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Comparative analysis of butorphanol or buprenorphine in combination with dexmedetomidine-ketamine for pre-emptive analgesia in cats

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The study evaluated the preemptive analgesia using butorphanol or buprenorphine in combination with dexmedetomidine and ketamine in 23 domesticated cats undergoing various surgical procedures. The cats were randomly assigned to groups receiving buprenorphine at different doses i.e., @ 20 mcg/kg body wt. for group DKBUP20, @ 30 mcg/kg body wt. for group DKBUP30 or butorphanol @ 0.2 mg/kg body wt. for group DKBUT, combined with dexmedetomidine @ 22.2 mcg/kg body wt. and ketamine @ 4.4 mg/kg body wt. Preoperative measures ensured health status, and postoperative pain assessments were done using the University of Melbourne Pain Scale for felines. Results indicated similar pre-emptive analgesic effects across groups, with the DKBUP30 combination showing slightly prolonged postoperative analgesia up to 24 hr. The study underscored the advantages of combining buprenorphine and butorphanol with dexmedetomidine and ketamine for feline anaesthesia for effective pain relief and safety. This pre-emptive analgesia holds promise for optimal pain control and smooth recovery in feline patients undergoing diverse surgical procedures.

Key words: *Buprenorphine, Butorphanol, Cats, Dexmedetomidine, Ketamine, Pain*

The cats are known for hiding weakness, including pain, until it becomes severe. Pain indicators in cats can be similar to those of anxiety and stress, making it challenging to identify. A significant reason for overlooking pain management in cats is the absence of reliable pain assessment methods (Simon *et al*., 2017). Felines exhibit only a few pain-related behaviours compared to dogs in similar circumstances, which potentially contributes to the under-treatment of pain in cats (Otero, 2005; Teixeira, 2005). Thus, recognizing and reducing discomfort is crucial in veterinary care for cats.

Opioids, particularly butorphanol and buprenorphine, play a pivotal role in managing pain in felines. Butorphanol, a kappa-opioid receptor agonist and μ-opioid receptor antagonist, offered rapid analgesia suitable for short procedures of mild to moderate pain intensity. On the other hand, buprenorphine, a partial μ-opioid receptor agonist, demonstrated superior and longer-lasting analgesia in various surgical procedures (Warne *et al*., 2014).

Research in veterinary anaesthesia aimed to develop techniques with a wide margin of safety. Combinations of different medications were used to achieve an effective and reliable anaesthetic effect in cats, as no single agent could provide the perfect result. Each medication in the combination helped to reduce side effects, lower the required anaesthesia dosage, and enhance the benefits of other drugs used (Henke *et al*., 2005). The objective of the present study was to evaluate the preemptive analgesic effects of butorphanol or buprenorphine in combination with dexmedetomidine and ketamine in domesticated cats undergoing various surgical procedures.

Materials and Methods

Twenty-three domesticated cats reported for various surgical procedures were included in this study. The cats were randomly assigned to receive either buprenorphine (20 mcg/kg body wt.) group DKBUP20, buprenorphine (30 mcg/kg body wt.) group DKBUP30 or butorphanol (0.2 mg/kg body wt.) group DKBUT, in combination with dexmedetomidine (22.2 mcg/kg body wt.) and ketamine (4.4 mg/kg body wt.) intramuscularly using a single syringe. The various surgical procedures performed included castration, ovariohysterectomy, femur fracture repair, tumour removal, aural haematoma, dental scaling and extraction.

Prior to surgery, food was withheld for 6 hr and water for 4 hr. Each cat underwent thorough clinical and haematological examinations to ensure their overall health status. After confirming relaxation of the jaws and absence of the pedal reflex (indicating muscle relaxation and analgesia onset), intubation was performed. Continuous physiological monitoring was carried out throughout the anaesthesia period. Antibiotics and intravenous fluids were administered as needed during anaesthesia.

Post-operative pain assessment was done for the cats immediately upon recovery and 24 hr later using the University of Melbourne Pain Scale (UMPS)for felines (Pohl *et al.,* 2012), consistently performed by the same evaluator.

Statistical analysis was carried out using IBM Corporation's SSPS Statistics software (Version 20.0)

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with results presented as Mean±SE. Statistical significance was determined using one-way analysis of variance (ANOVA) and Tukey's post-hoc test, considering P values less than 0.05 ($P < 0.05$) as statistically significant.

Results and Discussion

Ensuring optimal pain management and anaesthesia in cats is crucial for smooth surgeries and enhanced postoperative recovery. There were no discernible differences in age, sex, or body weight between the groups studied, most of which involved neutering procedures, among others. Biologically, dilated pupils, a common response to μ-opioids like butorphanol and buprenorphine, were observed in nearly all cats post-recovery, typically normalizing within 24 hr. Heart rates moderately increased in all cats after recovery, with a more substantial rise (>20%) noticed 24 hr later. Salivation and vocalization remained absent in all groups at both intervals.

Behaviourally, some cats in the DKBUT group exhibited reactions to touch post-recovery and 24 hr later, whereas none in the DKBUP20 and DKBUP30 groups displayed this response at either interval. Variations in responses to touch and motor activities were noted among groups which highlighting differences in analgesic effects. Motor activity remained consistent throughout the observation period, and all cats were awake post-recovery and eating properly after 24 hr.

Mentally, the cats displayed a demeanour between submissive and sociable, lacking cautious or aggressive behaviour. Posture scores indicating sitting, standing, or moving were consistent across all cats at both time points. The assessment, aligned with UMPS criteria, showcased relatively stable recovery patterns, with minor variations in parameters such as pupil dilation and reactions to touch.

Assessing pain using the UMPS for felines displayed consistency across both groups, revealing no significant differences in scores between recovery and 24 hours post-recovery. Yet, the DKBUP30 group showed slightly lower UMPS scores compared to DKBUT and DKBUP20, albeit non-significantly, immediately after recovery and 24 hr later. The mean±SE values of UMPS) in felines of three groups are shown in table 1.

Table 1: Mean±SE values for UMPS feline pain scoring in three groups immediately after recovery and 24 hr after recovery.

UMPS feline pain scoring	Soon after recovery	24 hr after recovery
KDBUT	3.38±0.65	3.75±0.56
KDBUP20	2.80±0.86	3.10±0.40
KDBUP30	2.70±0.41	3.09±0.27

Mu-opioid receptor agonists were widely recognized for their effective analgesic properties (Gaynor and Muir, 2014). Butorphanol, a mixed agonist-antagonist, provided rapid analgesia suitable for brief mild to moderate pain procedures (Robertson *et al*., 2003; Wells *et al*., 2008). The time for onset typically ranged from 5 min to 15 min, while the duration of action remained a topic of debate, with many experts estimating it to be approximately 2 hr (Lascelles and Robertson, 2004). Manufacturer-provided data suggested that butorphanol offers analgesia for a span of 4 to 6 hr. While buprenorphine, a partial μ-opioid receptor agonist, offered superior and prolonged analgesia in various surgeries of felines (Robertson *et al*., 2005; Bortolami *et al*., 2012). Buprenorphine had a strong binding affinity to the μ receptor and exhibited slow receptor activity, leading to a longer onset of action and a prolonged duration lasting approximately 6-8 hr offering superior and longer-lasting analgesia compared to butorphanol in cats (Taylor *et al*., 2010). Notably, in cats, thermal antinociceptive thresholds showed an increase from 4 hr to 12 hr following injection (Slingsby *et al.,* 2010). Buprenorphine undergoes hepatic metabolism via glucuronidation, which tends to prolong its duration of action in cats due to the absence of functional glucuronyl transferase (van Beusekom *et al.,* 2015; Taylor *et al*., 2001). Butorphanol might offer satisfactory analgesia for soft tissue surgery, but it often fall short for orthopaedic procedures due to its shorter duration of action (Robertson *et al*., 2003; Wells *et al*., 2008). As a partial μ-opioid receptor agonist, buprenorphine anticipated to yield greater analgesic effects than butorphanol, a ê-opioid receptor agonist, consistent with different clinical trials and prospective studies in felines (Robertson *et al*., 2005; Bortolami *et al*., 2012). These findings highlighted the potential of buprenorphine in offering prolonged and effective pain relief in cats undergoing different surgical procedures.

Ketamine and dexmedetomidine contribute to effective multimodal analgesia in cats by raising nociceptor thresholds and exhibiting analgesic responses pre-eminently (Muir and Woolf, 2001; Slingsby and Taylor, 2008; Sharma *et al*., 2017).

From this study, it was concluded that combining butorphanol and buprenorphine with dexmedetomidine and ketamine proved advantageous for feline general anaesthesia and analgesia, offering effective pain relief with favourable safety profiles. These opioids played pivotal roles in managing surgical pain, and their integration into a balanced approach, along with dexmedetomidine and ketamine, hold promise for achieving optimal pain control and facilitating enhanced recovery in feline patients. The utilization of pain assessment scales and the implementation of multimodal analgesia were supposed to be crucial elements in elevating

perioperative care in felines. While all protocols demonstrated similar pre-emptive analgesic effects, the DKBUP30 combination exhibited slightly longer postoperative analgesia, extending up to 24 hr.

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