The Pharma Innovation Journal 2022; SP-11(2): 1732-1736

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; SP-11(2): 1732-1736

www.thepharmajournal.com
Received: 07-12-2021
Accepted: 09-01-2022

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Study on management of post operative pain in dogs by using different drugs modalities

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Abstract
Postoperative pain is considered a form of acute pain due to surgical trauma with an inflammatory reaction and initiation of an afferent neuronal barrage. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and sometimes, improved efficacy over other dosage forms. The present study was planned to evaluate the efficacy of transdermal buprenorphine drug to alleviate the post operative pain after abdominal surgery.12 clinical cases of dogs presented to the Department of Veterinary Surgery and Radiology, VCC, College of Veterinary Science and A.H., Mhow were selected for the study. In group I (n=6) meloxicam was administered and in group II (n=6) buprenorphine transdermal patch was applied to the skin. The Glasgow Composite Measure Pain Scale was used to record the pain at different time intervals. The mean total pain score was more in meloxicam group than the buprenorphine group. Biochemical parameters *viz*. blood glucose and serum cortisol showed maximum significant increase in meloxicam and minimum in buprenorphine group at complete post recovery. Blood urea nitrogen and serum creatinine showed a non-significant deviation in both the groups and were within the normal levels at different time intervals. On the basis of above study, it was concluded that buprenorphine transdermal patch was considered to be most effective for controlling the visceral pain in comparison to meloxicam in dogs.

Keywords: Pain score, TDDS, abdominal surgery, meloxicam, buprenorphine

Introduction
Postoperative pain is considered a form of acute pain due to surgical trauma with an inflammatory reaction and initiation of an afferent neuronal barrage. It is a combined constellation of several unpleasant sensory, emotional and mental experience precipitated by the surgical trauma (Gupta *et al*., 2010) [1]. Pain is considered the 5th vital sign, after body temperature, heart rate, respiratory rate, and blood pressure, and veterinarians are aware of the importance of pain recognition and its central role in patient care and welfare (Blass *et al*., 2020) [12]. To meet the needs of individual patients for enhancing the quality of postoperative pain management, novel drug delivery are the effective drug delivery systems to improve the therapeutic efficacy of drugs by increasing drug circulation times, facilitating targeting of drugs, and enhancing stability without compromising safety or tolerability. A transdermal patch is defined as adhesive medicated patch that is placed on to above skin to deliver an exact dose of drug through skin into the bloodstream with a predetermined rate of release to reach in the body. Today most common transdermal system present in market mainly based on semi permeable membranes which were called as patches. Transdermal drug delivery systems (TDDS), also known as "Transdermal patches" or "Skin patches" are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin and in bloodstream resulting in reduced systemic side effects and sometimes improved efficacy over other dosage forms (Patel and Shah, 2018) [2]. For successful assessment of pain in animal's number of scales have been used such as Simple Descriptive Scale (SDS), Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), University of Melbourne pain scale (UMPS) and Glasgow Composite Measure Pain Scale (CMPS) (Bufalari *et al*., 2007) [16].
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) [9]. Hence, this pain scale was used in the present study as it is more sensitive and specific although it has one limitation that it was difficult to collect the score point of mobility category (Bendinelli *et al*., 2019) [4].

Materials and Methods

The study was conducted on 12 clinical cases of dogs operated for soft tissue surgery (Table No 01). All the animals were divided in two groups (I and II) and each has 6 dogs. In group I, inj. meloxicam @ 0.2-0.3 mg/kg b.wt. was administered ½ hr before the surgery then follow up by tab meloxicam at 10-12 hours interval for 3 consecutive days orally. In group II, buprenorphine analgesic patch containing 5 mg was applied to the skin anywhere on the back region before the surgery. 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 and patch was pressed firmly at the site for complete contact. After giving general anaesthesia dogs were operated for corrective abdominal surgeries as per the patient requirement. The following parameters were studied pre operatively (1 hour before surgery), complete post recovery, 24, 48 and 72 hours post operatively. The pain score was evaluated by using the Glasgow Composite Measure Pain Scale (GCMPS). A number of 0 to 5 were assigned for different behavioural parameters of dogs after the surgery as per (Table No 02) to ascertain the level of pain in both 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 (Reid *et al*., 2007) [9]. Biochemical parameters *viz*; blood glucose, serum cortisol, blood urea nitrogen, serum creatinine. The data analysis was done by the use of completely randomized design (CRD).

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	Pyometra	Radical OH
	Case 3	Pyometra	Radical OH
	Case 4	Intestinal obstruction	Enterotomy
	Case 5	Spaying	Elective OH
	Case 6	Dystocia	Emergency Caesarean section
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

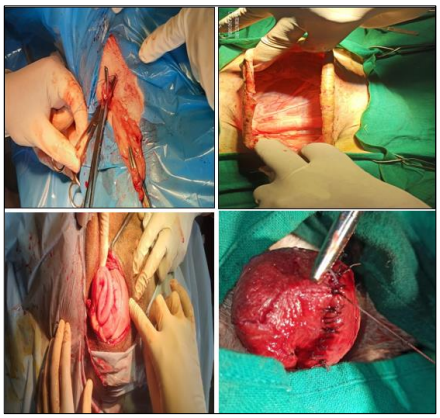

Fig 1: Different surgical affections and types of surgery performed

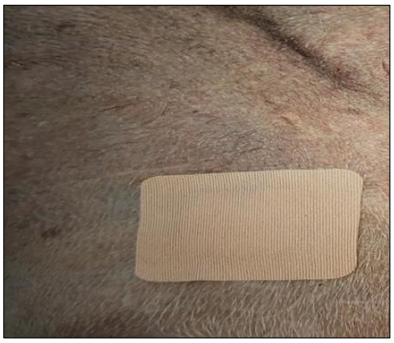

Fig 2: Application of Buprenorphine analgesic patch

Table 2: Glasgow Composite Measure Pain Scale

A. Look at dog in Kennel

I Is the dog		II	
Quiet	0	Ignoring wound or painful area	0
Crying or whimpering	1	Looking at wound or painful area	1
Groaning	2	Licking wound or painful area	2
Screaming	3	Rubbing wound or painful area	3
		Chewing wound or painful area	4

B. Put lead on dog and taken out of the kennel

When the dog rises/walk is it	
Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. Apply gentle pressure 2 inches around the site

Does it	
Do nothing	0
Look around	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

I Is the dog		II	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4
Total Score (1+2+3+4+5) = …….			

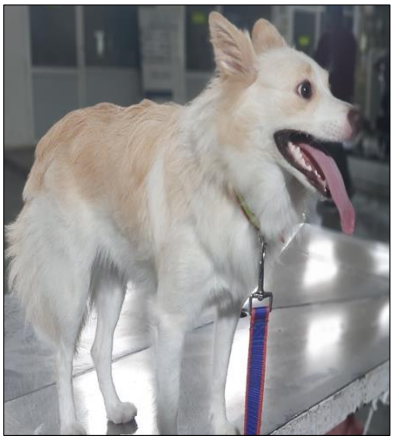

Fig 3: Happy and content behaviour at 1 hour before the surgery

Fig 4: Whimpering behaviour at post recovery stage

Fig 5: Nervous or anxious or fearful behaviour at 24 hours

Fig 6: Quiet behaviour at 24 hours

Result and Discussion

Mean Total Pain Score (MTPS)

The mean total pain score exhibited a significant (p<0.05) change in both the groups at complete post recovery stage with values of 4.83±0.40 and 3.16±0.47 in meloxicam and buprenorphine groups respectively. The pain scores decreased significantly at 48 hours in meloxicam group (0.83±0.40) and at 24 hours in buprenorphine group (1.50±0.22) (Table No 03). Further, more reduction in pain score observed in both the groups with minimum score in buprenorphine group followed by meloxicam group. Both the groups had significant high pain score after complete recovery as compared to preoperative score. This suggested that maximum pain after surgical procedure was present. Surgical manipulation of tissues results in a greatly enhanced nociceptor response (Beckmann, 2006) [3] which might be responsible for higher pain score immediately after the surgery. During the recovery period the effect of anaesthesia would be lessen and animal exhibits more signs of pain at complete post recovery stage. Present findings are in agreement with Moll *et al.* (2011) [7] 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 buprenorphine patch in comparison to meloxicam group. Kadapamannil *et al.* (2018) [6] and Pergolizzi *et al.* (2021) [8] also reported efficacy and safety of buprenorphine patch to manage adequate postoperative analgesia following major abdominal surgeries.

The therapeutic effects of buprenorphine are mediated through interactions with four different opioid receptors (mu, delta, Kappa and opioid receptor-like 1 [ORL1]), which are distributed throughout many tissues in the body. Buprenorphine exhibits slower dissociation from the mu-opioid receptor compared with other opioids, which may contribute to prolonged analgesia and less potential for withdrawal when used appropriately for pain. Buprenorphine promotes analgesia and limits side effects through unique downstream signalling events at the l-opioid receptor. Activation of the mu-opioid receptor results in G-protein signalling which inhibits the opening of voltage gated calcium channels and activates G-protein–gated potassium channels. These signalling events lead to reduced neurotransmitter release and membrane hyperpolarization thereby resulting in analgesia (Gudin and Fudin, 2020) [13]. Analgesic delivery through patch did not cause any skin irritation, well tolerated, avoids the discomfort associated with multiple injections and frequency of drug administration (Andaluz *et al*., 2009) [9]. The sustained release of novel delivery may improve tolerability because of the extended drug delivery. The extended-release formulation allows for single administration of a high drug dose with sustained release and targeted delivery (Patel and Shah, 2018) [2]. Hence patch is superior to the other route of administration of drug.

Table 3: Mean values (±SE) of total pain score at different time intervals within and between groups

Time of observations	Group I	Group II
1 hr before	0.16^{aA} ± 0.16	0.16^{aA} ± 0.16
Complete post recovery	4.83^{bA} ± 0.40	3.16^{bB} ± 0.47
24 hrs	3.83^{bA} ± 0.47	1.50^{bB} ± 0.22
48 hrs	0.83^{bA} ± 0.40	0.00 ± 0.00
72 hrs	0.00 ± 0.00	0.00± 0.00

Means bearing different superscripts in a row differ highly significantly (p<0.05) and in column differ significantly (p<0.05) with each other (A = between groups), (a = within group)

Biochemical parameter

Serum glucose increased significantly with the values of 107.79^{bA}±2.95and 104.28± 2.56 mg/dl in group I and II respectively at complete recovery in comparison to the base value of 101.16^{bA} ± 2.85 and 97.93± 1.09 (Table No: 04). The serum glucose was significantly higher in meloxicam group as compared to buprenorphine group. Similarly, Tsai *et al.* (2013) [10] noticed significant increase in blood glucose level in post operative period compared to preoperative values using meloxicam in dog during ovariohysterectomy. Moldal *et al.* (2018) [17] stated that blood glucose concentration is a useful measure of surgical stress in dogs. The pathophysiology behind postoperative hyperglycaemia is partly induction of a hyperglycaemic response by growth

hormone and partly insulin resistance and inhibition of insulin secretion, all induced by the neuroendocrine and metabolic stress in response to surgical manipulation. Hernandez *et al.* (2021) [18] 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.

Serum cortisol increased significantly with the values of 51.90^{bA} ± 7.73 and 47.66± 3.38 (ng/ml) in group I and II respectively at complete recovery. Cortisol level was gradually decreased from 24 hours and reached near to the normal level at 72 hours (Table No: 05). Serum cortisol levels were minimum in buprenorphine group than the meloxicam group which indicate less surgical trauma in this group. Similarly, Dharmaceelan *et al.* (2018) [5] detected significant increase in serum cortisol levels at complete post recovery period following ovariohysterectomy (OHE) 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.

Blood urea nitrogen and serum creatinine showed a non-significant increase both the groups at post recovery period and were within the normal levels at different time intervals (Table No: 06 and 07). These findings are in accordance with findings of Gupta *et al.* (2009) [19] and Ugwu *et al.* (2017) [11] In present study, non-significant elevated BUN and serum creatinine at post recovery stage in group I could be attributed to the pre-emptive administration of NSAIDs which inhibits the production of prostaglandin E_2 and prostaglandin I_2 responsible for renal blood flow maintenance. The reduction in cardiac output caused by sedative and anaesthetic agents affects the renal blood flow and delays the urea nitrogen clearance and creatinine level (Dharmaceelan *et al*., 2018) [5].

Table 4: Mean values (±SE) of blood glucose (mg/dl) at different time intervals within and between groups

Time of observations	Group I	Group II
1 hr before	94.26^{aA} ± 1.82	97.40^{aA} ± 3.51
Complete post recovery	107.79^{bA} ±2.95	104.28^{bA} ± 2.56
24 hrs	107.79^{bA} ± 3.21	103.02^{aA} ± 2.79
48 hrs	107.84^{bA} ± 3.40	101.60^{aA} ± 1.71
72 hrs	101.16^{bA} ± 2.85	97.93^{aA} ± 1.09

Means bearing different superscripts in a row and column differ highly significantly (p<0.05) with each other (A = between groups), (a = within group)

Table 5: Mean values (±SE) of cortisol hormone (ng/ml) at different time intervals within and between groups

Time of observations	Group I	Group II
1 hr before	26.38^{aA} ± 4.79	21.99^{aA} ± 1.21
Complete post recovery	51.90^{bA} ± 7.73	47.66^{bA} ± 3.38
24 hrs	46.81^{bA} ± 7.80	46.73^{bA} ± 2.99
48 hrs	42.64^{bA} ± 7.27	37.15^{bA} ± 1.71
72 hrs	36.53^{aA} ± 5.97	23.72^{aA} ± 1.41

Means bearing different superscripts in a row and column differ highly significantly (p<0.05) with each other (A = between groups), (a = within group)

Table 6: Mean values (±SE) of blood urea nitrogen (mg/dl) at different time intervals within and between groups

Time of observations	Group I	Group II
1 hr before	21.79^{aA} ± 0.76	19.42^{aA} ± 0.83
Complete post recovery	25.50^{aA} ± 0.27	20.04^{aA} ± 0.71
24 hrs	19.09^{aA} ± 0.89	20.00^{aA} ± 1.10
48 hrs	19.43^{aA} ± 0.88	19.42^{aA} ± 1.09
72 hrs	19.56^{aA} ± 1.05	19.08^{aA} ± 1.12

Means bearing same superscripts in a row and column differ non-significantly (p>0.05). (A = between groups), (a = within group)

Table 7: Mean values (±SE) of serum creatinine (mg/dl) at different time intervals within and between groups

Time of observations	Group I	Group II
1 hr before	0.79^{aA} ± 0.10	0.87^{aA} ± 0.07
Complete post recovery	0.93^{aA} ± 0.04	1.04^{aA} ± 0.06
24 hrs	0.93^{aA} ± 0.04	1.04^{aA} ± 0.06
48 hrs	0.93^{aA} ± 0.04	1.04^{aA} ± 0.06
72 hrs	0.93^{aA} ± 0.04	1.04^{aA} ± 0.06

Means bearing same superscripts in a row differ non- significantly (p>0.05) and different superscripts in column differ highly significantly (p<0.05) with each other (A = between groups), (a = within group)

Conclusion

Optimum pain management should start before surgery. This allows planning of optimal pain management techniques and facilitates early discussions to help alleviate fear of postoperative pain (Small and Laycock, 2020). Pain affects the pet's quality of life and their interaction with family members or another pet. If pain is left untreated, animals become depressed, lethargic, withdrawn, sleep deprived and eventually immobile. Our study was to maintain the post operative analgesia and better outcome of surgical cases reflect better owner satisfaction. On the basis of above study, it was concluded that buprenorphine transdermal patch was considered most effective for controlling the visceral pain in comparison to meloxicam in dogs.

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