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Research article

COMPARATIVE MULTIMODAL PALLIATIVE EFFICACY OF GABAPENTIN AND TRAMADOL BY USING TWO PAIN SCORING SYSTEMS IN CATS UNDERGOING OVARIOHYSTERECTOMY

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The analgesic efficacy of the gabapentin-tramadol combination was compared with meloxicam-tramadol and tramadol perioperative analgesic regimens in cats brought to the clinic for ovariohysterectomy. Thirty adult cats belonging to comparable demographics (age, body weight), were enrolled into a randomized, blinded study after due consent from their owners into four treatment groups. A Gabapentin-Tramadol group (GT-group, n = 10), Meloxicam-Tramadol group (MT-group, n = 10), and a Tramadol group (T-group, n = 10) were formed. Gabapentin capsules at 50 mg were administered orally 2 hours before surgery while the rest received a placebo dose. Tramadol (2 mg/kg, IM) and meloxicam at (0.2 mg/kg, SC) were injected immediately prior to anesthetic premedication. Anesthetic protocol involved premedication with ketamine and xylazine, while anesthesia was induced using propofol. Inhalant isoflurane anesthesia was used to maintain a surgical plane. GT group scored lower on IVAS as well as CPS than MT group, and T group for up to 8 hours after surgery. The mechanical nociceptive threshold remained higher (98±0) for up to 12 hours postoperatively and serum cortisol concentrations remained significantly lower during the 24hr period. The addition of gabapentin to the tramadol regimen significantly improved analgesia and mechanical nociceptive threshold than when used on its own.

Keywords: cat, composite pain scale, gabapentin, multimodal analgesia, serum cortisol concentrations

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INTRODUCTION

In cats, ovariohysterectomy results in a significant postoperative pain. Controlling postoperative pain is imperative to prevent needless suffering [1]. Studies have shown that pain can exuberate the incidence of postoperative complications [2,3]. Therefore, the efficacy of opioids such as tramadol has been evaluated meticulously as a perioperative analgesic in experimental settings [4,5]. As the efficacy of tramadol, when independently used has become questionable, further inquiries to mitigate its adverse effects have been initiated [6]. Owing to a myriad of drug interactions, contraindications, side effects and relatively short half-life of desmethyltramadol (4.3h IV), its use as a perioperative analgesic is hampered [7–9]. To this end, researchers have investigated several multimodal approaches to improve the efficacy of tramadol and counteract the side effects associated with its persistent use [10,11]. Bearing in mind its dual mechanism of action, tramadol is considered an opioid agonist and serotonin-norepinephrine reuptake inhibitor (SNRI) [12]. Such versatility in the pharmacodynamics of tramadol has been explained by the presence of two enantiomers which are capable of producing an exaggerated therapeutic effect by forming a racemic mixture [13]. Therefore, to confound its therapeutic effects the adjuvants must exhibit a different mode of action.

Recent investigations regarding the analgesic efficacy of gabapentin in felines undergoing soft tissue and orthopedic surgeries have been quite promising [14,15]. Gabapentin, which is similar in structure to Gamma aminobutyric acid (GABA), has exhibited a comparable pharmacological character [16]. The interest in using gabapentin for pain alleviation in veterinary patients was instigated by human drug trials showing its efficacy as a postoperative analgesic [17]. The exact mechanism of action for gabapentin is unknown, but studies have shown that it can function as an inhibitory neurotransmitter by interacting with voltage-gated calcium channels [18]. Gabapentin is believed to specifically bind with a supplementary section of voltage-activated Ca2+ channels, namely α2δ-1. Following a nerve injury, α1 pore forming units of calcium channels (principally N-type) found in the pre-synaptic terminals of dorsal root ganglion (DRG) neurons are transported from the cytoplasm to the cell membrane [18]. Administration of gabapentin, while inhibiting this traffic at the pre-synaptic terminal also impedes anterograde progression of such phenomenon across the axonal cytoplasm. Several other mechanisms ensuing gabapentin interaction with N-methyl-D-aspartate (NMDA) receptors and transient receptor potential channels may be responsible for the mitigation of neuropathic pain [18]. Additionally, modulation of noradrenergic supra-spinal receptors, cytokines and protein kinase C have also been related with gabapentin administration. After oral administration in cats, gabapentin has exhibited bioavailability as high as approximately 89% [19]. The rationale for using a multimodal perioperative analgesia is based upon impeding sensitization of peripheral and central inflammatory response systems as a preamble to surgical trauma [20].

Consequently, as tramadol and gabapentin have different pharmacological modes of action, it was hypothesized that when used in combination they would have a synergistic effect on their individual efficacies [21]. The primary objective of this research was to appraise the enhancement in the potency of gabapentin as an anodyne by a reduction in pain scores and serum cortisol concentrations when administered in combination with tramadol while comparing this combination with an established analgesic regimen of meloxicam and tramadol [22]. The second objective was to compare the utility of two different pain-scoring systems in cats experiencing pain and lethargy after ovariohysterectomy.

MATERIALS AND METHODS

The study was performed on clinical patients brought in for spaying at different Pet clinics in Lahore, Pakistan between January and November 2020.

Selection of Animals

Thirty cats of varied breeds and comparable demographics (average age and weight) were included in this study. Inclusion criteria of these cats were based on health status, pregnancy and mentation [23,24]. Detailed clinical and hematological analysis was conducted to rule out pregnancy and verify good health. Animals having fractious or highly aggressive mentation were excluded from the study. Animals were kept off feed for at least 6 to 8 hours prior to surgery.

Ethical considerations

This research was a prospective trial. Therefore, only clinical patients were inducted into the study after informed consent was obtained from their owners. Experimental design conformed to the guidelines outlined by Pakistan's Prevention of Cruelty to Animals Act (1890), Punjab Wildlife Protection, Preservation, Conservation and Management Act (1974) and complied with the "Guide for the Care and Use of Laboratory Animals in Research and Teaching". Furthermore, the experimental design of the research followed operating protocols prescribed by the animal welfare committee of the Faculty of Veterinary Sciences, Cholistan University of Veterinary and Animal Sciences, Bahawalpur-Pakistan.

Experimental design

Anesthesia

Cats included in this study were pre-medicated with ketamine at 10 mg/kg and xylazine at 1 mg/kg intramuscularly (IM) [25]. A 24-gauge intravenous catheter was placed. When individuals were adequately tranquilized with the aforementioned cocktail, the

induction dose of propofol calculated at 4 mg/kg was administered in bulk. Anesthesia was maintained using isoflurane.

Anesthetic monitoring and surgical procedure

A heating pad covered by a thick blanket was placed underneath the dorsally recumbent and anesthetized cats. Monitoring of physiological norms perioperatively was performed using a multi-parametric anesthetic monitor (URIT-A63A Vet, URIT Medical Electronics Co., Ltd.), which included pulse oximetry, electrocardiography, esophageal thermometry and Non-invasive Blood Pressure (NIBP) monitoring. A constant rate infusion at 5 ml/kg/h of Lactated Ringer's Solution was administered intravenously during the course of surgery [26]. Preoperative preparation and surgical procedure were conducted utilizing standard methodology [27]. One veterinarian experienced in feline spaying was responsible for all the surgeries included in this study. Time duration elapsed subsequent to skin incision till the placement of final suture was termed as the time taken for surgery. Whereas, period of anesthetic induction to a resumption of palpebral reflexes was determined to be the duration of anesthesia [28].

Treatment groups

Thirty adult cats were assigned randomly into one of the following four treatment groups. Group GT; The Gabapentin–Tramadol group (GT-group, n=10) received gabapentin capsules (50 mg, PO; corresponding to 10mg/kg, body weight on average) 2 hours before surgery and tramadol (2 mg/kg, IM) immediately prior to anesthetic premedication [15]. Group MT; The Meloxicam– Tramadol group (MT-group, n=10) was administered with meloxicam at (0.2 mg/kg, SC) and tramadol at (2 mg/kg, IM) immediately prior to anesthetic premedication. Howbeit, a placebo capsule was offered orally 2 hours before surgery as well. Group T; The Tramadol group (T-group, n=10) received tramadol (2 mg/kg, IM) immediately prior to anesthetic premedication and a placebo capsule PO 2 hours before surgery.

Deglutition of capsules was assisted by 3 ml of water given orally using a syringe. Individuals responsible for the assessment of pain were blinded to assigning animals to different groups.

Assessment of pain

Assessment of pain was accomplished using two different pain scoring systems keeping in view either the extent of consciousness or perception of pain. A basal value for animal pain scores was established 2h preoperatively. Postoperatively animals were scored at 1h, 2h, 4h, 6h and 8h intervals by an observer who was blinded to the patient group assortment of treatment they had received. All felines were diligently observed for the incidence of any adverse symptoms such as ataxia, diarrhea and vomiting throughout the investigative period.

(a) Scoring for Consciousness (IVAS)

The degree of tranquilization and euphoria was determined employing an Interactive Visual Analogue Scale (IVAS) equipped with (0-100 mm) equidistant lines used for feline evaluation. Lines in millimeters were used to mark states of consciousness, whereby a higher numerical figure indicated elevated sensation of pain.

(b) Scoring for the perception of pain (CPS)

A modified version of Glasgow feline Composite Pain Scale (CPS) devised by Brondani et al. (2009) was used to score pain. The modifications in the original scoring system were designed to incorporate observations regarding changes in physiological norms such as temperature, pulse and respiration with behavioral signs that indicate pain in cats (over grooming, teeth grinding and trembling or shivering) [29]. Post-operatively body temperature was taken through rectal thermometry; pulse was counted by applying digital pressure on femoral artery while respiration rate was estimated by thoracic expansion upon inspiration. The multiparametric anesthetic monitoring unit was equipped with an NIBP along with multiple-sized inflatable cuffs to determine blood pressure.

Mechanical nociceptive threshold

Mechanical nociceptive threshold of pain was determined in numerical figures. Two hours before surgery, a base line value was interpreted at the site of future surgical incision by using homemade von Frey filaments as described by de Sousa *et al.* (2014). Post-operatively, the peri-incisional area was probed to check threshold of pain at 1h, 4h, 8h and 12h intervals of time. Nylon filaments of different lengths with gradually increasing force (0.5, 2.0, 20.0, 39.0, 78.0, 98.0 mN), were used perpendicularly (1-3mm) in the peri-incisional areas until they started to bend [30]. Attempt to bite, vocalization due to unease or swift movement were used to indicate a positive response upon probing.

Laboratory testing for plasma and serum analysis

Blood samples were collected to establish baseline values 2h preoperatively followed by collections at 1h, 8h and 24h after surgery. A butterfly catheter of 24 gauge was used for phlebotomy and samples were collected in jelled vacutainers which were centrifuged for 10-15 mins at 3000 rpm to separate the serum.

(a) Blood glucose concentration

A drop of blood was placed on the glucometer strip before transferring blood samples from the syringe to the vacutainer. Values for blood glucose concentration were noted in mg/dl.

(b) Serum cortisol concentration

Serum cortisol concentration is one of the biochemical indicators of inflammation and pain. Collected serum was stored temporarily until shipment to laboratory at 4°C for analysis using solid phase radioimmunoassay.

Statistical analysis

Data for physiological norms (temperature, pulse rate, respiration rate, systolic arterial pressure) were analyzed by repeated measures two-way ANOVA while post-hoc analysis was performed using a Tukey test. Time for surgery, duration of anesthesia, serum cortisol concentration, blood glucose concentration, pain scores for subjective (IVAS and CMS) and objective (Mechanical nociceptive threshold) assessment were evaluated by employing non-parametric one-way ANOVA (Kruskal-Wallis test). The level of Significance was considered $p < 0.05$. All analyses were performed using GraphPad Prism (version 8.4.3).

RESULTS

All animals included in the study were of comparable age and body weight. Average time taken for surgery in GT (27.1 ± 3.14min), MT (29 ± 3.43min) and T (30.7 ± 2.83min) were statistically similar (P=0.0531) (Figure 1). Duration of anesthesia for GT (49.3 ± 6.12min), MT (47.6 ± 6.38min) and T (44.5 ± 6.32min) were non-significantly different, as well (P=0.2408) (Figure 1).

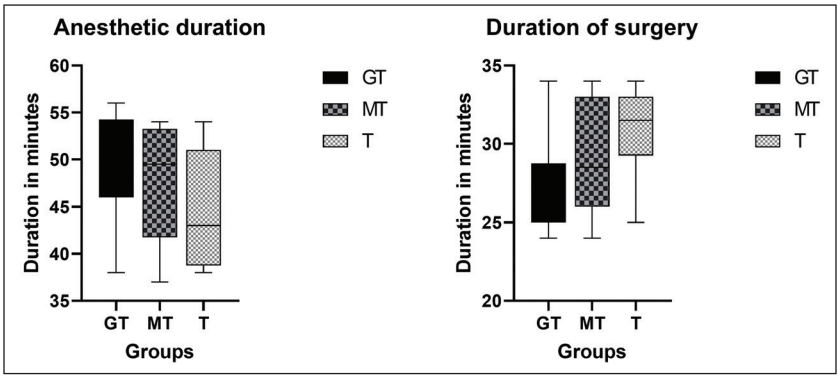

Figure 1. Box and Whisker plot illustrating average duration of anesthesia and surgery amongst experimental groups i.e., GT, MT, and T.

Physiological parameters

All physiological parameters or norms (body temperature, pulse, respiration and systolic arterial blood pressure) at base line preoperatively were found to be analogous in patients inducted into this study. Values for temperature, pulse rate, respiration

rate and systolic arterial pressure have been tabulated (Table 1). Temperature was significantly higher in GT group at 1h, 2h, and 4h after anesthetic induction when compared against MT and T group (Table 1). However, by 8h mark the difference became non-significant amongst all groups. Pulse rate was higher in all groups after surgery compared to baseline values taken before anesthetic administration. The pulse was significantly elevated in MT group at 1h, 2h, 4h, and 6h time intervals with reference to other treatment groups whereby mean values ranged between 176 beats/min to 234 beats/min (Table 1).

Table 1. Pre- and Post-operative values of Body temperature (°F), Pulse rate (Heart beats/min), Respiration rate (Breaths/min) and Systolic arterial pressure (mmHg) of Surgical patients undergoing ovariohysterectomy. Values are represented as Mean and SD.

Parameters	Time	GT group	MT group	T group
		Mean ± SD	Mean ± SD	Mean ± SD
Temperature (°F)	Basal value	102.23±0.37	102.05±0.44	102.34±0.33
	1h	99.19±0.57[a]	98.28±0.33[b]	98.46±0.32[b]
	2h	101.20±0.30[a]	100.29±1.12[b]	100.57±1.13[b]
	4h	101.64±0.30[a]	100.38±0.66[b]	100.63±0.86[b]
	6h	101.87±0.25[a]	101.14±0.58[a]	101.36±0.61[a]
	8h	102.17±0.20[a]	101.77±0.40[a]	102.08±0.41[a]
Pulse rate (Beats/min)	Basal value	175.70 ± 10.71	176.00±9.42	177.00±9.80
	1h	222.70±5.38[b]	234.60±8.34[a]	225.40±6.40[b]
	2h	212.90±6.26[b]	224.80±6.89[a]	215.60±4.84[b]
	4h	210.20±6.60[b]	222.10±6.69[a]	207.50±4.81[b]
	6h	191.20±6.60[b]	203.10±8.43[a]	194±5.73[b]
	8h	189.30±6.80[a]	194.30±9.25[a]	192.70±5.72[a]
Respiration rate (Breaths/min)	Basal value	39.30±6.27	38.60±6.69	40.80±5.05
	1h	34.50±5.97[a]	31.80±7.58[a]	27.3±5.18[b]
	2h	36.70±6.68	33.90±8.23	35.30±7.63
	4h	38.90±7.17	39.90±8.23	40.10±6.47
	6h	38.10±6.51	40.80±7.58	41.00±5.94
	8h	34.70±6.62	41.70±6.96	41.90±5.47
Systolic arterial pressure (SABP) (mmHg)	Basal value	128.30±15.17	124.90±16.19	128.10±12.74
	1h	167.30±8.58	169.20±6.97	168.40±8.45
	2h	144±7.12[a]	135.30±9.19[b]	147±6.63[a]
	4h	129.50±7.29[b]	152.10±9.70[a]	137.50±7.58[b]
	6h	138±7.12[b]	143.60±8.97[a]	149±6.63[a]
	8h	121.50±7.29[b]	127.10±9.23[a]	132.50±7.58[a]

Significant differences ($P < 0.05$) among groups are indicated in a row by the presence of letters, where the value of 'a' is greater than 'b' which is greater than 'c'.

A dramatic decrease in respiratory rates were observed in group T at 1h time marker in comparison with groups GT (P<0.0001) and MT (P<0.0001). While respiratory rates at 2h, 4h, 6h, and 8h intervals were nonsignificant (Figure 2). Systolic arterial blood pressure (SABP) increased comparably over the basal value, 1hour after surgery in all groups. By 4th hour SABP in GT (129.50 ± 7.29mmHg) was significantly lower than in MT (152.10 ± 9.70mmHg) whereby P<0.0001 (Figure 2).

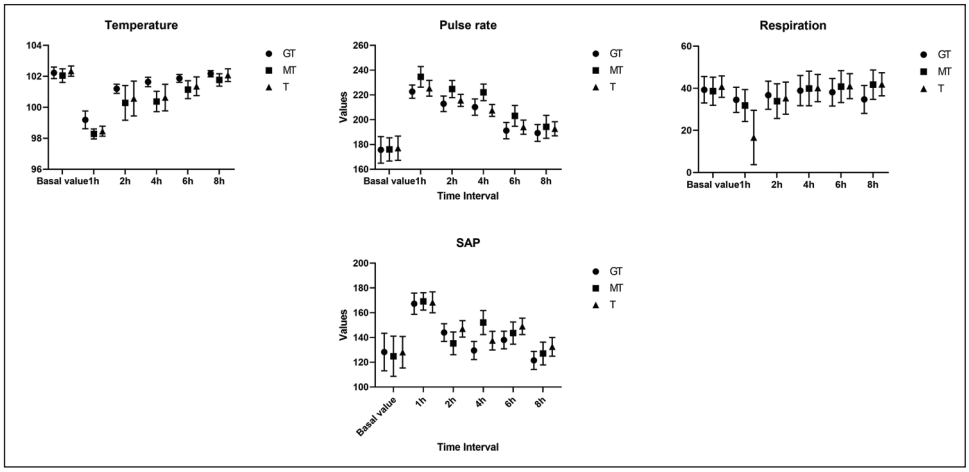

Figure 2. Interleaved symbols graph illustrating Pre- and Post-operative values of Body temperature (°F), Pulse rate (Heart beats/min), Respiration rate (Breaths/min) and Systolic arterial pressure (mmHg) in surgical patients at Basal value (preoperative assessment 2h before surgery), 1h, 2h, 4h, 6h, and 8h postoperatively. Values are represented as Mean and SD.

Scoring for consciousness (IVAS)

When pain was scored according to the Interactive Visual Analogue Scale, significant difference in scoring values were observed between groups all across 1h, 2h, 4h, 6h, and 8h time markers. At 1h postoperative time interval pain scores observed in the GT group were significantly lower than in MT (P<0.0001) or T (P<0.0001) groups. Pain scores in the GT group continued to exhibit significantly lower values than other groups up until 8th hour postoperatively (Figure 3).

Scoring for perception of pain (CPS)

According to Composite Pain Scale, higher pain scores than pre-operative assessment values were observed in all the treated groups after surgery. Scores for all the treated groups at 1h, 2h, 4h, 6h, and 8h were significantly different from each other whereby GT group followed a similar steep decline as in the case of scoring by IVAS. However, lowest and most significant values were observed by 6th hour postoperatively against MT (P<0.0001) and T (P<0.0001) groups (Figure 4).

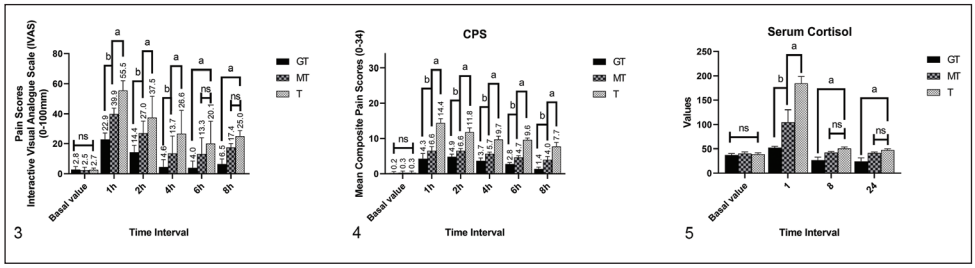

Figure 3. Interactive Visual Analogue Scale pain scores (Median ± SD) for cats undergoing ovariohysterectomy treated with GT (Gabapentin and Tramadol, n=10), MT (Meloxicam and Tramadol, n=10), and T (Placebo capsule and Tramadol, n=10) at Basal value (preoperative assessment 2h before surgery), 1h, 2h, 4h, 6h, and 8h postoperatively. Significant differences ($P < 0.05$) among groups are indicated by the presence of letters, where the value of 'a' is greater than 'b'.

Figure 4. Composite Pain Scale scores (Median ± SD) for cats undergoing ovariohysterectomy treated with GT (Gabapentin and Tramadol, n=10), MT (Meloxicam and Tramadol, n=10), and T (Placebo capsule and Tramadol, n=10) at Basal value (preoperative assessment 2h before surgery), 1h, 2h, 4h, 6h, and 8h postoperatively. Significant differences ($P< 0.05$) among groups are indicated by the presence of letters, where the value of 'a' is greater than 'b'.

Figure 5. Serum cortisol concentrations (Median ± SD) for cats treated with GT (Gabapentin and Tramadol, n=10), MT (Meloxicam and Tramadol, n=10), and T (Placebo capsule and Tramadol, n=10) at Basal value (preoperative assessment 2h before surgery), 1h, 8h, and 24h after ovariohysterectomy. Significant differences ($P< 0.05$) among groups are indicated by the presence of letters, where the value of 'a' is greater than 'b' which is greater than 'c'.

Mechanical nociceptive thresholds

Animals included in the GT group maintained a mechanical threshold of pain at 98mN for the duration of 12hours while MT and T groups exhibiting comparable threshold values following a decremental path as time progressed. By hour 12, their mean threshold values plummeted to 68.4 ± 26.59mN ($P=0.0067$) and 62.7 ± 34.11mN ($P=0.0009$) respectively (Table 2).

Table 2. Mechanical nociceptive threshold (Mean ±SD, mN) for cats undergoing ovariohysterectomy and treated with GT (Gabapentin and Tramadol, n=10), MT (Meloxicam and Tramadol, n=10), and T (Placebo capsule and Tramadol, n=10) at Basal value (preoperative assessment 2h before surgery), 1h, 4h, 8h, and 12h postoperatively.

Mechanical nociceptive threshold (mN)	Pre- and postoperative time	Groups		
		GT group	MT group	T group
	Basal value	98 ± 0[a]	98 ± 0[a]	98 ± 0[a]
	1h	98 ± 0[a]	98 ± 0[a]	70.5 ± 32.12[b]
	4h	98 ± 0[a]	80.3 ± 28.35[a]	76.4 ± 31.1[a]
	8h	98 ± 0[a]	76.4 ± 31.23[a]	68.6 ± 34.65[b]
	12h	98 ± 0[a]	68.4 ± 26.59[b]	62.7 ± 34.11[c]

Significant differences ($P< 0.05$) among groups are indicated in a row by the presence of letters, where the value of 'a' is greater than 'b' which is greater than 'c'.

Blood glucose concentration

Significantly different blood glucose concentrations were observed for the groups inducted into this study over a period of 24 hours after surgery (Table 3). At 1h sampling, blood glucose concentrations in GT were significantly lower than MT and T groups. While at 8h and 24h intervals, blood glucose concentrations of GT were significantly higher than MT ($P<0.0001$) and T ($P<0.0001$) groups.

Table 3. Blood Glucose Concentration (Mean ±SD, mg/dl) for cats undergoing ovario-hysterectomy and treated with GT (Gabapentin and Tramadol, n=10), MT (Meloxicam and Tramadol, n=10), and T (Placebo capsule and Tramadol, n=10) at Basal value (preoperative assessment 2h before surgery), 1h, 8h, and 24h postoperatively.

	Pre- and postoperative time	Groups		
		GT group	MT group	T group
Blood Glucose Concentration (mg/dl)	Basal value	95.5±4.16[a]	94±3.12 [a]	94.8±2.61[a]
	1	109.4±1.07[c]	114.7±2.6[b]	122.3±1.82[a]
	8	117.2±1.75 [a]	97.5±2.01 [c]	110.5±1.35[b]
	24	120.4±1.64 [a]	107±2.4 [b]	102.5±1.50[c]

Significant differences ($P< 0.05$) among groups are indicated in a row by the presence of letters, where the value of 'a' is greater than 'b' which is greater than 'c'.

Serum cortisol concentration

Serum cortisol levels were significantly higher in all groups after surgery. However, at 1h postoperatively greatest cortisol values were observed in patients of group T while the lowest was seen for GT group ($P<0.0001$). This disparity continued to narrow as time progressed (Figure 5). By 8th and 24th hour difference between the values for MT and T groups became nonsignificant.

DISCUSSION

Gabapentin and tramadol, when used in conjunction, produced lower cortisol concentrations and pain scores than tramadol being used independently or in combination with meloxicam during the span of the study. Latter, two therapeutic combinations have been frequently used to manage postoperative pain in cats [22]. Howbeit, recent studies in humans investigating the efficacy of gabapentin to manage pain have generated interest amongst the veterinary community to develop combinations in which this drug may be appropriately utilized [14,19,31,32]. Despite the fact that perioperative administration of gabapentin has been found to relieve distress after hip replacement surgery [33], hysterectomy [34], and lumbar spine surgery [35] in humans, reliable and firm indications for its use in veterinary practice are still elusive. To this end, an elaborate study has validated deductions pertaining to gabapentin by illustrating its potency in the mitigation of acute feline pain by using it in

combination with buprenorphine [5,7]. Consequently, in our study the gabapentin and tramadol combination was used to attenuate the adverse effects often associated with perioperative usage of tramadol. Dosages of gabapentin, meloxicam, and tramadol were based upon previously published data, however; investigations are still required to further assess dosage regimens of gabapentin considering its efficacy shown by this study.

Gabapentin has been known to cause sedation in humans as a side effect [33,36,37]. In our study, we observed a confounding effect of xylazine, tramadol, and gabapentin in recovering cats administered with the said drugs. These effects were relatively more pronounced in the case of IVAS as compared to CPS. Gabapentin-tramadol (GT group) treated group indicated prolonged effects of sedation which can be attributed to gabapentin [38]. As in prior study, sedation scores were significantly better immediately following anesthetic recovery in patients that received gabapentin [19]. No side effects other than the perceived notion of prolonged sedation were observed [14,39]. This phenomenon could be explained by the fact that in the case of GT and MT groups smaller dosage of propofol had to be administered to maintain the surgical plane of anesthesia, which resulted in a quicker recovery slightly hampered by gabapentin [40].

A current analysis published about pain scale validation in feline practices showed a slightly modified version of the Composite Pain Scale i.e. UNESP-Botucatu multidimensional Composite Pain Scale, to be extremely reliable concerning its consistent sensibility [29,41,42]. Therein, certain scoring parameters were added to UNESP-Botucatu multidimensional Composite Pain Scale, so it may better facilitate English language speakers while scoring for perception of pain in cats. A strong correlation between both pain evaluation scales was noted despite behavior-based scoring in the case of IVAS as opposed to the multiparametric approach of CPS. Retracted limbs, squinted eyes, anxiety, and frequent licking or biting of the wound were some behavioral markers used to identify pain post-operatively [11,43]. While physiological parameters were also scored and evaluated along with behavioral markers to score for multidimensional CPS scale [29].

Adequate experience regarding feline behavior was required for monitors to evaluate pain in cats due to their reserved nature. Same observers experienced in determining pain scores were responsible for scoring with both of the pain evaluation scales as it has been demonstrated previously that experience or change in observers may influence the results [26]. Therefore, a strong correlation between both scales validates their effectiveness and confirms the results. After anesthetic recovery, animals included in the T group often responded aggressively and vocalized discomfort when their wound was palpated or irritated [41,44]. A combination of gabapentin and tramadol scored best on both of the subjective pain assessment scales at 1h, 2h, 4h, 6h, and 8h following ovariohysterectomy amongst all the treatment groups.

Cortisol concentrations have been evaluated in prior studies as objective pain biomarkers [45]. Elevated cortisol levels were expected in laparotomic surgeries as

opposed to superficial ones [46]. The elevated serum cortisol concentrations observed in T group indicating pain were justified by prior studies [47,48]. Cortisol has been considered a reasonable indicator for postoperative pain since its use was validated by a study undertaken in cats after orthopedic surgery [49]. Little variation amongst treatment groups in overall blood glucose concentrations throughout the study period indicated limited clinical significance [50]. SABP has also been indicated as a good parameter for analysis of pain however, its effectiveness has been debatable [51]. Systolic arterial blood pressure has been reported to be discreetly correlated with cortisol concentration however it was not true in our case. Opioids such as tramadol have been known to cause depression of SABP [52]. Similar to prior reporting, under the effect of adequate analgesia pulse and respiratory rates did not correlate with cortisol concentration either [53]. Using tramadol perioperatively has been reported to have a dramatic effect on baseline values of pulse, respiration and temperature [5,28]. In our study, the fluctuations in temperature, pulse, and respiration were attributed to tramadol, as well. Whereby pulse was observably elevated 1h following surgery but continued to return to baseline values as serum concentrations of the drug continued to wean off. Respiration rate and body temperature were conversely lowered due to independent or combination use of opioids initially and consequently increased up until the 8th hour. Likewise, Robertson (2005) has stated that cats are at risk of developing hyperthermia as a result of administering mu (μ) agonist opioids, namely tramadol [54]. In contrast to present findings, prior studies have indicated appropriate analgesia with individual use of tramadol and several other NSAIDs [52]. This could be rationalized by differential bio-availability durations of gabapentin, meloxicam, and tramadol. When given orally, gabapentin is believed to acquire adequate serum concentrations within 1-2 hours of consumption and retain a half-life of about 2.8 hours [19]. However, limited research has been available regarding Gabapentin pharmacokinetics in cats.

Considering all surgeries were performed by the same surgeon possessing satisfactory skill and duration of surgery was relatively brief, the study design did not take it into account as a variable. In our study, we used placebo doses in MT and T groups to ensure the unbiased evaluation of treatment regimens. We avoided employing rescue analgesia by implementing a stringent experimental design and maintaining an extremely short duration of trial similar to prior investigations due to inherent difficulties and dilemmas such function may introduce to the research design [55,56]. Considering the fact that tramadol and meloxicam combination had been proven effective previously [22,57,58], a combination of these drugs was used to test the efficacy of gabapentin as an adjuvant. To this end, cats that received gabapentin along with tramadol produced a significantly higher mechanical pain threshold even 12h after surgery. This fact could relate to the potency of said combination. The efficacy of gabapentin, when used with buprenorphine, has been reported previously and similar results were produced when buprenorphine was substituted with tramadol in the present study.

CONCLUSION

In conclusion, a combination of gabapentin and tramadol produced a consistent analgesia for up to 8hrs after surgery while improving anesthetic depth and recovery. Its administration helped avert incidences of hyperalgesia ensuing lower serum cortisol concentrations and pain scores on subjective as well as objective scales. Both scales (IVAS and CPC) were adequately effective in determining the status of the patient however CPS was far more precise. Therapeutic advantages of perioperative preventive analgesia using the multimodal approach with different drugs were adequately demonstrated for controlling post-operative pain following ovariohysterectomy.

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Authors' contributions

AHR, QU, MS, and TS drafted the manuscript and performed surgical procedures. AA and YRK scored the animals for pain. FHG and AW performed the hematological tests for blood glucose as well as serum cortisol concentrations. AHR, ON, and KH conceived the study design and helped draft the primary manuscript. KH and AA performed the statistical analysis of the collected data while ON finalized the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement of Informed Consent

The owner understood procedure and agrees that results related to investigation or treatment of their companion animals, could be published in Scientific Journal Acta Veterinaria-Beograd.

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ISPITIVANJE KOMPARATIVNE MULTIMODALNE PALIJATIVNE EFIKASNOSTI GABAPENTIN-A I TRAMADOL-A UPOTREBOM DVA SKOR SISTEMA ZA BOL KOD MAČAKA POSLE OVARIOHISTEREKTOMIJE

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Obavljeno je poređenje efikasnosti u smislu analgezije sa kombinacijom preparata gabapentin-tramadol-a, u odnosu na meloxicam-tramadol i tramadol-a kod perioperativnog režima analgezije mačaka koje su primljene na kliniku radi ovariohisterektomije. Studijom je obuhvaćeno trideset odraslih mačaka sa sličnim demografskim karakteristikama (starost, telesna masa) uz saglasnost njihovih vlasnika. Mačke su po principu slepog slučajnog odabira podeljene po grupama i to: Gabapentin-Tramadol grupa (GT-grupa, n=10), Meloxicam-Tramadol grupa (MT-grupa, n=10) i Tramadol grupa (T-grupa, n=10). Kapsule Gabapentin-a (50 mg) su oralno aplikovane 2 sata pre operacije; ostale mačke su primile placebo. Tramadol (2 mg/kg, intramuskularno) i Meloxicam (0.2 mg/kg, supkutano) aplikovani su neopsredno pre davanja premedi-

kacije za anesteziju. Protokol anestezije je obuhvatao premedikaciju sa ketaminom i ksilazinom. Anestezija je rađena sa propofol-om. U cilju održavanja anestezije, tokom operacije davan je isofluran, inhalaciono. Skor GT grupe bio je manji za IVAS kao i CPS u poređenju sa MT grupom i T grupom i to u trajanju do 8 sati posle operacije. Mehanički prag receptora za bol ostajao je viši (98±0) i do 12 sati posle operacije, a koncentracije kortizola u serumu su ostajale značajno niže tokom perioda od 24 sata. Može da se zaključi da je dodavanje gabapentin-a tramadol-u, značajno poboljšalo analgeziju i prag osetljivosti mehaničkih receptora za bol u poređenju sa aplikacijom pojedinačnih preparata.