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Comparison of the Analgesic Effects of Meloxicam with those of Ketoprofen in Male Stray Dogs Undergoing Pinhole Castration

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ABSTRACT

The adequacy of analgesia using meloxicam and ketoprofen was assessed in 12 male stray dogs following pinhole castration. The analgesics were started preemptively and repeated daily up to 72 h post castration. The study was conducted under blind conditions. The pain assessment was made adopting "The University of Melbourne Pain Scale" (UMPS) preoperatively and at 06, 12, 18, 24, 36, 48, 60, 72, 84 and 96 h post operatively. Mean±SD total pain score values in animals of meloxicam group were highest MTPS (7.5) at 48 h but in animals of ketoprofen group the highest score (8.3) was recorded at 12 and 24 h following castration. In both the groups, lowest values (3.5, 2.7, respectively) were obtained preoperatively (0 h). The values in both the groups were significantly ($p<0.05$) higher continuously from 6 to 84 h following castration and showed decreasing trend towards the end of observation period. The values obtained at the last observation period (96 h) was slightly more and equal in both the groups than the values obtained preoperatively. Between the groups, the values did not differ significantly ($p>0.05$) at any time interval. The dogs were maintained for one month and were watched for any complications and adverse reactions of the analgesic drugs used. Vomiting, diarrhea or gross evidence of fecal blood did not occur in any of the dogs throughout the study period. In summary both drugs provided good and similar analgesia. However, administration of one more dose of the analgesic is recommended at 96 h post ligation.

Key words: Meloxicam, ketoprofen, pinhole castration, dog, preemptive, analgesia

INTRODUCTION

Pain involves both the peripheral and the central sensory nervous systems. Moreover, it is an unpleasant experience affecting processes of higher consciousness (Lamont *et al*., 2000). During castration the testes are either removed or rendered nonfunctional in situ. Modification of the undesirable behavior, prevention of health problems and control of population are the main reasons for canine castration. Pinhole castration involves in situ spermatic cord ligation without incising scrotum (Ponvijay, 2007). In these cases pain due to testicular ischemia must be managed effectively. Methods of recording pain intensity currently used for animals are adaptations of scale

used in pain management of human beings. In small animals the University of Melbourne Pain Scale (UMPS) has been found suitable for clinical use (Firth and Haldane, 1999; Robertson, 2003).

Analgesics have become an integral component of the postoperative management (Haskins, 1987). Meloxicam and ketoprofen are non-steroidal anti-inflammatory drugs used frequently in veterinary medicine (Montoya *et al.*, 2004). Meloxicam is an oxicam (enolic acid) derivative. Meloxicam has preferential COX-2 activity and is also a mild inhibitor of COX-1 in platelets and kidneys (Deneuche *et al.*, 2004). It is indicated for the management of inflammation and pain arising from acute and chronic diseases (Doig *et al.*, 2000; Lascelles *et al.*, 2001). Ketoprofen, a propionic acid derivative is an effective analgesic in dogs (Mathews, 2002). It acts by inhibiting both COX-1 and COX-2 activity (Poulsen and Justus, 1999).

The purpose of the study reported here was to compare the efficacy of two commonly used analgesics (meloxicam and ketoprofen) started preemptively in stray dogs subjected to pinhole castration.

MATERIALS AND METHODS

The study was conducted on apparently healthy 12 adult male stray dogs. These dogs were fed and handled individually for a period of ten days before the actual initiation of the study. During this period all of them were dewormed once using fenbendazole 150 mg with praziquental (Tab. Fentas Plus, Intas pharmaceuticals, India) 150 mg per 10 kg^{-1}. A thorough clinical examination was conducted one day prior to the actual start of the study in all the animals. None of these animals had been under influence of any medication including anti-inflammatory drugs or corticosteroids 24 h before spermatic cord ligation. They were kept off-feed for 24 h and water was withheld for 12 h before inducing anaesthesia.

Animals were randomly divided into two equal groups; T_1 and T_2 for receiving two different analgesics, Meloxicam and Ketoprofen, respectively. On the day of ligation (Day 0) assessment of pain was done using University of Melbourne Pain Scale (UMPS). Animals of subgroup T_1 (6 dogs) received Meloxicam (Melonex Intas pharmaceuticals, India), 0.2 mg kg^{-1}, I/M (plus equal volume of distill water) and those of group T_2 (6 dogs) were administered Ketoprofen (Ketop, Alembic, India), 2 mg kg^{-1}, I/M preemptively (30 min before induction of anaesthesia). After a gap of 25 min sedation with xylazine (Izine, Intas pharmaceuticals, India), 1.5 mg kg^{-1} IM followed five min later by ketamine hydrochloride (Ketmin, Themis chemicals, India), 10 mg kg^{-1}, I/M was induced in all the animals. All the animals of T_1 and T_2 subgroups (n = 12) were subjected to bilateral spermatic cord ligation (Pinhole castration) as per the technique described by Fazili *et al.* (2009a). During the post ligation period all the animals of T_1 and T_2 received same analgesic (meloxicam and ketoprofen, respectively) daily up to 72 h.

All the dogs were maintained for a total of one month from the start of the actual study. During this period they were watched for any complications and adverse reactions (like vomiting, diarrhea/dysentery and hematoma) of the analgesic drugs used.

The study was conducted under blind conditions. Analgesic drugs under investigation were administered by one of the authors and the investigator who was not aware of the drug used in the case carried out assessments. The pain assessment was made adopting "The University of Melbourne Pain Scale" (UMPS). Six parameters included in the scale were Physiological data, Response to palpation, Activity, Mental status, Posture and Vocalization. The minimum possible total pain score obtained by use of this scale is 0 and the maximum possible total pain score cumulates to 27. The UMPS forms were completed preoperatively and at 6, 12, 18, 24, 36, 48, 60,

72, 84 and 96 h post operatively. At the end of the study Mean Total Pain Scores (MTPS) were calculated at different assessment periods in every animal.

The data was statistically analyzed by using repeated measurement ANOVA and Mann-Whitney U test.

RESULTS

All the 12 male stray dogs included in this study were adult (with permanent dentition) and apparently healthy with both testes descended at the time of clinical examination. The time of 10 days provided for the dogs was sufficient to adjust to the chain and cage confinement and to the human proximity, individual feeding and handling before start of the actual study.

The Mean±SD values of individual physiological data and individual behaviours (included in UMPS) of each group have been shown in Table 1.

Physiological data: In group T_1, score 1 was obtained in one dog each at 12, 60 and 84 h and three dogs at 96 h following spermatic cord ligation. Score 2 was recorded at 36 and 48 h in one dog. In group T_2, score 1 was recorded in three dogs at 12 h, one dog at 24 h and two dogs at 96 h. Score 2 was obtained in one dog each at 24, 36 and 96 h following castration. Score 3 was obtained in two dogs at 18 h and one dog each at 24, 36 and 60 h.

Response to palpation: In T_1 group, score 2 was obtained in six animals at 6 h, five animals from 12 to 72 h, four animals at 84 h and two animals at 96 h following castration. In T_2 group, score 2 was obtained in six animals at 6, 12 and 72 h, four animals at 18 and 84 h, five animals from 24 to 60 h and in one animal at 96 h.

Activity: In both the groups, score 1 was obtained in all animals pre-operatively. In animals of group T_1, score 1 was obtained in two dogs at 6, 24, 48, 60 and 72 h, in three dogs at 12, 36 and 84 h, four dogs at 18 and 96 h. In group T_2, score 1 was obtained in three dogs at 6, 12 and 72 h, in four dogs at 18 and 24 h, in two dogs from 36 to 60 h and again at 84 h. Five dogs showed score 1 at 96 h following castration.

Table 1: Mean±SD score of the individual parameters of the UMPS used to assess pain in pinhole castrated dogs

Category	Subgroup/ Day	0	6	12	18	24	36	48	60	72	84	96
		----------h----------										
Physiological data	T_1	0.0±0.0	0.0±0.0	0.2±0.4	0.0±0.0	0.0±0.0	0.3±0.8	0.3±0.8	0.2±0.4	0.0±0.0	0.2±0.	0.5±0.5
	T_2	0.0±0.0	0.0±0.0	0.5±0.5	1.0±1.5	1.3±1.2	0.8±1.3	0.0±0.0	0.5±1.2	0.0±0.0	0.0±0.0	0.7±0.8
Response to palpation	T_1	0.0±0.0	2.0±2.0	1.7±0.8	1.7±0.8	1.7±0.8	1.7±0.8	1.7±0.8	1.7±0.8	1.7±0.8	1.3±1.0	0.7±1.0
	T_2	0.0±0.0	2.0±2.0	2.0±0.0	1.3±1.0	1.7±0.8	1.7±0.8	1.7±0.8	1.7±0.8	2.0±0.0	1.3±1.0	0.3±0.8
Activity	T_1	1.0±0.0	0.3±0.5	0.5±0.5	0.7±0.5	0.3±0.5	0.5±0.5	0.3±0.5	0.3±0.5	0.3±0.5	0.5±0.5	0.7±0.5
	T_2	1.0±0.0	0.5±0.5	0.5±0.5	0.7±0.5	0.7±0.5	0.3±0.5	0.3±0.5	0.3±0.5	0.5±0.5	0.3±0.5	0.8±0.4
Mental status	T_1	1.1±0.4	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	0.8±0.4	0.8±0.4	1.0±0.0
	T_2	0.8±0.4	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	1.0±0.0	0.8±0.4	0.8±0.4	1.0±0.0
Posture	T_1	0.7±0.5	2.7±0.5	2.7±0.8	2.7±0.8	2.7±0.8	2.5±1.2	2.5±1.2	2.5±1.2	2.5±1.2	2.3±1.0	1.3±1.0
	T_2	0.8±0.4	2.8±0.4	2.8±0.4	2.3±1.0	2.7±0.8	2.7±0.8	2.7±0.8	2.7±0.8	2.7±0.5	1.8±1.5	1.2±1.4
Vocalization	T_1	0.6±1.0	1.0±1.1	1.3±1.0	1.0±1.1	1.7±0.9	1.3±1.0	1.7±0.8	1.7±0.8	0.7±1.0	0.0±0.0	0.0±0.0
	T_2	0.0±0.0	1.3±1.0	1.5±0.8	1.3±1.0	1.0±1.1	1.3±1.0	1.3±1.0	1.0±1.1	0.3±0.8	0.7±1.0	0.0±0.0

Table 2: Mean total pain score (MTPS) of both groups at various intervals (Mean±SD)

Group	0 h	6 h	12 h	18 h	24 h	36 h	48 h	60 h	72 h	84 h	96 h
$T_{1(n=6)}$	3.5±0.8	7.0±1.1*	7.3±0.8*	7.0±1.1*	7.3±1.2*	7.3±0.8*	7.5±0.8*	7.3±1.2*	6.0±1.4*	5.2±1.8*	4.0±1.4
$T_{2(n=6)}$	2.7±0.8	7.7±1.0*	8.3±1.4*	7.7±1.4*	8.3±1.7*	7.8±2.0*	7.0±2.5*	7.2±2.7*	6.2±1.0*	5.0±0.9*	4.0±0.9

*Differ significantly ($p<0.05$) from the base value

Mental status: In both the groups, each, the score was 1 at 0 h and again at 72 and 84 h in five dogs. However, one more dog showed a score of 2 at 0 h in group T_1. In both the groups six dogs each showed the score 1 from 6 h continuously to 60 h and again at 96 h post ligation.

Posture: In group T_1, score 1 was shown by four dogs at 0 h, one dog at 12 to 24 h, two dogs at 84 h and three dogs at 96 h post spermatic cord ligation. Score 2 was detected in two dogs at 6 h and one dog at 96 h post castration. The score 3 was noticed in four dogs at 6 h, five dogs at and beyond 12 up to 72 h. However, four dogs showed this score at 84 h and one dog was having a score of 3 at 96 h. In group T_2, score 1 was evident in five dogs at 0 h and again at 96 h, two dogs at 18 h and one at 24 to 60 h. The score 2 was shown by one dog at 6, 12, 84 and 96 h. The score 3 was detected in five dogs at 6 to 60 h except 18 h, four dogs at 72 h and three dogs at 84 h.

Vocalization: In group T_1 animals, score 2 was shown by two dogs at 0 and 72 h and by three, four and five dogs at 6 and 18 h, 12 and 72, 24, 48 and 60 h post castration, respectively. In T_2 group score 1 was shown by one dog at 12 h post ligation. Score 2 was revealed by four dogs at 6, 18 and 36 to 48 h, by three dogs at 24 and 60 h; two dogs at 84 h and one dog at 72 h post castration.

The Mean±SD total pain score values in animals of group T_1 and group T_2 have been presented in Table 2. In animals of group T_1, the highest MTPS (7.5) was obtained at 48 h following pinhole castration. In animals of group T_2, the highest MTPS (8.3) was recorded at 12 and 24 h following castration. In both the groups, lowest values (3.5, 2.7, respectively) were obtained preoperatively (0 h). The values in both the groups were significantly ($p<0.05$) higher continuously from 6 to 84 h following castration and showed decreasing trend towards the end of observation period. The values obtained at the last observation period (96 h) were slightly more and equal in both the groups than the values obtained preoperatively. Between the groups, the values did not differ significantly ($p>0.05$) at any time interval.

Vomiting, diarrhea or gross evidence of fecal blood did not occur in any of the dogs throughout the study period.

DISCUSSION

Pain is recognized as one of the most challenging problems in medicine and biology (Sanford *et al.*, 1986). The complexity of the pain phenomenon, the inadequacy of pain assessment instruments and the lack of verbal communication make pain assessment more challenging in animals (Conzemius *et al.*, 1994).

Successful management of pain in animals must begin with an accurate assessment of the degree of pain. The only tools at a veterinarian's disposal are the behavioural and physiological responses of animals (Firth and Haldane, 1999). The pain assessment in the dogs of this study was done by using University of Melbourne Pain Scale (UMPS) (Firth and Haldane, 1999) at frequent

intervals from 0 h up to 96 h following pinhole castration. According to Abu-Seida (2012), UMPS accurately assesses postoperative pain in dogs. Six parameters included in the UMPS are physiological data, response to palpation, activity, mental status, posture and vocalization.

In the parameter: 'Physiological data' the maximum score of 3 was detected in two dogs at one recording and one dog at three occasions in group T_2 but none of the animals in group T_1 showed this score. Since interpretation of a pain response is subjective, attempts have been made to measure various physiologic parameters to quantitate pain (Fazili *et al*., 2009c). Such physiologic postulates have been derived that explain ways in which a painful stimulus could alter the autonomic nervous system in a manner that could be objectively measured.

Score 2 was the highest score recorded in 'response to palpation' in almost similar number of animals in both the groups. Wound palpation is an important component of pain assessment in all species of animals (Watson *et al*., 1996; Robertson, 2003). Animals may vocalize or cry out in an aggressive fashion to defend the painful area if touched or manipulated (Haskins, 1987).

The score 1 in the parameters: 'Activity' and 'mental status' was detected in many animals of both the groups before as well as after ligation. Evaluation of 'Posture' indicated that score 1 was shown by some of the animals of both the groups subjected to pinhole castration even before performing the castration and the highest score of 3 was also detected in similar number of animals of group T_1 and T_2 during post-ligation period. Low hung head, recumbency and tensing of abdominal and back muscles to produce a tucked up appearance are indicative of pain in dogs (Spinelli and Markowitz, 1987; Watson *et al*., 1996; Robertson, 2003). Dull eyes, dilated pupils, sleepy or photophobic appearance have been reported to be signs of pain (Robertson, 2003). Additionally the animal may appear wide-eyed, anxious, nervous, trembling or uncomfortable (Haskins, 1987). In dogs, facial expression can be useful in indicating pain (Robertson, 2003).

Vocalization with the highest score of 2 was detected in two dogs of T_1 group against four dogs of T_2 group at some or the other interval following castration. Vocalization was the most frequently nominated indicator of pain in dogs and cats by 5054 Australian Veterinarians surveyed (Watson *et al*., 1996). A dog vocalizing during the postoperative period may be expressing pain. Vocalization, however, may also represent anxiety, fear or anaesthesia induced delirium (Conzemius *et al*., 1997). It has, therefore been stated as an insensitive and non-specific indicator of pain and is unreliable as the sole criterion for the treatment of pain (Hellyer, 1999).

Among the various objective and subjective parameters examined in the present study the highest mean score of 3 was detected in the parameters; physiological data and posture. It was followed by the score 2 in response to palpation and vocalization. Deneuche *et al*. (2004) reported agitation, response to palpation pressure and manipulation as the best indicators of pain in dogs. According to one more study, response to palpation, facial expression and mental status seemed to be the best indicators of pain following long bone fracture repair in dogs (Fazili *et al*., 2008).

One has to remember that not all signs may be present at one time and no single sign can indicate the degree of pain (Morton and Griffiths, 1985). Physiological parameters like respiration rate, heart rate, plasma glucose and cortisol are not reliable indicators of pain in dogs (Fazili *et al*., 2009b). Abnormal behaviours as well as reduced performance of 'normal' behaviour suggest pain or anxiety and reflect poor welfare status of an animal (Zimmerman, 1986; Morton and Griffiths, 1985; Bateson, 1991; Anonymous, 1998; Hellyer, 1999; Robertson, 2003).

The highest MTPS of 7.5 and 8.3 was recorded in animals of group T_1 (once) and T_2 (twice) following castration, respectively. The values in both the groups (T_1 and T_2) were significantly ($p<0.05$) higher continuously from 6 to 84 h post ligation. In the present study, the values did not

show significant difference ($p>0.05$) between the groups at any occasion indicating comparable effects of the two analgesics (meloxicam and ketoprofen) used. The highest pain score assessed in one study that included dogs undergoing ovariohysterectomy using UMPS was 14 of a possible 27 points (Firth and Haldane, 1999). The pinhole castration procedure causes ligation of all the structures in the spermatic cord including nerves responsible for pain transmission (Fazili *et al.*, 2009a). Kent *et al.* (1995) also opined that the damage to the nerves of the spermatic cord and scrotum by the application of the Burdizzo clamp may block the nervous pathways thereby reducing pain and discomfort in lambs. Pinhole castration also avoids trauma and related complications of conventional castration techniques (Fazili *et al.*, 2009a).

Both the analgesics investigated in present trial were solely effective in controlling postoperative pain in all the animals and there was no significant ($p>0.05$) difference in their effects between the two groups. This important clinical finding corresponds well with the observation of several investigators who used meloxicam or ketoprofen preemptively or preoperatively in dogs subjected to abdominal or orthopaedic surgery (Mathews *et al.*, 2001; Caulkett *et al.*, 2003; Deneuche *et al.*, 2004; Laredo *et al.*, 2004; Fazili *et al.*, 2008). Despite the fact that no significant difference was detected in the analgesic effects of the two drugs, yet the MTPS values of the group T_2 animals were always slightly higher than that of group T_1 postoperatively.

Frequent assessments as done in present study are necessary as pain is not a static process and the benefits of interaction with analgesics must be evaluated (Robertson, 2003). The MTPS returned towards the pre-ligation values at 96 h following pinhole castration in animals of both the groups but were still slightly more than the pre-ligation values. Although, the UMPS recording was not done thereafter but all the animals were eating, defecating and urinating routinely and also were comfortable requiring no rescue analgesia. Rescue analgesia is used if the animals show signs of pain (Slingsby, 2010). A clean surgical incision heals faster by primary intention (Harari, 2004). Intensity of acute pain following tissue insult is greatest within the first 24 to 72 h (Anonymous, 1998). Chemical and pinhole castration methods on the other hand, cause coagulative necrosis of the testes whose resolution are protracted and accompanied by fibrosis akin to secondary intention healing (Jana *et al.*, 2005; Ponvijay, 2007; Okwee-Acai *et al.*, 2008).

Xylazine and ketamine combination used in the present study possess analgesic property (Hellyer, 1999; Fazili and Bhattacharyya, 2008). With one time administration in dogs their analgesic duration does not normally exceed 15 to 30 min (Gross, 2001). The combination of fentanyl-detomidine-midazolam although, reported to produce excellent results during minor surgical operations (Ahmad *et al.*, 2011), was not used in this trial due to its comparatively longer analgesia that could mask the effects of the analgesics under investigation. The Xylazine-ketamine combination was given once only to all the animals of both the groups (T_1 and T_2), so are expected to have similar effects on the outcome of both the analgesics administered.

In clinical practice, the choice of analgesic is based on the efficacy, duration of action, ease of administration, safety, availability and cost of the particular agents (Slingsby, 2010). The drug should successfully be co-administered with antibiotics without alteration of their dosage regimen (Abu-Seida, 2012; Patel *et al.*, 2012). In this study, the postoperative analgesic effects of two NSAIDs - meloxicam and ketoprofen, were investigated by a blind study. Ketoprofen, a propionic acid derivative, is a potent NSAID with well-established analgesic properties in dogs (Grisneaux *et al.*, 1999; Mathews, 2002; Deneuche *et al.*, 2004). It is an inhibitor of both COX-1 and COX-2 (Ricketts *et al.*, 1998). Meloxicam, a NSAID of the oxicam group, is a potent inhibitor of prostaglandin synthesis that has anti-inflammatory, analgesic and anti-pyretic properties

(Brown, 1989). Meloxicam has preferential COX-2 activity (Engelhardt *et al*., 1996) and is also a mild inhibitor of COX-1 in platelets and kidneys (Poulsen and Justus, 1999). The efficacy of meloxicam has been compared with other analgesic drugs in the perioperative period (Pascoe, 2000; Mathews *et al*., 2001).

The volume of meloxicam to be administered was doubled by adding distilled water to arrive at the same volume as that of ketoprofen before injection. It also augmented the blind conditions of the assessments throughout the study.

The first dose of analgesic was administered 30 min prior to the induction of anaesthesia in both groups. NSAIDs usually take 30 to 60 min for an analgesic effect to be recognized (Mathews, 2000). Ideally, analgesic therapy initiated before surgery is more effective and requires decreased amount of medication than therapy initiated after surgery (Anonymous, 1998). Preemptive pain therapy has the potential to reduce the total amount of an analgesic drug (Muir and Woolf, 2001).

In both groups analgesic administration was repeated daily for 3 postoperative days i.e., in each case four doses were used. The NSAIDs provide pharmacological effect for 12 to 24 h or longer permitting once daily dosing for short or long term use (Lees, 1998; Crandell *et al*., 2004). Anti-inflammatory activity of NSAIDs lasts longer than the measurable concentrations in plasma (Montoya *et al*., 2004). Similar redosing schedule of the drugs under present investigation makes a study valid for comparison (Caulkett *et al*., 2003).

NSAID administration for postoperative analgesia in dogs may be associated with side effects on renal function, on the gastrointestinal tract and on coagulation (Papich, 2000; Mathews, 2002). Such effects were not noticed in the animals of this study. No overt signs or increase in the serum concentration of creatinine were detected in a clinical study where in meloxicam and rofecoxib were used in dogs undergoing long bone fracture repair for similar period as in the present study (Fazili *et al*., 2009d).

From the results of this study, it is concluded that meloxicam and ketoprofen are equally effective and safe for its perioperative analgesia in dogs undergoing pinhole castration when administration is started preemptively and repeated daily for three days. However, an additional dose at 96 h is also suggested.

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