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Analgesic and Sedative Effects of Piroxicam, Ketamine and Lidocaine Combined With Local Anesthesia for Canine Bone Marrow Aspiration

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Dogs as a valuable large animal model display important roles for investigation of diagnosis and treatment of different disorders of human diseases such as pain relieving procedures. Analgesic efficacy of preoperative administration of piroxicam, ketamine and lidocaine combined with local anesthesia for management of intra and early post-operative pain in the three equal groups of dogs undergoing bone marrow aspiration was evaluated in twenty-four immature female stray dogs that had been referred for FNA technique. Some clinical, physiological and biochemical parameters of the animals were studied before and during the three hours after the BMA. In the ketamine group, hyperglycemia was found to be less than piroxicam and lidocaine groups. A maximum increase of heart rate and respiratory rate was recorded 0.5 h after premedication in all the groups and these variations were significantly recorded in the piroxicam group. Immediately after FNA, clear increments of rectal temperature, especially in the piroxicam group, were also seen in all used drug groups. Evaluation of sedation and analgesia results of the present study indicated no analgesic effect of piroxicam in bone marrow FNA and minor sedative effect just immediately before aspiration. Ketamine with its analgesic nature provided more sedation and adequate pain relief due to FNA technique rather than other groups. Therefore, pain therapy can be improved using preoperative sub-anesthetic dose of ketamine combined with local anesthesia for bone marrow FNA in dogs.

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Introduction

Bone marrow assessment as an important diagnostic tool for evaluating hematologic disorders in dogs has been recommended in different studies, which have shown the following results [1]. Canine bone marrow aspiration is a relatively simple, rapid, and inexpensive technique and can be performed in different sites [2]. Pain management during collection of bone marrow specimens as a minor surgery is necessary and various regimes such as local anesthesia and mild sedation are recommended [1]. In fact, the administration of an analgesic before bone marrow aspiration (BMA) as a preemptive regime for controlling pain during BMA and postoperative time was the main objective of the present study.

Recently, preemptive analgesia or preoperative pain control has been introduced for reduction or prevention of postoperative pain [3]. Preemptive analgesia via avoidance of nociceptive input and prevention of any memory of pain in the central nervous system (CNS) could reduce analgesic consumption [4, 5]. In fact, analgesics binding to their receptors prior to the surgical trauma can provide effective and permanent analgesia during and after surgery. Some physiological parameters such as respiratory rate (RR), heart rate (HR) and body temperature (T) are used for assessment of animal pain. Increase of HR and RR indicates pain presence [6, 7]. Significant increases in blood glucose and serum cortisol above their baseline values are the physiological response of body to acute pain [8, 9]. Piroxicam is a non-steroidal anti-inflammatory drug used to relieve the symptoms of pain and inflammation. It acts by preventing the production of prostaglandins, which are involved in the mediation of pain, stiffness, tenderness and swelling [9]. Also, it is valuable as a chemopreventative and anti-tumor agent [10]. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist and has analgesic effects in subanesthetic doses [11]. Its analgesic effects have been approved in the presence and absence of nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates [12]. Lidocaine as an amide local anesthetic and antiarrhythmic agent and sodium-calcium channel blocker has been used for years in canine clinical practice to provide regional analgesia and to treat ventricular dysrhythmias [13]. Because of its beneficial effects on the peri- and post-operative sympathetic response [14] intravenous use of lidocaine as a supplement to canine general anesthesia has been reported [15,16].

Different animal models can propose to explain the effects of different analgesics and sedatives on pain control. Canine models as a large model with similarity of their vital systems included respiratory, cardiovascular, and gastrointestinal tract with human could be used for scientific investigations in the different of human disorders such as human hereditary diseases and their gene therapy and cancer studies. So, results of this study can support positive information about fine needle aspiration techniques in dog's models and human.

Two main purposes of the present study was creation of painless condition without induction of general anaesthesia with its complications and limitations and using of opium administration. Opium has many side effects especially respiratory depression and constipation. Most of previous studies investigated injection of opium to achieve analgesia but the present study was performed to compare the analgesic efficacy of preoperative administration of piroxicam, ketamine and lidocaine for managing early intra and postoperative pain in dogs undergoing BMA.

Materials and methods

Twenty-four immature female stray dogs that had been referred for collection of bone marrow were studied. All animals had no history of treatment with any analgesics and were in American Society of Anesthesiologists categories 1 and 2. They were starved for 8-12 h before bone BMA and were randomly assigned into three equal groups. Before any drug administration (BeP), baseline values of some physiological and biochemical parameters of the animals were determined for their clinical health confirmation. The body weights (kg), respiratory rates (breaths/min), heart rates (beats/min) and rectal temperatures (°C) of all the dogs were recorded as the baseline values. Approximately 10 minutes before BMA, the dogs

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of groups 1 and 2, were premedicated separately with piroxicam (0.3 mg/kg, IM, Ampule 20 mg/ml, Caspian Tamin Pharmaceutical Co. Rasht, Iran), and ketamine (4 mg/kg, IM, Vial 5%, TRITTAU, Germany). The animals of group 3 received lidocaine (2 mg/kg, LIGNODIC 1% AMP, Caspian Tamin Pharmaceutical Co. Rasht, Iran) five minutes before BMA intravenously. Five minutes before BMA, all dogs received about 1.5 ml lidocaine (2%) subcutaneously at proximal of their left femur for doing fine needle aspiration (FNA).

All animals were evaluated for analgesia, heart and respiratory rates and rectal temperature at times of 0.5, 2, and 3 h after the BMA. The blood glucose and serum cortisol levels of the animals were also measured at the same time intervals.

Postoperative analgesia was assessed by descriptive scale of Lascelles *et al.* [17] (Score 0: Complete analgesia, with no overt signs of discomfort and no reaction to firm pressure applied to the injured region; Score 1: Good analgesia, with no overt signs of discomfort but reaction to firm pressure; Score 2: Moderate analgesia, with some overt signs of discomfort which were made worse by firm pressure; Score 3: No analgesia, with obvious signs of persistent discomfort made worse by firm pressure).The sedative scoring was performed by numerical rating scale, with 0 representing a fully awake animal and 4 an animal that was unresponsive to light stroking and handclapping (Score 0: Completely awake, able to stand and walk, normal posture; Score 1: Stands but staggers when attempting to walk; Score 2: Sternal recumbency, able to lift head up, occasionally makes weak attempts to rise but unable to do so; Score 3: Lateral recumbency, responsive to light stroking and handclapping can slightly lift up head, tail or limb; Score 4: Lateral recumbency, unresponsive to light stroking and handclapping). The degree of sedation was also measured using a visual analogue scale (VAS), with 0 representing a fully alert animal and 4 an animal that was heavily sedated.

Values obtained were summarized as mean±SD. Mean values of blood glucose level, heart rate, respiratory rate, rectal temperature, and serum enzyme activities were compared using one-way analysis of variance. Duncan multiple range test (DMRT) was used to separate variant means among different groups and compared via repeated measure test at different times in each group. Kruskal–Wallis test and Friedman test were used for statistical analysis of analgesic and sedative scores at the same times in different groups and different times in each group respectively. Probability of less than 0.05 was considered significant. This investigation was designed based on the approved DVM thesis (06.09.2014) at Razi University of Kermanshah. All of the animals used in the present study received humane care in compliance with the institutional animal care guidelines.

Results

Evaluation of physiologic parameters

Statistical comparison of some physiologic parameters among the different drug groups at the same time is presented in Table 1. The results showed increase in heart rate before premedication time which reached maximum rate 0.5 h after premedication and then decreased in all drug groups. A maximum increase of rectal temperature was recorded at 0.5 h after premedication in all different drug groups. Significant increase of heart rate was recorded in the piroxicam group compared with other groups. Heart rate decreased in the lidocaine group before bone marrow aspiration. All drug groups showed increase in plasma glucose and cortisol concentrations before premedication until 0.5 h after BMA, while significant increase was recorded in the piroxicam group.

Table 1. Statistical comparison of some physiologic parameters among the different drug groups at the same time

Time	BeP (Before Premedication)					IbA (Immediately before Aspiration)					0.5 (hour after premedication)					2 (hour after premedication)					3 (hour after premedication)				
	HR	RR	RT	GLU	COR	HR	RR	RT	GLU	COR	HR	RR	RT	GLU	COR	HR	RR	RT	GLU	COR	HR	RR	RT	GLU	COR
Ketmanine	82.38 ±6.30^{a}	24.13±5.99^{a}	38.7±.33^{a}	89.75±9.65^{a}	2.1±.66^{a}	107.75±7.05^{a}	31.13±3.8^{a}	39.54±.34^{a}	98.25±7.13^{a}	2.57±.32^{a}	121.38±4.9^{a}	30.13±3.18^{a}	39.65±.21^{a}	106.63±5.71^{a}	3.29±.30^{a}	105.88±6.96^{a}	28.13±2.47^{a}	38.77±.27^{a}	104.25±9.1^{a}	2.55±.21^{a}	107.75±7.05^{a}	23±2.73^{a}	37.37±3.47^{a}	107.13±7.02^{a}	2.32±.26^{a}
Lidocaine	81.88 ±7.59^{a}	24±4.6^{a}	38.72±.38^{a}	90.75±11.31^{a}	2.16±.53^{a}	100.13 ±8.22^{b}	20.25±2.25^{b}	38.76±.26^{b}	103.63±5.78^{b}	2.6±.57^{a}	158.25 ±12.43^{b}	29.75±2.71^{a}	39.79±.43^{a}	117.25±6.65^{b}	3.96±.80^{b}	100.75 ±7.19^{b}	22.5±2.2^{b}	39.41±.20^{b}	111.63±5.85^{b}	3.75±.38^{b}	91.5 ±3.74^{b}	22.63±2.67^{a}	38.95±.44^{b}	108.12±8.37^{a}	3.36±.55^{b}
Piroxicam	77.63 ±6.05^{a}	24.63±3.54^{a}	38.67±.3^{a}	90.5±8.78^{a}	2±.40^{a}	94.25 ±4.77^{c}	37.25±4.8^{c}	38.97±.14^{b}	114.5±6.68^{c}	3.38±.36^{b}	176 ±12^{c}	49.63±5.58^{b}	40±.57^{b}	146.63±10.21^{c}	5.92±.42^{c}	126.25 ±5.77^{c}	35.13±3.64^{c}	38.84±.37^{a}	126.38±5.4^{c}	4.51±.33^{c}	106.75 ±8.31^{a}	27.5±3.93^{b}	38.9±.19^{b}	121±4.69^{b}	3.79±.2^{c}

Presented as mean ± SD, Different superscript letters in each column indicate significant differences (One way ANOVA, P<0.05); HR (Heart Rate); RR (Respiratory Rate); RT (Rectal Temperature); GLU (Glucose); COR (cortisol).

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Evaluation of sedative and analgesic effects

Tables 2 and 3 summarize the comparison of sedative and analgesic values due to administration of three different drugs based on drug and time. In fact, piroxicam had no sedative and analgesic effect clinically, but, ketamine and lidocaine showed clinically acceptable and mild sedative and analgesic effect respectively. In the ketamine group FNA technique was performed in proper condition with no pain and disturbances in the animals.

Table 2. Comparison of sedative degree due to different drugs administration in dogs.

	BeP (Before Premedication)	**IbA (Immediately before Aspiration)**	**0.5 (hour after premedication)**	**2 (hour after premedication)**	**3 (hour after premedication)**
Piroxicam	0^{aA}	0.5 ± 0.535^{aB}	0^{aA}	0^{aA}	0^{aA}
Ketamine	0^{aA}	3.87 ± 0.354^{bB}	2.5 ± 0.535^{bC}	1.25 ± 0.463^{bD}	0.5 ± 0.535^{bE}
Lidocaine	0^{aA}	2.25 ± 0.463^{cB}	1.25 ± 0.463^{cC}	0.25 ± 0.463^{cD}	0.13 ± 0.354^{cD}

Data are presented as mean ± SD, Different small superscript letters in each column indicate significant differences (Kruskal–Wallis test, p <0.05). Different large superscript letters in each row indicate significant differences (Friedman test, P<0.05).

Table 3. Comparison of analgesic degree due to different drug administration in dogs.

	BeP (Before Premedication)	IbA (Immediately before Aspiration)	0.5 (hour after premedication)	2 (hour after premedication)	3 (hour after premedication)
Piroxicam	3 ± 0^{aA}	$2.38\pm.744^{aA}$	3 ± 0^{aA}	3 ± 0^{aA}	3 ± 0^{aA}
Ketamine	3 ± 0^{aA}	$0.13\pm.354^{bB}$	$1.63\pm.518^{bB}$	$2.75\pm.463^{aA}$	3 ± 0^{aA}
Lidocaine	3 ± 0^{aA}	$0.5\pm.535^{cB}$	$2.38\pm.518^{cC}$	3 ± 0^{aA}	3 ± 0^{aA}

Data are presented as mean ± SD, Different small superscript letters in each column indicate significant differences (Kruskal–Wallis test, p <0.05). Different large superscript letters in each row indicate significant differences (Friedman test, P<0.05).

Discussion

Acute pain due to trauma, surgery and some diagnostic procedures such as bone marrow aspiration is the result of stimulation of nociceptors and increased release of catecholamines and other endocrine hormones which consequently lead to increase in respiratory rate, heart rate, body temperature, and the secretion of cortisol [18, 19]. The use of less expensive and easy to use analgesic procedure before stimulation of nociceptors is an ideal and preferable technique compared to post-trauma pain alleviation in minor surgery and painful diagnostic procedure such as BMA. So, the administration of piroxicam, ketamine and lidocaine as preemptive analgesics before BMA was evaluated in the present study.

Determination of the level of plasma glucose is viewed as an efficient method to evaluate the nociceptive stimulus in dogs [20, 21]. Also, the use of serum cortisol has been recognized as one of the most efficient methods to evaluate pain in small animals and humans, and is therefore of importance in the evaluation of the analgesic efficiency of different drugs by measuring the serum cortisol levels [21, 22]. In dogs that were

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subjected to different surgical procedures and systemic diseases and anesthetized by thiopental and halothane, it was concluded that the act of anesthesia by itself caused an increase in the levels of cortisol; even though all other situations demonstrated increase in plasma cortisol [21]. Increase of plasma glucose level is the metabolic response to acute pain (traumatic, surgical, or infectious event) due to elevation of the levels of cortisol and catecholamine and reduction of insulin [21]. According to some studies that suggested the secretion of cortisol rapidly following the surgical intervention as a result of stimulation by ACTH [22, 23], anesthesia intervention can reduce cortisol secretion [23]. The results of the present experiment have demonstrated an increase of plasma glucose level (hyperglycemia) following bone marrow FNA in all drug groups. In the ketamine group hyperglycemia is less than piroxicam and lidocaine groups. Variation of cortisol level is similar to the glucose level changes. As such, the analgesic effect of ketamine based on the cortisol and glucose level due to bone marrow FNA in the dog is more obvious.

In this study, monitoring of heart rate (HR) and respiratory rate (RR) showed increases immediately after needle insertion as a mild acute pain. However, in the lidocaine group a significant decrease of RR was recorded immediately after injection of lidocaine and 0.5 h after premedication. Increase of HR in ketamine group was less than others. A maximum increase of HR and RR was recorded 0.5 h after premedication in all the groups and these variations were recorded as significant in the piroxicam group.

Ketamine as NMDA antagonist via norepinephrine release due to increased sympathetic tone can increase HR and RR, but, due to its analgesic effect provides more sedation and analgesia than piroxicam and lidocaine in the bone marrow FNA and less effect on HR and RR. It is clear those inflammation mediators especially prostaglandins produced by surgical intervention and acute pain can result in fever and hyperthermia [24]. Significant increase of rectal temperature (RT) immediately after needle insertion (as a mild stimulus) at 0.5 h after FNA (maximum hyperthermia) was recorded in all the drug groups, but there was reduction afterwards. This reduction was prominent in the ketamine group, particiullary three hours after premedication. Immediately after FNA (as a severe stimulus), a prominent increase of RT was observed in all used drug groups, especially in the piroxicam group.

Evaluation of sedation and analgesia results of the present study indicates no analgesic effect of piroxiacam on bone marrow FNA and minor sedative effect just immediately before aspiration. In all drug groups maximum clinical sedative effects were observed just immediately before aspiration and after that a significant reduction pathway was recorded. Ketamine with its analgesic nature provides more sedation and pain relief due to FNA technique compared to other groups.

Although the pain relief effects of systemic lidocaine administration have been proven for chronic pain, particularly for neuropathic pain conditions [25,26], conflicting results have been reported for acute pain, such as surgical pain [15]. The mechanisms and exact site of action of systemic lidocaine remain uncertain. Some different mechanisms of action for lidocaine have been introduced such as sodium channel blockade, inhibition of G protein coupled receptors and NMDA receptors [27]. Lidocaine properties have been reported to interact with mu and kappa opioid receptors [28]. Despite the minor analgesic effect of lidocaine observed in the present study, its sole administration prior bone marrow FNA has not been recommended.

Piroxicam by inhibiting the enzyme cyclo-oxygenase and preventing the central and peripheral synthesis of prostaglandins reduces the inflammatory component of pain generation. Some studies showed preemptive analgesic effects of NSAIDs while the others showed no benefits [29]. O'Hanlon and others (1996) suggested administration of piroxicam two hours before surgery to achieve reduction of pain score postoperatively [30] but in this study, clinical and laboratory evaluation of piroxicam as a preemptive analgesic showed no analgesic effect on bone marrow FNA.

Based on the present experiment, pain management can be improved using preoperative ketamine for bone marrow FNA in dogs.

Conflict of interest

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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