Composite Measure Pain Scale (GCMPS) (Reid *et al*., 2007). A number of 0 to 5 were assigned for different behavioural parameters to ascertain the level of pain in all the groups. It includes 30 descriptor options within six behavioural categories. The pain score is the sum of rank scores. The maximum score for the six categories was 20-24. Biochemical parameters blood glucose and serum cortisol were estimated. The data analysis was done using completely randomized design (Snedecor and Cochran, 1994).

Results and Discussion

All the dogs of both groups were subjected to different types of elective and emergency major abdominal surgical interventions (Table 1).The time required for different types of surgical procedure were approximately 50 to 80 min in both the groups. There was not much difference between the groups in respect to the duration of surgery. All the surgical procedures were successful without any anaesthetic complications and all the animals were recovered smoothly.

The calculated mean total pain score was significantly least in buprenorphine group than the ketoprofen at different time intervals (Table 2). The pain score was significantly ($p<0.05$) higher (6.50±0.50) in ketoprofen group and least (3.16±0.47) in buprenorphine group at the time of complete recovery from anaesthesia. Thereafter pain scores decreased significantly at 48 h in ketoprofen group (2.00±0.51) and at 24 h in buprenorphine group (1.50±0.22). Further, more reduction in pain score was observed in buprenorphine group in comparison to ketoprofen group. In ketoprofen group, some animals had higher pain score with the signs of discomfort. Hence in such animals, meloxicam was administered at 24 h as rescue analgesia. Present findings agree with Moll *et al*. (2011) who also reported significantly lower pain score 2.02±0.24 in NRS (Numerical rating scale) and 2.67±0.23 in UMPS (University of Melbourne Pain Scale) scores in dogs after using transdermal buprenorphine patch. Various workers also reported adequate efficacy and safety of transdermal buprenorphine patch to manage adequate postoperative analgesia following major abdominal surgeries (Das *et al*., 2017; Kadapamannil *et al*., 2018; Pergolizzi *et al*., 2021). Affinity of buprenorphine for μ receptors at peripheral nerves, dorsal horn of spinal cord, brainstem medulla and the cerebral cortex would produce prolonged duration of action and good analgesic effect. Buprenorphine's characteristics of low molecular weight, high lipophilicity and high affinity for the μ-opioid receptor make it well suited for transdermal delivery system (Pergolizzi *et al*., 2021). The major side effect of ketoprofen is bleeding disorders therefore it is not recommended before surgery due to risk of haemorrhage as it inhibits platelet aggregation (Verma *et al*., 2016). Due to

Table 1: Different surgical affections and types of surgery performed.

Groups	Case	Case history / Surgical affections	Type of surgery
I (n=6)	Case 1	Spaying	Elective OH
	Case 2	Spaying	Elective OH
	Case3	Dystocia	Emergency Caesarean Section
	Case 4	Spaying	Elective OH
	Case 5	Dystocia	Emergency Caesarean section
	Case 6	Pyometra	Radical OH
II (n=6)	Case 1	Spaying	Elective OH
	Case 2	Dystocia	Emergency Caesarean section
	Case 3	Urolithiasis	Cystotomy
	Case 4	Spaying	Elective OH
	Case 5	Intestinal obstruction	Enterotomy
	Case 6	Pyometra	Radical OH

OH= Ovariohysteroctomy

Table 2: Mean values (±SE) of behavioural, physiological and biochemical parameters after administration of different drugs at different time intervals

Parameters	Groups	1 h before	Complete postoperative anaesthetic recovery	24 h	48 h	72 h
Pain score	I	$0.16^{aA} \pm 0.16$	$6.50^{bB} \pm 0.50$	$6.16^{bB} \pm 0.65$	$2.00^{bB} \pm 0.51$	$0.33^{bA} \pm 0.21$
	II	$0.16^{aA} \pm 0.16$	$3.16^{bB} \pm 0.4^{7}$	$1.50^{bB} \pm 0.2^{2}$	0.00 ± 0.00	0.00 ± 0.00
Glucose (mg/dL)	I	$86.42^{aB} \pm 1.45$	$112.65^{bA} \pm 1.94$	$98.81^{bB} \pm 0.78$	$83.73^{aB} \pm 1.32$	$85.58^{aB} \pm 1.22$
	II	$97.40^{aA} \pm 3.51$	$104.28^{bA} \pm 2.56$	$103.02^{aA} \pm 2.79$	$101.60^{aA} \pm 1.71$	$97.93^{aA} \pm 1.09$
Cortisol (ng/dL)	I	$22.18^{aA} \pm 0.91$	$99.24^{bB\pm} 3.92$	$78.32^{bB} \pm 7.29$	$47.15^{bA} \pm 8.47$	$38.65^{bA} \pm 6.73$
	II	$21.99^{aA} \pm 1.21$	$47.66^{bA} \pm 3.38$	$46.73^{bA} \pm 2.99$	$37.15^{bA} \pm 1.71$	$23.72^{aA} \pm 1.41$

Means bearing uncommon superscripts (A, B) within the row differ significantly between periods, and those (a. b) within the column differ between groups for a parameter at p<0.0.5.

this side effect, ketoprofen was not used preoperatively in this study. Surgical manipulation of tissues results in a greatly enhanced nociceptor response (Beckman, 2006) which might be responsible for higher pain score immediately after the surgery. Further, during the recovery period the effect of anaesthesia would be lessen and animal exhibits more signs of pain at complete post recovery stage. Glasgow Composite Measure Pain Scale (CMPS) scale is in the form of a structured questionnaire completed by an observer following a standard protocol which includes assessment of spontaneous and evoked behaviours, interactions with the animal and clinical observation (Reid *et al*., 2007).

Serum cortisol increased significantly (p<0.05) (99.24 ± 3.92 vs 47.66± 3.38 ng/mL) in group I and II respectively at complete recovery which was decreased gradually from 24 h and reached near to the normal level at 72 h in buprenorphine group (Table 2). Serum cortisol levels were minimum in buprenorphine group than the ketoprofen group which indicates better analgesic property of buprenorphine. Similar results were reported by Jamra (2017), Dharmaceelan *et al*. (2018) and Avalosi *et al*. (2020) with buprenorphine and ketoprofen, respectively in dogs. The increased level of serum cortisol could be due to nociceptive stimuli and surgical trauma which initiates the release of cytokines (interleukin 1, interleukin 6) into the bloodstream and activation of the hypothalamo-pituitary-adrenocortical (HPA) system axis and sympathetic nervous system. Activation of hypothalamus and pituitary releases adrenocorticotropic hormone (ACTH) and sympathetic nervous system activation initiates the release of cortisol (Dharmaceelan *et al*., 2018).

Serum glucose level was more at complete recovery period in both the group (Table 2). The serum glucose was significantly (p<0.05) higher in ketoprofen group as compared to buprenorphine group at complete recovery. The present finding agrees with the observations of Jamra (2017) after administration of buprenorphine during post recovery period in dogs. Selmi *et al*. (2009) concluded that glucose level was significantly higher during post recovery period in bitches using ketoprofen under ovariohysterectomy. Moldal *et al*. (2018) stated that blood glucose concentration is a useful measure of surgical stress in dogs. Hernandez *et al*. (2021) stated that the induction of anaesthesia and surgical stimulation causes insulin resistance due to the activation of α-adrenergic receptors and the inhibition of pancreatic α-cells to equalize catabolism in response to hyperglycaemia. The approximate cost of ketoprofen transdermal patch was Rs 195.00/- and buprenorphine transdermal patch was Rs 300.00/-. Although cost of buprenorphine patch was higher in comparison to ketoprofen, but the animals were more comfortable with faster recovery in buprenorphine group which reflects better owner satisfaction in buprenorphine group.

Conclusions

It is concluded that buprenorphine has less pain score and more effective to control the visceral pain in comparison to ketoprofen in dogs undergoing abdominal surgery. Further, transdermal drug avoided the repeated administration of analgesics and minimize dosage of analgesic with adequate dosing to manage the post-operative pain.

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