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## Evaluation of Butorphanol-lidocaine-ketamine and fentanyl-lidocaine-ketamine constant rate infusion protocols for pain management in small animal orthopaedic patients

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### Abstract

Butorphanol-Lidocaine-Ketamine and Fentanyl-Lidocaine-Ketamine constant rate infusion (CRI) protocols for pain management in small animal orthopaedic patients have not been well-documented in the literature. The present study aimed to define the optimal dosage of these combinations for CRI in dogs for pain management and its effects on physiological body parameters.

**Keywords:** dogs, long bone fractures, constant rate infusion, rescue analgesia

### Introduction

In the veterinary field, prevention and treatment of pain have been neglected for many years. However, recently, the value of prevention and treatment of pain in animals has been recognized (Jones, 2008) [3], and there has been considerable progress in the development of safer anesthetic agents, knowledge of the pathophysiology and treatment of pain, and understanding of the importance of perioperative care (Kehlet and Dahl, 2003) [4]. Pain management includes analgesic techniques before, during, and after surgery to decrease somatic and autonomic reflex responses to nociceptive stimuli, reduce stress and anxiety, and ensure comfort and well-being (Kehlet and Dahl, 2003) [4]. With these objectives, the adoption of various protocols of multimodal analgesia and balanced anaesthesia has been effective in establishing adequate analgesia and, potentially, reducing the adverse effects of each drug (Muir *et al.* 2003; Ortega and Cruz, 2011; Aguado *et al.* 2011) [8, 9, 11].

Constant rate infusion (CRI) allows constant low-dose administration of various analgesics. CRI analgesia is also quite effective in the management of hospitalized patients with pre-existing or persistent medical pain. Analgesia can be safely and efficaciously administered by CRI. Constant rate infusion (CRI) techniques are superior to intermittently re-dosing schemes for many analgesic and anaesthetic drugs (Lucas *et al.* 2001) [6]. They are better able to maintain plasma drug concentration within the target therapeutic range, avoiding peaks and troughs in plasma drug concentration and therefore variability in drug effect.

The objective of CRI is to maintain a stable plasma or tissue concentration of the drug in the body. This can only be achieved by administering drugs at a constant rate. Once a drug is administered, part of it is also eliminated. A steady-state is considered to be achieved if the rate of infusion matches the rate of elimination (Muir *et al.* 2009) [7]. Because of the constant plasma drug concentration with CRI, pain control will be uniform and consistent.

The aim of the study was to study the effect of the constant rate infusion protocols in the reduction of gas anaesthetic usage and postoperative pain in orthopaedic patients.

### Materials and Methods

#### Selection of animals

Dogs presented with a history of long bone fractures to the Small Animal Orthopaedic Out-Patient Unit of Madras Veterinary College Teaching Hospital, Chennai were selected for the study. The dogs were subjected to clinical and orthopaedic examination and diagnosis of fractures was confirmed by radiography.

Twelve dogs were randomly divided into two groups, in Group I butorphanol-lidocaine-ketamine and in Group II fentanyl-lidocaine-ketamine constant rate infusion protocols were used under low flow isoflurane anaesthesia.

### Clinical and Diagnostic evaluation

After attaining the history and signalment of all the dogs, they were subjected to clinical examination.

**Signalment:** Age, breed, sex, body weight and etiology of the fracture were recorded.

**Clinical and orthopaedic examination:** The dog was examined for lameness, swelling in the fracture site, open or closed fracture and pain score was recorded.

**Radiographical evaluation:** The dogs were subjected to radiography after clinical examination; orthogonal views of the affected limb were taken to diagnose the fracture. Radiographs of the contralateral limb were also taken for the selection of implant and for contouring of the implant (Langley-Hobbs, 2003) [5]. Oblique views of the fractured bone will be helpful to rule out the fissure fractures if any (Langley-Hobbs, 2003) [5].

### Haematological evaluation

Total erythrocyte count, haemoglobin, packed cell volume, total leucocyte count were estimated using the method described by Coles (1986).

### Serum Biochemical evaluation

Diacetyl monoxime procedure was used to estimate Blood Urea Nitrogen (BUN) and the values were expressed in milligram per decilitre, and Jaffe's alkaline picrate method was used to estimate creatinine and the values was expressed in milligram per decilitre as described by Coles (1986) [2].

**Pain score:** Short form of the Glasgow composite measure pain score was used to assess the pain in dogs in the present study.

**Preparation of the patient:** Food and water were withheld for 8 hrs. and 6 hrs. Respectively prior to the surgery.

Premedication was done with Butorphanol at a dose rate of 0.2mg/Kg in Group I and Fentanyl at a dose rate of 0.02mg/kg i.m followed by Diazepam at a dose rate of 0.25 mg/Kg i.v. induction of anaesthesia was by Inj. Propofol at a dose of 3mg/Kg, titrated to effect and increments administered till the adequate depth of anaesthesia was achieved to allow smooth intubation. After intubation, anaesthesia was maintained with isoflurane at 2.5%. The patients were positioned for the required surgical procedure and prepped and draped for the procedure to be performed. Based on the group they were allotted to; constant rate infusion was initiated with butorphanol-lidocaine-ketamine and fentanyl-lidocaine-ketamine. The surgery was started once the patient achieved adequate depth of anaesthesia, which was determined by the heart rate, respiratory rate, muscle relaxation and absence of reflexes.

In Group 1, Butorphanol at a dose rate of 0.02 mg/kg/hr, Lidocaine at a dose rate of 1.5 mg/kg/hr and Ketamine at a dose rate of 0.6 mg/kg/hr was used. All the drugs were added to normal saline after the total dose was calculated for each patient. In Group 2, Fentanyl was used at a dose rate of 2.4µg/kg/hr, Lidocaine at a dose rate of 1.5 mg/kg/hr and Ketamine at a dose rate of 0.6 mg/kg/hr. An equal amount of normal saline was removed before the total calculated volume of drug was infused into the bottle. The constant rate infusion was done with an infusion pump.

### Other drugs

All the dogs were given ceftriaxone @ 20 mg/kg per body weight preoperatively and for every 90 minutes during the surgical procedure. Pantoprazole was given @ 1mg/kg body weight preoperatively.

### Intraoperative monitoring

The patient was monitored using a Schiller multi parameter monitoring device connected to the patient during the entire period of surgery. Heart rate, SpO<sub>2</sub>, Respiratory rate, temperature, NIBP parameters were recorded for the entire duration of surgery.

### Results

1. Haematobiochemical parameters – Pre, intra and post-treatment (Table 1 and 2).

**Table 1:** Haematological parameters

GROUP I			
Parameter	Before CRI	During CRI	After CRI
Hb	13.25 <sup>a</sup> ± 0.43	12.63 <sup>b</sup> ± 0.47	12.33 <sup>b</sup> ± 0.44
PCV	36.26 <sup>a</sup> ± 1.07	35.05 <sup>a</sup> ± 1.09	34.68 <sup>b</sup> ± 1.64
RBC	5.6 <sup>a</sup> ± 0.28	5.18 <sup>a</sup> ± 0.26	4.96 <sup>b</sup> ± 0.27
WBC	10496.67 <sup>a</sup> ± 497.66	10976.67 <sup>a</sup> ± 481.04	11366.67 <sup>b</sup> ± 459.43
GROUP II			
Hb	12.46 <sup>a</sup> ± 0.16	11.8 <sup>b</sup> ± 0.25	11.58 <sup>b</sup> ± 0.24
PCV	37.85 <sup>a</sup> ± 1.18	35.7 <sup>b</sup> ± 0.66	35.08 <sup>b</sup> ± 0.82
RBC	6.05 <sup>a</sup> ± 0.24	5.65 <sup>b</sup> ± 0.13	5.28 <sup>b</sup> ± 0.12
WBC	12966.67 <sup>a</sup> ± 298.51	13068.33 <sup>b</sup> ± 386.52	13126.67 <sup>b</sup> ± 371.4

Means bearing different superscripts differ significantly at P<0.05

**Table 2:** Serum biochemical Parameters

Group I			
Parameter	Before CRI	During CRI	After CRI
Bun	24.33 <sup>a</sup> ± 1.42	25.83 <sup>b</sup> ± 1.4	26.17 <sup>b</sup> ± 1.49
Creatinine	1.18 <sup>a</sup> ± 0.09	1.2 <sup>a</sup> ± 0.08	1.28 <sup>a</sup> ± 0.07
Total protein	6.58 <sup>a</sup> ± 0.12	6.15 <sup>a</sup> ± 0.07	6.03 <sup>a</sup> ± 0.08
Albumin	3.35 <sup>a</sup> ± 0.08	3.3 <sup>a</sup> ± 0.11	3.16 <sup>a</sup> ± 0.13
Alt	53 <sup>a</sup> ± 4.27	55 <sup>a</sup> ± 3.44	55.17 <sup>a</sup> ± 3.15
Alkaline phosphatase	80.67 <sup>a</sup> ± 1.58	83.67 <sup>b</sup> ± 2.45	82.83 <sup>b</sup> ± 2.72
Glucose	115.83 <sup>a</sup> ± 3.2	109 <sup>b</sup> ± 1.46	104.83 <sup>c</sup> ± 2.03
Cholesterol	166 <sup>a</sup> ± 5.13	166 <sup>a</sup> ± 4.5	166.67 <sup>a</sup> ± 4.77
Group II			
Bun	23.17 <sup>a</sup> ± 1.81	24.33 <sup>b</sup> ± 1.89	24.5 <sup>b</sup> ± 1.76
Creatinine	0.91 <sup>a</sup> ± 0.09	0.95 <sup>a</sup> ± 0.1	0.98 <sup>a</sup> ± 0.1
Total protein	6.41 <sup>a</sup> ± 0.12	6.15 <sup>a</sup> ± 0.09	6.03 <sup>a</sup> ± 0.1
Albumin	3.38 <sup>a</sup> ± 0.1	3.28 <sup>a</sup> ± 0.03	3.11 <sup>a</sup> ± 0.04
Alt	50.33 <sup>a</sup> ± 3.67	50.5 <sup>a</sup> ± 2.97	51.17 <sup>a</sup> ± 2
Alkaline phosphatase	76.83 <sup>a</sup> ± 2.58	76.33 <sup>a</sup> ± 2.36	80.17 <sup>b</sup> ± 2.82
Glucose	114.83 <sup>a</sup> ± 2.18	108.17 <sup>b</sup> ± 2.67	109 <sup>b</sup> ± 3.04
Cholesterol	164.33 <sup>a</sup> ± 5.28	159.17 <sup>b</sup> ± 5.96	159.37 <sup>b</sup> ± 5.16

Means bearing different superscripts differ significantly at P<0.05

2. Physiological parameter – Temperature (Table 3)

**Table 3:** Temperature

	Before CRI	During CRI	After CRI
Group I	101.53 <sup>a</sup> ± 0.32	99.41 <sup>b</sup> ± 0.73	99.38 <sup>b</sup> ± 0.48
Group II	101.93 <sup>a</sup> ± 0.18	99.9 <sup>b</sup> ± 0.22	99.42 <sup>b</sup> ± 0.5

Means bearing different superscripts differ significantly at P<0.05

3. Cardio-pulmonary parameters – Heart rate, Blood Pressure, Respiratory Rate and Saturated Partial Pressure

of oxygen (SpO<sub>2</sub>) (Table 4).

**Table 4:** Cardio-pulmonary parameters

Heart Rate			
	Before CRI	During CRI	After CRI
Group I	124.33 <sup>a</sup> ± 1.74	111.33 <sup>b</sup> ± 1.68	123.33 <sup>a</sup> ± 1.38
Group II	128 <sup>a</sup> ± 2.87	119.67 <sup>b</sup> ± 2.26	127.5 <sup>a</sup> ± 2.14
Blood Pressure			
Group I	132.5 <sup>a</sup> ± 1.7	116 <sup>b</sup> ± 1.8	128.17 <sup>c</sup> ± 0.54
Group II	132.33 <sup>a</sup> ± 1.64	122 <sup>b</sup> ± 1.93	128.33 <sup>c</sup> ± 1.35
SpO <sub>2</sub>			
Group I	98.83 <sup>a</sup> ± 0.4	99.17 <sup>a</sup> ± 0.3	99 <sup>a</sup> ± 0.45
Group II	99.33 <sup>a</sup> ± 0.21	98.33 <sup>a</sup> ± 0.49	98.5 <sup>a</sup> ± 0.43
Respiratory Rate			
Group I	27 <sup>a</sup> ± 1.09	16 <sup>b</sup> ± 1.29	24.66 <sup>c</sup> ± 1.05
Group II	27.16 <sup>a</sup> ± 0.94	19.5 <sup>b</sup> ± 0.76	25.33 <sup>c</sup> ± 0.71

Means bearing different superscripts differ significantly at P<0.05

4. Percentage of isoflurane required to maintain anaesthetic depth throughout the procedure.

#### Percentage of isoflurane required to maintain adequate depth of anaesthesia:

In Group I patients, constant rate infusion of butorphanol-lidocaine-ketamine was initiated after induction and it was noted that adequate anaesthetic depth was maintained with isoflurane concentration of 1.5% in all the patients in the group. There were no abnormal changes in the cardio-pulmonary and physiological parameters when the concentration of isoflurane was maintained at 1.5%. The recovery was uneventful in all the patients in the group.

In Group II patients, constant rate infusion of fentanyl-lidocaine-ketamine was initiated after induction and it was noted that adequate anaesthetic depth was maintained with isoflurane concentration of 2% in all the patients in the group. Increased heart rate and respiratory rate were noticed when the isoflurane level was maintained at 1.5% in this group. There were no abnormal changes in the cardiopulmonary and physiological parameters when the concentration of isoflurane was maintained at 2%. The recovery was uneventful in all the patients.

**Pain score:** Short form of the Glasgow composite measure pain score was used to assess the pain in dogs in the present study (Table 5).

**Table 5:** Pain score

Patient no	Group I		Group II	
	Preoperative	Postoperative	Preoperative	Postoperative
1	9	4	9	6
2	8	6	8	5
3	9	5	9	6
4	8	3	8	5
5	9	4	8	4
6	9	4	9	7

#### Rescue analgesia

Rescue analgesia in this study was given when the pain score is greater than 5 in the Glasgow composite measure pain score evaluated in the postoperative period. One patient in group I was given rescue analgesia 12 hrs. Postoperatively. In group II, rescue analgesia was given to three patients whose pain scores were more than 5 during the postoperative period.

In group II patient number 1 was given rescue analgesia 4 hrs. Postoperatively, patient 3 was given 12 hrs. Postoperatively and in patient 6 rescue analgesia was given 20 minutes after

the surgery in the recovery phase. The drug used for the rescue analgesia was tramadol at the dose rate of 2.5mg/kg body weight.

#### Discussion

Butorphanol-Lidocaine-Ketamine constant rate infusion was effective in achieving appropriate anaesthetic depth with a reduced concentration of isoflurane providing peri and postoperative analgesia when compared to Fentanyl-Lidocaine-Ketamine constant rate infusion. No adverse effects were noticed during the surgical procedure and also in the recovery phase in group I animals compared to group II.

The cardiopulmonary parameters were stable during and after the procedure indicating good anaesthetic depth. The recovery from anaesthesia was smooth and no vocalization or other signs of pain or discomfort were seen in five out of six animals in group I. In group II, three patients have shown signs of vocalization, pain or discomfort when evaluated for pain in the post-operative period necessitating rescue analgesia.

In both the groups, haematology and serum biochemistry parameters did not vary much during the surgical procedure and also in the post-operative period indicating no adverse effects of drugs were noticed.

The isoflurane concentration is maintained at 1.5% in group I and 2% in group II animals, indicating a reduced quantity of isoflurane usage. The appropriate anaesthetic depth was attained in group I animals even with isoflurane concentration of 1.5% when compared to the group II animals.

Butorphanol-Lidocaine-Ketamine combination showed good postoperative analgesia when compared to the Fentanyl-Lidocaine-Ketamine combination. The postoperative pain scores in the group I animals were less compared to the group II animals thus reducing the use of rescue analgesia. Only one animal in group I was given postoperative rescue analgesia when compared to group II in which three animals received postoperative rescue analgesia.

The use of butorphanol-lidocaine-ketamine combination was seen to decrease the MAC of inhaled anaesthetics and also reduce the risk of cardiopulmonary depression by means of decreasing the inhalant anaesthetic requirements during anaesthesia. In addition, the combination of these agents with different pharmacological mechanisms of action may provide better analgesia and a greater inhalant-sparing effect.

In the present study, the butorphanol-lidocaine-ketamine combination has provided good anaesthetic depth, greater inhalant sparing effect, and provided good postoperative analgesia when compared to the fentanyl-lidocaine-ketamine combination. Based on the results obtained it can be concluded that the Butorphanol-Lidocaine-Ketamine combination is a better protocol for peri and post-operative pain in small animal orthopaedic patients.

To date, no such comparative clinical studies were performed to evaluate butorphanol-lidocaine-ketamine and fentanyl-lidocaine-ketamine constant rate infusion protocols for pain management in small animal orthopaedic patients. Hence more clinical studies are suggested with a large sample size to further evaluate these combinations to bring them into routine usage for pain management in small animal orthopaedic patients.

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