RESEARCH ARTICLE

Evaluation of Cardiopulmonary Effects and Postoperative Analgesia of CRIs of Fentanyl Alone and Fentanyl, Lignocaine and Ketamine Combination (FLK) in Dogs Undergoing Unilateral Chain Mastectomy

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Abstract

The present study was undertaken to evaluate effects of continuous rate infusions (CRIs) of fentanyl alone and fentanyl, lignocaine and ketamine (FLK) combination in dogs undergoing unilateral chain mastectomy. Clinical cases (n=12) irrespective of age, breed and body weight were randomly divided into two groups of six animals each. All dogs were premedicated with diazepam and tramadol, induced with propofol and maintained under isoflurane anaesthesia. Group I received fentanyl CRI (5 µg/kg Loading dose [LD] & 10 µg/kg/h CRI), whereas Group II received a combination of fentanyl 5 µg/kg LD & 10 µg/kg/h CRI; lignocaine 2 mg/kg LD & 3 mg/kg/h CRI; ketamine 1 mg/kg LD & 0.5 mg/kg/h CRI. Physiological, cardiopulmonary and anaesthetic parameters were recorded. Blood gas analysis was done. Postoperative pain score was evaluated using the short form of the Glasgow Composite Measure Pain Scale (SF-CMPS). Heart rate (52.83±3.54 fentanyl & 68.00±4.58 FLK) and mean arterial pressure (51.67±4.01 fentanyl & 38.33±3.07 FLK) showed a significant decrease following CRI administration in both groups, while other parameters remained within acceptable physiological limits with inhalational anaesthetic sparing effect. Anaesthetic recovery was faster in Group I compared to Group II with mean time to standing 25.17±2.54 and 54.00±2.08 min, respectively. Postoperative pain assessment revealed superior analgesia in the Group II (0/6), with lower pain scores and reduced requirement for rescue analgesia compared to the Group I (3/6, 50%). The study concluded that the FLK combination provided superior postoperative analgesia with minimal cardiopulmonary compromise, making it an effective multimodal analgesic protocol.

Keyrords: Anaesthetic adjuncts, Continuous rate infusion, Dogs, Pain assessment, Unilateral chain mastectomy.

Ind J Vet Sci and Biotech (2026): 10.48165/ijvsbt.22.5.08

Introduction

Canine mammary tumours are among the most common neoplasms affecting intact female dogs (Misdorp, 2002). Surgical removal remains the primary treatment modality, and unilateral chain mastectomy is frequently indicated in dogs with multiple mammary masses, extensive mammary gland involvement, or lesions affecting a substantial portion of a mammary chain (Stratmann *et al.*, 2008). Despite its therapeutic benefits, unilateral chain mastectomy is associated with considerable tissue trauma, inflammation, edema and moderate-to-severe postoperative pain (Marques *et al.*, 2023). Consequently, provision of effective perioperative analgesia is a critical aspect of anaesthetic management in these patients.

Continuous rate infusion (CRI) techniques are widely employed to maintain stable plasma drug concentrations and minimize the fluctuations associated with intermittent bolus administration (Duke, 2013). Multimodal CRI protocols incorporating fentanyl, lignocaine and ketamine (FLK) have gained popularity in veterinary anaesthesia due to their potential synergistic analgesic effects. Although opioids, lidocaine and ketamine are commonly administered as CRIs in dogs, studies directly comparing the efficacy of the combined FLK protocol with fentanyl administered alone remain limited. Previous research demonstrated that a morphine-lidocaine-ketamine CRI reduced the minimum alveolar concentration (MAC) of isoflurane to a degree comparable with morphine

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How to cite this article: Vigneshwaran, S., Mohamed, S., Mohamed Ali, M. G., & Hemalatha, S. (2026). Comparative Evaluation of Cardiopulmonary Effects and Postoperative Analgesia of CRIs of Fentanyl Alone and Fentanyl, Lignocaine and Ketamine (FLK) Combination in Dogs Undergoing Unilateral Chain Mastectomy. Ind J Vet Sci and Biotech, 22(5), 39-43.

Source of support: Nil

Conflict of interest: None

Submitted 11/06/2026 **Accepted** 12/07/2026 **Published** 10/09/2026

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alone (45% and 48%, respectively) (Muir III *et al*., 2003). Nevertheless, information regarding the clinical benefits of such multimodal analgesic combinations remains insufficient. Therefore, the present study was designed to compare the effects of CRIs of fentanyl alone and the FLK combination in dogs undergoing unilateral chain mastectomy, with particular emphasis on physiological and cardiopulmonary responses, perioperative analgesia, and quality of recovery.

Materials and Methods

The anaesthetic study was conducted at the Small Animal Surgery Unit, Madras Veterinary College Teaching Hospital, Chennai (India) from September 2025 to June 2026 on clinical cases registered for unilateral chain mastectomy. Twelve dogs were selected irrespective of breed, age and body weight and subjected to preoperative examinations such as complete blood count, serum biochemistry and thoracic radiographs. Animals with no comorbidities were used for the research.

The selected 12 dogs were randomly divided into two groups comprising of six animals each. All dogs were premedicated with diazepam (0.25 mg/kg BW, IV) and tramadol (2 mg/kg BW, IV), induced with propofol (2-4 mg/kg BW, IV), until titrated to effect and maintained under isoflurane anaesthesia (1.5%). Group I received fentanyl CRI (5 µg/kg Loading dose [LD] & 10 µg/kg/h CRI), whereas Group II received fentanyl, lignocaine and ketamine combination CRI (fentanyl 5 µg/kg LD & 10 µg/kg/h CRI; lignocaine 2 mg/kg LD & 3 mg/kg/h CRI; ketamine 1 mg/kg LD & 0.5 mg/kg/h CRI). In the FLK group, the three drugs were mixed in the same syringe. The solutions for the CRIs were diluted in normal saline (0.9%) solution and administered by a vented IV flow regulator.

At the end of instrumentation, a stabilization period of 5 min was allowed, after which all baseline variables were recorded (T_0). The variables were reassessed 3 min after administration of the loading dose (LD) (T_1). Surgical intervention was initiated 5 min after commencement of the loading dose. During the surgical procedure, all variables were recorded at 10-min intervals. The collected data were grouped according to the surgical stages, namely during incision and tissue dissection (T_2) and during apposition and closure of the surgical wound (T_3). The values presented for T_2 and T_3 represented the arithmetic mean of all measurements obtained during the respective surgical stages.

Physiological and cardiopulmonary parameters such as heart rate, respiratory rate, rectal temperature, oxygen saturation (SpO_2), end-tidal carbon dioxide ($EtCO_2$) were recorded at T_0, T_1, T_2 and T_3 phases using a vital sign monitor (CONTEC CMS8000 multi-parameter patient monitor). Mean arterial pressure (MAP) was monitored non-invasively using an ultrasonic doppler BP machine (VMED Vet-Dop2 Veterinary Doppler), and arterial blood gas analysis was performed using blood gas analyser (EPOC Host Handheld Analyzer Unit Reader Device, USA) at predetermined intervals (T_0, T_1 and T_3).

At the end of the surgery, 0.1 mg per kg BW meloxicam was administered IV. The parameters pertaining to the pain were studied in both the groups using Short Form of the Glasgow Composite Measure Pain Scale (CMPS - SF) at different time interval (after recover and at 3, 6, 12, 24 and 48 h postoperative period). Anaesthetic parameters such as surgery time, anaesthetic time, extubation time, time to head lift, time to sternal recumbency and time to standing were recorded.

Statistical analysis was performed using a SPSS (version 20) software for Windows platform. Demographic data, intraoperative and postoperative times were compared between groups by an unpaired 't' test. For intraoperative variables, comparisons from T_0 were performed by a 1-way repeated measures analysis of variance followed by the Dunnett's test. Differences between groups in pain scores were compared by the Mann Whitney test. Postoperative pain (CMPS-SF) scores were compared over time (vs. Baseline) using the Kruskal-Wallis test.

Results and Discussion

All the 12 dogs completed the study. The mean (±SE) age and body weight of the animals did not differ significantly between groups. Vaporizer settings were significantly reduced during the T_1, T_2 and T_3 phases in both the fentanyl ($p \leq 0.01$) and FLK ($p \leq 0.01$) groups (Table 1). Although the FLK protocol was anticipated to provide a greater inhalant anaesthetic-sparing effect than fentanyl alone, no significant difference in isoflurane requirement was detected between the two groups. This observation is probably explained by factors such as the achievement of effective plasma fentanyl concentrations in both groups, the relatively short duration of CRI administration and the limited sample size of the study (Marques *et al*., 2023).

Compared to T_0, a marked decrease in heart rate was observed during the T_1 phase in both fentanyl (52.83 ± 3.54, $p \leq 0.01$) and FLK (68.00 ± 4.58, $p \leq 0.01$) groups, with a significantly ($p \leq 0.05$) lower heart rate in the fentanyl group compared with the FLK group (Table 2). Thereafter, heart rate gradually returned toward baseline values. In contrast to this, Marques *et al.* (2023) and Cardozo *et al.* (2024) found that the FLK group did not differ significantly from the fentanyl group at T_1 phase. The reduction in heart rate observed immediately after administration of the CRI protocols is attributed primarily to the Vago-mimetic action of fentanyl (Simões *et al*., 2016). The comparatively higher heart rate observed in FLK group is explained by the sympathomimetic effects of ketamine, which tends to increase heart rate through stimulation of the sympathetic nervous system.

Respiratory rate (RR) values were non-significantly increased at T_3 phase in fentanyl group (15.33 ± 0.33, $p > 0.05$) and significantly reduced at T_2 phase in FLK group (11.00 ± 0.52, $p \leq 0.05$). Non-significant difference noticed in the rectal temperature within the groups. There was no significant difference between the groups in RR and rectal temperature

values (Table 2). Oxygen saturation (SpO_2) values were non-significant between and within groups throughout the study indicating good tissue perfusion. End-tidal carbon dioxide ($EtCO_2$) values increased significantly during anaesthesia in both groups but remained within acceptable physiological limits (Table 3). This increase in $EtCO_2$ observed during surgery may be attributed to mild respiratory depression caused by fentanyl and isoflurane (de Moura *et al.*, 2022).

Table 1: Mean (± SE) vaporizer settings (%) recorded during the maintenance phase of anaesthesia in two groups

Variable	T_0	T_1	T_2	T_3	F value
Isoflurane (%) in Group I (Fentanyl)	1.25^{a} ±0.02	1.05^{b} ±0.02	1.22^{a} ±0.03	1.16^{a} ±0.02	19.62**
Isoflurane (%) in Group II (FLK)	1.28^{a} ±0.02	1.05^{b} ±0.03	1.15^{b} ±0.05	1.13^{b} ±0.04	7.73**
t value	-1.19^{NS}	-0.87^{NS}	1.13^{NS}	-0.707^{NS}	--

Mean (±SE) values with different superscripts within the row differ significantly ($p \leq 0.01$), NS Non-significant.

Table 2: Mean (± SE) heart rate (bpm), respiratory rate (bpm) & rectal temperature (°C) recorded during the anaesthetic study in two groups

Variable	Time point	Group I (Fentanyl)	Group II (FLK)	t value
Heart rate (bpm)	T_0	$115.50^{a} \pm 6.89$	$127.17^{a} \pm 9.03$	-1.027^{NS}
	T_1	$52.83^{b} \pm 3.54$	$68.00^{b} \pm 4.58$*	-2.618*
	T_2	$100.83^{a} \pm 6.06$	$113.00^{a} \pm 7.61$	-1.251^{NS}
	T_3	$123.67^{a} \pm 6.25$	$122.33^{a} \pm 2.43$	-0.199^{NS}
	F value	29.57**	17.61**	
Respiratory rate (bpm)	T_0	$13.17^{ab} \pm 0.54$	$13.33^{ab} \pm 0.49$	-0.227^{NS}
	T_1	$12.67^{a} \pm 0.80$	$12.67^{bc} \pm 0.71$	0.000^{NS}
	T_2	$12.00^{a} \pm 0.45$	$11.00^{c} \pm 0.52$	1.464^{NS}
	T_3	$15.33^{b} \pm 0.33$	$15.17^{a} \pm 0.31$	0.368^{NS}
	F value	6.66**	10.63**	
Rectal temperature (°C)	T_0	$37.50^{a} \pm 0.17$	$37.45^{a} \pm 0.20$	0.191^{NS}
	T_1	$37.28^{a} \pm 0.21$	$37.20^{a} \pm 0.16$	0.319^{NS}
	T_2	$37.16^{a} \pm 0.13$	$37.28^{a} \pm 0.12$	-0.666^{NS}
	T_3	$37.31^{a} \pm 0.08$	$37.41^{a} \pm 0.12$	-0.676^{NS}
	F value	1.04^{NS}	0.58^{NS}	

Mean (±SE) values with different superscripts within the column differ significantly ($p \leq 0.01$).
*Significantly different from the Fentanyl group ($p \leq 0.05$), NS Non-significant.

Table 3: Mean (± SE) oxygen saturation (SpO_2) (%), $EtCO_2$ (mm Hg) and Mean arterial pressure (mm Hg) recorded during the anaesthetic study in two groups

Variable	Time point	Group I (Fentanyl)	Group II (FLK)	t value
Oxygen saturation (SpO_2) (%)	T_0	$99.50^{a} \pm 0.22$	$99.33^{a} \pm 0.21$	0.542^{NS}
	T_1	$99.67^{a} \pm 0.21$	$99.50^{a} \pm 0.22$	0.542^{NS}
	T_2	$99.33^{a} \pm 0.21$	$99.50^{a} \pm 0.22$	-0.542^{NS}
	T_3	$99.00^{a} \pm 0.00$	$99.33^{a} \pm 0.21$	-1.581^{NS}
	F value	2.33^{NS}	0.19^{NS}	
$EtCO_2$ (mm Hg)	T_0	$40.67^{a} \pm 0.67$	$39.83^{a} \pm 1.78$	0.439^{NS}
	T_1	$45.17^{b} \pm 0.95$	$45.00^{b} \pm 0.82$	1.133^{NS}
	T_2	$45.00^{b} \pm 0.86$	$43.50^{a} \pm 0.92$	1.192^{NS}
	T_3	$48.67^{c} \pm 0.84$	$46.00^{b} \pm 0.86$	2.219^{NS}
	F value	15.42**	9.48**	
Mean arterial pressure (mm Hg)	T_0	$78.33^{a} \pm 3.07$	$81.67^{a} \pm 3.07$	-0.767^{NS}
	T_1	$51.67^{b} \pm 4.01$	$38.33^{b} \pm 3.07$*	2.638*
	T_3	$75.00^{a} \pm 4.28$	$81.67^{a} \pm 3.07$	-1.265^{NS}
	F value	14.43**	66.27**	

Mean (±SE) values with different superscripts within the column differ significantly ($p \leq 0.01$).

Compared to T_0, both groups exhibited a significant reduction in MAP during the T_1 phase. The decrease was significantly greater in FLK group (38.33 ± 3.07, p ≤ 0.01) compared with fentanyl group (51.67 ± 4.01, p ≤ 0.01) (Table 3). The transient hypotension observed during the T_1 phase in the present study may be attributed to the administration of the loading dose, which likely increased the depth of anaesthesia. Fentanyl, a μ-opioid receptor agonist acts in the medullary centres, leads to enhanced vagal tone and subsequent bradycardia. The decrease in heart rate may, in turn, reduce cardiac output, thereby contributing to a decline in MAP (Marques *et al.*, 2023). One dog from FLK group was administered 0.02 mg/kg atropine sulphate to counter hypotension associated with bradycardia.

In relation to blood gas analysis, compared to T_0, pH values significantly decreased in fentanyl (7.37 ± 0.01, p ≤ 0.0]) and FLK group (7.33 ± 0.01, p ≤ 0.01) at T_1 phase, suggesting the development of mild respiratory acidosis, which is commonly encountered during inhalational anaesthesia. Compared to T_0, $PaCO_2$ values were significantly increased at the T_3 and T_1 phase in the fentanyl (45.98 ± 0.94, p ≤ 0.01) and FLK group (44.96 ± 1.19, p ≤ 0.01), respectively. There was significant difference between the groups noticed in pH values at T_1 and in $PaCO_2$ values at all three phases. PaO_2, HCO_3 and SaO_2 values were non-significant between or within groups (Table 4).

Extubation time (p ≤ 0.05), time to head lift (p ≤ 0.01), time to sternal recumbency (p ≤ 0.01) and time to standing (p ≤ 0.01) were significantly longer in FLK group than fentanyl group. However, Surgery and anaesthetic time were non-significant (Table 5). The delayed recovery observed in FLK group is probably attributed to the additive sedative and analgesic effects of lignocaine and ketamine (Gutierrez-Blanco *et al.*, 2015). Conversely, in previous study by Marques *et al.* (2023), time to sternal recumbency and standing were indifferent between the groups.

Postoperative pain score was significantly higher in fentanyl than FLK group (p ≤ 0.05) at 3-h postoperative period. At this time point, 3/6 (50%) animals in the fentanyl group received rescue analgesia with tramadol at 4 mg/kg BW (Table 6). While in FLK group none of the animals received rescue analgesia. The lower postoperative pain scores observed in dogs receiving FLK, CRI could be attributed to the synergistic analgesic actions of fentanyl, lignocaine and ketamine. Fentanyl provided potent opioid-mediated analgesia (Davis *et al.*, 2017), lignocaine contributed systemic analgesic and anti-inflammatory effects (Doherty *et al.*, 2007), while ketamine prevented central sensitization through NMDA receptor antagonism (Soares *et al.*, 2021; Marques *et al.*, 2023). The prolonged recovery times observed in FLK group may also reflect persistence of analgesic activity during the early postoperative period.

Table 4: Mean (± SE) Blood gas analysis values recorded during the anaesthetic study in two groups

Variable	Time point	Group I (Fentanyl)	Group II (FLK)	t value
pH	T_0	$7.39^{a} \pm 0.01$	$7.38^{a} \pm 0.02$	0.405^{NS}
	T_1	$7.37^{a} \pm 0.01$	$7.33^{b} \pm 0.01$*	3.022*
	T_3	$7.33^{b} \pm 0.01$	$7.36^{ab} \pm 0.02$	-1.755^{NS}
	F value	8.55**	3.58^{NS}	
$PaCO_2$ (mm Hg)	T_0	$39.41^{a} \pm 1.09$	$35.66^{a} \pm 0.94$*	2.593*
	T_1	$39.76^{a} \pm 0.82$	$44.96^{b} \pm 1.19$**	3.586**
	T_3	$45.98^{b} \pm 0.94$	$37.40^{a} \pm 0.64$**	7.508**
	F value	14.82**	26.81**	
PaO_2 (mm Hg)	T_0	$91.46^{a} \pm 1.51$	$95.33^{a} \pm 1.78$	-1.651^{NS}
	T_1	$92.6^{a} \pm 1.88$	$93.53^{a} \pm 1.20$	-0.410^{NS}
	T_3	$94.1^{a} \pm 0.65$	$95.73^{a} \pm 0.59$	-1.824^{NS}
	F value	0.84^{NS}	0.82^{NS}	
HCO_3 (mmol/L)	T_0	$22.56^{a} \pm 0.18$	$22.60^{a} \pm 0.18$	-0.175^{NS}
	T_1	$22.31^{a} \pm 0.18$	$22.50^{ab} \pm 0.18$	-0.818^{NS}
	T_3	$22.53^{a} \pm 0.16$	$21.9^{b} \pm 0.29$	1.791^{NS}
	F value	0.60^{NS}	3.59^{NS}	
SaO_2 (%)	T_0	$99.28^{a} \pm 0.21$	$98.80^{a} \pm 0.40$	1.056^{NS}
	T_1	$99.25^{a} \pm 0.21$	$98.80^{a} \pm 0.17$	1.634^{NS}
	T_3	$97.68^{a} \pm 1.26$	$99.16^{a} \pm 0.15$	-1.160^{NS}
	F value	1.47^{NS}	0.62^{NS}	

Mean (±SE) values with different superscripts within the column differ significantly (p ≤ 0.01).
*p ≤ 0.05 significantly, **p ≤ 0.01 highly significantly different from the Fentanyl group.

Table 5: Mean (± SE) anaesthetic parameters time (in minutes) recorded during the anaesthetic study in two groups

Times	Group I (Fentanyl)	Group II (FLK)	t value
Surgery time	67.83 ± 3.36	66.33 ± 4.12	0.282^{NS}
Anaesthesia time	92.33 ± 3.30	89.50 ± 3.78	0.564^{NS}
Extubation time	9.67 ± 1.22	14.83 ± 1.32*	-2.856*
Time to head lift	13.50 ± 1.43	24.83 ± 1.70**	-5.097**
Time to sternal recumbency	18.17 ± 1.62	35.33 ± 3.30**	-4.665**
Time to standing	25.17 ± 2.54	54.00 ± 2.08**	-8.762**

*p ≤ 0.05 significantly, **p ≤ 0.01 highly significantly different from the Fentanyl group

Table 6: Median (interquartile range) pain score at specified time intervals post-recovery using Short Form of Glasgow Composite Measure Pain Scale during the anaesthetic study in two groups

Group/Time	Baseline	After recovery	3 h	6 h	12 h	24 h	48 h	KW P value
Group I (Fentanyl)	0^{a} (0–1) $^{n=6}$	3^{b} (3–4) $^{n=6}$	7^{b} * (3–8) $^{n=6}$	2^{b} (1–2) $^{n=3}$	2^{b} (1–2) $^{n=3}$	1^{a} (0–1) $^{n=3}$	0^{a} (0–1) $^{n=3}$	0.00**
Group II (FLK)	0^{a} (0–1) $^{n=6}$	3^{b} (2–3) $^{n=6}$	3^{b} (2–4) $^{n=6}$	2^{b} (1–2) $^{n=6}$	1^{a} (1–2) $^{n=6}$	0^{a} (0–1) $^{n=6}$	0^{a} (0–1) $^{n=6}$	0.00**
Mann-Whitney U	18.00^{NS}	6.00^{NS}	4.50*	12.00^{NS}	15.00^{NS}	3.00^{NS}	18.00^{NS}	

Median (interquartile range) values with different superscripts within the row differ significantly (p≤0.01). * Significantly different from the Fentanyl, Lignocaine and ketamine (FLK) group (p ≤ 0.05).

Conclusion

The study concluded that both fentanyl and FLK CRI protocols were safe and effective for providing perioperative analgesia in dogs undergoing unilateral chain mastectomy. Both protocols resulted in a transient decrease in heart rate and mean arterial pressure (MAP) during the T_1 phase was the most concerning effect, which was fortunately easily manageable. From the perspective of anaesthetic recovery, fentanyl CRI demonstrated superior recovery characteristics. However, the FLK combination offered more effective postoperative analgesia while maintaining minimal cardiopulmonary compromise, making it a valuable multimodal analgesic approach for perioperative pain management in dogs.

Acknowledgement

The authors express their sincere gratitude to the Dean and the Department of Veterinary Surgery and Radiology, Madras Veterinary College, Chennai for providing the necessary facilities, encouragement and support to conduct this study.

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