Comparison of the Analgesic Efficacy and Stress Responses Following Intraperitoneal Administration of Bupivacaine, Tramadol, and Their Combination in Dogs Undergoing Ovariohysterectomy

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Abstract

Ovariohysterectomy (OHE) is associated with substantial visceral and somatic pain that can trigger significant physiological stress responses. This study evaluated and compared the analgesic efficacy and biochemical changes following intraperitoneal administration of bupivacaine, tramadol, and their combination in dogs undergoing OHE. In this experimental study, 18 adult female dogs were randomly allocated to three groups (n = 6 per group): Group B (0.5% bupivacaine, 2 mg/kg), Group T (tramadol, 4 mg/kg), and Group BT (combination of both agents). Drugs were administered intraperitoneally using the splash technique immediately before abdominal closure. Biochemical variables (cortisol, glucose, lipid profile, urea, and creatinine), estrogen concentrations, physiological parameters, and pain scores were evaluated before surgery and up to 24 hours postoperatively using the Simple Descriptive Scale (SDS), Sammarco Pain Scale, University of Melbourne Pain Scale (UMPS), and Glasgow Composite Measure Pain Scale–Short Form (CMPS-SF). Group BT demonstrated the most stable physiological parameters and the smallest increase in plasma cortisol concentrations during the first 1–6 hours after surgery ($p < 0.05$). Pain scores obtained using all assessment scales, particularly CMPS-SF and UMPS, were significantly lower in Group BT than in Groups B and T ($p < 0.05$). The need for rescue analgesia was markedly reduced in Group BT compared with the monotherapy groups. Although recovery time was longer in the combination group, renal function markers and other safety parameters remained within normal physiological limits.

Conclusion: Intraperitoneal administration of combined bupivacaine and tramadol provided superior postoperative analgesia and more effective attenuation of stress-related metabolic responses than either drug alone. This multimodal analgesic approach appears to be a safe and effective strategy for improving postoperative pain management and welfare in dogs undergoing ovariohysterectomy.

Keywords: Bupivacaine; Tramadol; Intraperitoneal analgesia; Ovariohysterectomy; Dogs; Postoperative pain

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Introduction

Ovariohysterectomy (OHE), while routinely performed in small animal practice, represents a significant nociceptive insult involving both visceral and somatic pain components. The procedure entails abdominal wall incision, mechanical traction of the suspensory ligaments, and ligation of the uterine body, all of which trigger a complex cascade of neuroendocrine responses (Slingsby and Waterman-Pearson, 2000). Inadequate perioperative pain management does not merely compromise animal welfare; it fosters the development of "central sensitization," a phenomenon characterized by an altered pain threshold and wind-up effect. Such pathological pain states exacerbate the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, ultimately driving a profound catabolic state (Ciammaruconi *et al*., 2024).

The current paradigm in veterinary anesthesia has shifted toward multimodal analgesia, a strategy that utilizes pharmacologically diverse agents to achieve synergistic effects. This approach aims to provide superior antinociception while concurrently reducing the required dosage of individual drugs, thereby mitigating dose-dependent adverse effects (Steagall *et al*., 2020). Among various regional techniques, the intraperitoneal "splash" administration of analgesics has gained clinical traction due to its technical simplicity, minimal equipment requirements, and high efficacy in blocking nociceptive transmission from visceral receptors before it reaches the dorsal horn of the spinal cord (Zaki *et al*., 2022).

Bupivacaine, a long-acting amide-type local anesthetic, exerts its effect by reversibly binding to voltage-gated sodium channels in nerve fibers, thus inhibiting the propagation of depolarization. Recent evidence suggests that intraperitoneal bupivacaine significantly enhances the "opioid-sparing" effect during the critical postoperative period (Campagnol *et al*., 2012; Kim *et al*., 2021). Conversely, tramadol serves as an atypical analgesic with a dual mechanism of action: it exhibits a weak affinity for μ\muμ-opioid receptors and modulates descending inhibitory pathways by inhibiting the reuptake of norepinephrine and serotonin (KuKanich and Papich, 2004). The potential of tramadol to attenuate peripheral inflammatory mediators further positions it as a robust candidate for combination with local anesthetics (Tarkila *et al*., 2023).

The systemic response to surgical trauma is reflected in a series of biochemical and hormonal fluctuations. Plasma cortisol remains the "gold standard" biomarker for quantifying surgical stress in dogs; its elevation triggers gluconeogenesis and lipolysis, resulting in transient hyperglycemia and alterations in the lipid profile (Sano *et al*., 2008). Furthermore, monitoring acute-phase proteins and renal biomarkers (urea and creatinine) is essential for assessing the physiological

stability and safety of anesthetic protocols (Iff *et al*., 2021). Given the gonadectomy-induced decline in estrogen levels, tracking hormonal shifts alongside metabolic parameters provides a more holistic view of the patient's recovery.

Despite advancements in pain research, a comprehensive comparison of the synergistic effects of intraperitoneal bupivacaine and tramadol on the broad spectrum of biochemical, hormonal, and behavioral parameters in the canine OHE model remains sparse. Therefore, the present study was designed to test the hypothesis that the intraperitoneal combination of these two agents provides superior attenuation of metabolic stress and enhanced clinical analgesia compared to their individual administration.

Materials and methods

Ethical approval and study setting

This prospective, randomized, blinded experimental study was conducted at the Veterinary Teaching Hospital of Mahrouyan (Ahvaz, Iran) following approval from the Institutional Animal Care and Use Committee (Ethics Code: IR.IAU.AHVAZ.REC.1403.483). All biochemical, hormonal, and lipid profile analyses were performed at the Zist Avin Bonyan Gene Research Institute (affiliated with Shahid Chamran University of Ahvaz) in accordance with Good Laboratory Practice (GLP) standards.

Animals and experimental groups

Eighteen healthy adult intact female mixed-breed dogs, weighing 15.6±1.3 kg and aged 1 to 2 years, were enrolled. Dogs underwent a 14-day acclimatization period under standardized conditions (22±2°C, 12-hour light/dark cycle) with ad libitum access to water and a consistent commercial diet. General health was confirmed via physical examination, complete blood count (CBC), and deworming (mebendazole 100 mg and praziquantel 50 mg). Using a randomized block design, animals were allocated into three equal groups (n=6n=6n=6 per group):

- Group B (Bupivacaine): Received 0.5% bupivacaine (2 mg/kg) intraperitoneally.
- Group T (Tramadol): Received tramadol (4 mg/kg) intraperitoneally.
- Group BT (Combination): Received a simultaneous intraperitoneal combination of bupivacaine (2 mg/kg) and tramadol (4 mg/kg).

Anesthetic protocol and surgical procedure

To standardize the noxious stimulus, all ovariohysterectomies (OHE) were performed by a single surgical team. Premedication and Induction: After a 12-hour fast, dogs were premedicated with acepromazine (0.05 mg/kg, IM). Anesthesia was induced intravenously with a combination of 10% ketamine (10 mg/kg) and diazepam (0.5 mg/kg) (Mathews *et al*., 2014). Maintenance: Following endotracheal intubation, anesthesia was maintained with

isoflurane (1.5% end-tidal concentration) in 100% oxygen (1.5 L/min). Vital signs were monitored continuously (Bionet BM5, South Korea). Intraperitoneal Intervention: Immediately prior to the complete closure of the Linea alba, the assigned treatment (diluted with 0.9% saline to a total volume of 0.2 mL/kg) was administered via the "intraperitoneal splash" technique. The solution was applied directly onto the ovarian pedicles, uterine stumps, and adjacent visceral surfaces (Campagnol *et al*., 2012).

Physiological monitoring and multidimensional pain scoring

Clinical assessments were performed by a blinded observer at baseline (pre-surgery), 30 minutes, and 1, 3, 6, 12, and 24 hours post-surgery. Vital Signs: Rectal temperature, heart rate (HR), and respiratory rate (RR) were recorded using digital thermometry and esophageal stethoscopes. Pain Assessment Scales: Four validated scoring systems were utilized: the Simple Descriptive Scale (SDS), the modified Sammarco scale (Sammarco *et al*., 1996), the University of Melbourne Pain Scale (UMPS) (Firth and Haldane, 1999), and the Short Form of the Glasgow Composite Measure Pain Scale (CMPS-SF) (Reid *et al*., 2007). Rescue Analgesia: Morphine (0.5 mg/kg, IM) was administered as rescue analgesia if the CMPS-SF score exceeded 6/24 or the UMPS score exceeded 10/27 (Mathews *et al*., 2014; Reid *et al*., 2007).

Advanced biochemical and laboratory analysis

Venous blood samples were collected at baseline, pre-intervention, and 1, 3, and 6 hours post-administration. Plasma was separated and stored at $-80^{\circ C}$ until analysis. Hormonal and Stress Analysis: Plasma cortisol and estrogen levels were quantified using competitive enzyme-linked immunosorbent assay (ELISA) kits (Monobind Inc., USA) and a BioTek microplate reader (Sano *et al*., 2008). Metabolic and Lipid Profile: Glucose (enzymatic method), blood urea nitrogen (kinetic urease), and creatinine (modified Jaffe method) were determined using commercial kits (Pars Azmun, Iran). A comprehensive lipid profile, including total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL), was analyzed to evaluate metabolic responses to surgical stress. Protein Analysis: Total protein was measured via the Biuret method, and albumin via the bromocresol green method. Globulin levels were calculated by subtracting albumin from total protein.

Statistical analysis

Data were analyzed using SPSS version 24.0. Normality was assessed via the Shapiro-Wilk test. Biochemical parameters and vital signs were analyzed using a two-way repeated-measures ANOVA followed by LSD post-hoc tests. Pain scores (ordinal data) were analyzed using the Kruskal-Wallis test for inter-group comparisons and the Friedman test for intra-group temporal

changes. Statistical significance was set at $p<0.05$.

Results

Baseline parameters and demographic characteristics

All 18 dogs included in the study were within the age range of 1 to 2 years. Statistical analysis revealed no significant differences in mean body weight or surgical duration among the three experimental groups ($p>0.05$). However, the recovery time (the interval from the cessation of isoflurane to extubating) was significantly longer in Group BT compared to Groups B and T ($p<0.05$), suggesting a potential systemic synergistic effect of the drug combination on sedation depth (Table 1).

Table 1: Potential systemic synergistic effect of the drug combination on sedation depth

Parameter	Unit	Group B (n=6)	Group T (n=6)	Group BT (n=6)	*P*-value
Body Weight	kg	17.33±4.00	15.02±1.35	17.95±4.12	0.412
Surgical Duration	min	29.00±4.18.	31.25±2.9	30.40±6.18	0.655
Recovery Time	min	63.00±17.88a	80.12±14.14a	105.02±11.18b	0.002

Note: Different superscript letters (a, b) within a row indicate statistically significant differences ($p<0.05$).

Hemodynamic and respiratory indices

Regarding heart rate (HR), Group B exhibited a significant increase between 1 and 6 hours post-surgery compared to baseline and Group (P=0.015). In contrast, Group BT maintained superior hemodynamic stability throughout the observation period. No statistically significant differences were observed in respiratory rate (RR) or rectal temperature among groups ($p>0.05$). Although a mild decrease in rectal temperature was noted in all groups at 1-hour post-surgery, these values returned to physiological norms in subsequent assessments.

Biochemical profile and hormonal stress responses

The biochemical and hormonal fluctuations are summarized in Table 2.

Table 2: Comparison of biochemical, hormonal, and lipid parameters across time intervals (Mean ± SD)

Parameter	Unit	Baseline (pre-op)	1h post-op	6h post-op
Cortisol	µg/dL	4.55±1.4	7.49±2.3B	2.94±0.9BT*
Estrogen	pg/mL	24.8±3.1	18.2±2.5	9.4±1.8†
Glucose	mg/dL	89.1±6.2	96.5±7.8	102.8±8.1
Urea	mg/dL	32.4±4.5	35.1±5.2	39.6±4.8
Creatinine	mg/dL	0.9±0.1	1.1±0.2	1.2±0.2
Cholesterol	mg/dL	165±12	178±15	189±14
Triglycerides	mg/dL	45.3±5.145.	52.1±6.4	58.7±7.2
Total Protein	g/dL	6.42±0.56	5.32±0.4†	5.80±0.6
Albumin	g/dL	3.2±0.3	2.7±0.2†	2.9±0.3

(B) indicates significant inter-group difference vs Group B (p<0.05); (BT∗BT*BT∗) indicates significant difference vs other groups (p<0.05); (†\dagger†) indicates significant difference from baseline within the group (p<0.05). Hormonal Response: Plasma cortisol increased postoperatively in all groups; however, Group BT exhibited significantly lower cortisol levels at 1, 3, and 6 hours, indicating more effective suppression of the HPA axis. Estrogen levels significantly declined by the 6-hour mark across all groups (p<0.01), a direct physiological consequence of ovariectomy. Renal and Lipid Profile: Urea and creatinine remained within physiological limits. A non-significant trend towards elevation at 6 hours was attributed to transient perioperative hypotension and reduced glomerular filtration. Progressive increases in cholesterol and triglycerides were noted in Groups B and T, consistent with stress-induced lipolysis, while this response was markedly attenuated in Group BT. Protein Balance: A significant transient reduction in total protein and albumin was observed at 1 and 3 hours post-surgery in Groups T and BT (p<0.05), likely due to hemodilution from perioperative fluid therapy.

Behavioral pain assessment and rescue analgesia

Pain scores across all four validated scales (SDS, Sammarco, UMPS, and CMPS-SF) demonstrated that Group BT experienced the lowest pain levels throughout the 24-hour study period (Table 3).

Table 3: Median (range) pain scores across multiple scales during the 24-hour postoperative period

Pain Scoring Scale	Group B	Group T	Group BT	*P*-value
CMPS-SF (Glasgow)	3 (2–4)	3.5 (2–7)	0 (0–3)	0.008
UMPS (Melbourne)	3 (1–6)	4 (2–4)	2 (1–2)	0.042
Sammarco Scale	7 (6–8)	6 (4–7)	6 (4–6)	0.340
SDS	2 (0–3)	1 (0–3)	0 (0–0)	0.015

Pain Scale Analysis: In Group BT, scores for UMPS and CMPS-SF were significantly lower than both Group B and Group T at the 1, 12, and 24-hour assessments (p<0.01). Rescue Analgesia Requirements: The highest demand for rescue morphine was observed in Group B (8 interventions), whereas Group BT required only 1 rescue dose (P=0.001). This stark contrast confirms the superior and sustained analgesic efficacy of the intraperitoneal bupivacaine-tramadol combination.

Discussion

Analysis of multimodal analgesia in visceral pain management

Ovariohysterectomy (OHE) is among the most frequently performed intra-abdominal procedures in canine practice, inducing a complex

nociceptive profile that combines somatic pain (from the abdominal wall incision) and visceral pain (stemming from the stretching of ovarian ligaments and vascular ligation). Our results demonstrate that the intraperitoneal (IP) combination of bupivacaine and tramadol is significantly more effective than the administration of either agent alone in mitigating physiological and behavioral pain responses. This finding aligns with the principles of "multimodal analgesia," which advocates for the integration of drugs with distinct mechanisms of action to achieve synergistic effects while minimizing individual dose-related side effects (Mathews *et al*., 2014).

Mechanisms and efficacy of the intraperitoneal (IP) route

The efficacy of IP bupivacaine stems from its ability to block voltage-gated sodium channels in the peripheral nerve endings of the peritoneum, thereby inhibiting the transmission of nociceptive signals to the spinal cord (Ziener *et al*., 2015). Conversely, tramadol exerts a dual-action mechanism: it inhibits the reuptake of norepinephrine and serotonin while acting as a weak μ-opioid receptor agonist. Beyond its systemic absorption, tramadol likely contributes to analgesia through peripheral effects on opioid receptors within inflamed peritoneal tissues (Kukanich and Papich, 2004). The clinical superiority of the BT group in this study is likely due to the simultaneous blockade of peripheral nociceptive pathways by bupivacaine and the modulation of central and peripheral pain pathways by tramadol. This synergistic interaction resulted in a profound reduction in rescue analgesia requirements, with only one intervention required in the BT group compared to eight in the Bupivacaine group.

Hormonal and metabolic stress response analysis

Cortisol and Glucose Dynamics**:** Plasma cortisol remains the most reliable biomarker for assessing the activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to surgical trauma. In our study, the BT group exhibited the lowest cortisol concentrations, indicating superior suppression of catabolic stress responses. This is consistent with findings by Sano *et al*. (2008), who reported that optimal perioperative analgesia effectively blunts secondary surges in cortisol and glucose. The relative stability of glucose levels across groups, despite cortisol fluctuations, may be attributed to precise anesthetic depth control and the prevention of extreme sympathetic surges. Lipid Profile and Protein Balance: A novel aspect of this research was the evaluation of the lipid profile as a stress indicator. The moderate elevations in cholesterol and triglycerides observed in Groups B and T reflect stress-induced lipolysis mediated by catecholamine release. The higher metabolic stability observed in the BT group further validates the efficacy of the combined

protocol. Additionally, the transient decline in albumin and total protein during the early postoperative phase (1–3 hours) is likely associated with negative acute-phase responses and interstitial fluid shifts, corroborating the biochemical patterns described by Slingsby and Waterman-Pearson (2000). Gonadal Hormone Response: The significant reduction in estrogen levels by 6 hours post-surgery across all cohorts not only confirms the surgical success of the ovariectomy but also illustrates the rapid clearance of gonadal steroids following the removal of their primary biosynthetic source.

Behavioral pain assessment and hemodynamic stability

The utilization of four distinct pain scales (SDS, Sammarco, UMPS, and CMPS-SF) enhanced the diagnostic sensitivity of our pain assessment. Our data indicate that behavior-based tools, particularly the Glasgow Composite Measure Pain Scale (CMPS-SF), possess higher sensitivity in discriminating analgesic quality between treatment protocols. The BT group demonstrated not only superior pain scores but also enhanced hemodynamic stability. The heart rate elevation observed in Group B between 1 and 6 hours may be attributed to the "analgesic escape" phenomenon, where the localized effect of bupivacaine diminishes due to its relatively short duration; this limitation was effectively neutralized by the addition of tramadol (Campagnol *et al*., 2012).

Clinical safety and recovery dynamics

In the present study, the recovery time in the BT group (105.02±11.18) was significantly longer than that observed in groups B and T (p<0.05). This prolongation is likely attributable to the synergistic interaction between bupivacaine and tramadol, alongside the systemic absorption of tramadol, which may enhance the sedative effects of general anesthetics through its μ\m-opioid receptor affinity and inhibition of monoamine reuptake (Kogel *et al*., 2024). Despite the extended recovery duration, all respiratory parameters and rectal temperatures remained within clinically acceptable ranges, indicating that the combination does not induce significant cardiopulmonary depression or thermoregulatory impairment (Cerasoli *et al*., 2020). Furthermore, the maintenance of serum urea and creatinine levels within narrow physiological limits underscores the safety of the intraperitoneal doses administered (Sano *et al*., 2008).

Conclusion

Based on the findings of this study, the intraperitoneal administration of a bupivacaine (2 mg/kg) and tramadol (4 mg/kg) combination provides a safe, cost-effective, and highly efficacious strategy for postoperative pain management in dogs undergoing abdominal surgery. By ensuring hemodynamic stability, modulating endocrine-metabolic stress responses, and markedly reducing the necessity for rescue opioids, this protocol is highly recommended for inclusion in

multimodal analgesic frameworks for similar surgical procedures.

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Authors' contributions

All authors contributed equally to the study design, data collection, statistical analysis, and preparation of this manuscript. All authors have read and approved the final version of the article.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this research.

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