Thesis for the degree of Master of Veterinary Medicine

Effects of Bupivacaine Infiltration Anesthesia using Temperature-responsive Hydrogel in Dogs undergoing Celiotomy

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Abstract

The multimodal analgesic strategy involving local anesthesia at the incision site is effective for postoperative pain relief in dogs undergoing celiotomy. Numerous studies have been conducted on drug delivery systems, such as ez:AP® (TGel Bio, Co., Ltd., Republic of Korea), a temperature-responsive hydrogel (TRH). TRH exhibits unique properties, including transitioning from a liquid state at 2–8 °C to a gel state at above 30 °C. This study aimed to investigate whether combining TRH with bupivacaine, a commonly used local anesthetic, could prolong the analgesic effect in dogs undergoing celiotomy compared with administering bupivacaine alone. Eleven dogs that underwent celiotomy were included in this study. Bupivacaine alone or combined with TRH was used for local infiltration anesthesia. Subsequent pain assessment was conducted at 2-h intervals during the next 24 h using the short form of the Glasgow composite measure pain scale. The results showed that the sensory recovery commenced 16–22 h after a single

administration of TRH combined with bupivacaine for infiltration anesthesia, with the analgesic effect lasting for more than 24 h. In the case of bupivacaine alone, both sensory recovery and the duration of the analgesic effect commenced and lasted for about 6-8 h. This study revealed that the use of bupivacaine combined with TRH for local infiltration anesthesia during celiotomy can extend the duration of local analgesic effects, thus providing substantial benefits in postoperative pain management.

Keywords: Infiltration anesthesia, Temperature-responsive hydrogel, Bupivacaine, Dog, Celiotomy

Ⅰ. Introduction

Postoperative pain management is crucial in small animal clinical veterinary medicine. Unrelieved pain leads to weight loss, muscle loss, impaired respiratory function, increased blood pressure, and prolonged recovery time. Unmanaged pain can lead to self-mutilation or progress to chronic pain in animals [44]. The pathway associated with pain perception and transmission is multidimensional and highly complex. Therefore, completely blocking pain signal transmission to the central nervous system using a single class of analgesics is challenging. Using a combination of classes of analgesics with different mechanisms of action is considered logical. This is the basis of multimodal analgesia [9]. Multimodal analgesia allows for the sparing of drug doses, thereby reducing potential side effects of medications. Furthermore, it can lead to additive or synergistic pain-relieving effects [47]. The perioperative pain of celiotomy is a multifactorial process that includes somatic and visceral pains caused by various factors such as peritoneal distension, tearing of blood vessels, traction on nerves, and release of inflammatory mediators [46]. For perioperative pain management during celiotomy, various useful analgesic protocols, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and other classes of analgesics, have been developed and can be administered systemically, locally, or through epidural routes. In addition, administering local anesthetics at the incision site for infiltration anesthesia is also an effective method [14].

Local anesthetics can be divided into esters or amides based on their chemical structures. Examples of esters are cocaine and procaine, whereas examples of amides are lidocaine, bupivacaine, and ropivacaine [50]. In veterinary medicine, the most commonly used agents are lidocaine, mepivacaine, and bupivacaine [28].

Differences exist in effect onset and duration among local anesthetics, and many consistent findings related to this topic exist [12, 33]. Several reviews have focused on veterinary medicine, and although individual differences exist, the general duration of lidocaine and bupivacaine is 60–90 and 240–360 min, respectively [42]. Local anesthetics with higher lipid solubility exhibit increased protein binding, resulting in a prolonged duration of the blocking effect. Therefore, local anesthetics with higher lipid solubility, such as bupivacaine, induce a more prolonged effect than those with lower lipid solubility, such as lidocaine [19]. In dogs, the signs of postoperative pain related to soft tissue procedures tend to decrease significantly within 24 h after surgery [51]. During this period, extending the duration of local anesthesia to ensure adequate analgesic effects is highly beneficial. Methods to extend the duration of local anesthesia include performing periodic infiltration anesthesia and implanting devices to deliver the anesthetics. However, periodic needle insertion can cause stress and pain in the patient, and the risks of infection and potential side effects from excessive drug use cannot be ignored [1].

Drug delivery systems are commonly classified into three categories: injectable particles (nanoparticles and liposomes), liquids (cyclodextrins, injectable polymers, and hydrogels), and hybrid formulations [45]. A multivesicular liposome, known as Nocita® (Elanco Inc., IN, USA), has become a commercially accessible drug delivery system in the field of veterinary medicine [19]. ez:AP® (TGel Bio, Co., Ltd., Republic of Korea), which was developed relatively recently, is a temperature-responsive hydrogel (TRH) composed of a central hydrophobic chain of polypropylene glycol (PPG) surrounded by two hydrophilic chains of polyethylene glycol (PEG), resulting in a PEG-PPG-PEG three-block copolymer, known as poloxamer P407 [39, 48]. TRH exhibits a liquid state at 2–8 °C and transitions to a gel state at above 30 °C owing to micellization. PF-72® (TGel Bio, Co., Ltd.,

Republic of Korea), a product containing the same components approved by the Republic of Korea's Ministry of Food and Drug Safety for human use, induced minimal inflammatory reactions and no negative impact on wound healing in rats, as reported in both in vivo and vitro [27, 39, 48]. Furthermore, when bupivacaine and ropivacaine are combined with PF-72® and administered subcutaneously or intra-articularly, the duration of their effect lasts for 24–72 h in both rats and humans [13, 27, 39]. In a recent study, bupivacaine combined with PF-72® prolonged the duration of femoral and sciatic nerve block in beagle dogs [25].

We hypothesized that the effect of TRH combined with bupivacaine would have a longer duration than that of bupivacaine alone at the same dosage. This hypothesis is based on TRH properties and the high lipid solubility of bupivacaine, which both contribute to a prolonged duration of action. TRH exhibits a liquid state at lower temperatures and transitions to a gel state at higher temperatures. Combining it with bupivacaine, which possesses high lipid solubility, extends its duration of action. Furthermore, various studies have reported that bupivacaine combined with TRH enhances drug delivery efficiency, providing a sustained analgesic effect for more than 24 h post-infiltration anesthesia. This study aimed to investigate whether combining TRH with bupivacaine could prolong the analgesic effect in dogs undergoing celiotomy compared with administering bupivacaine alone.

Ⅱ. Materials and Methods

Animals

Eleven dogs that visited the Veterinary Medical Teaching Hospital of Jeju National University for celiotomy owing to various reasons were included in this study. Of them, one was a normal female, four were castrated males, and six were spayed females. Their mean body weight and age were 9.2 ± 7.12 kg and 9.7 ± 3.95 years, respectively (Table 1).

Table 1. Baseline characteristics of the dogs

		Dogs (*n*=11)
Sex	Female	1
	Castrated male	4
	Spayed female	6
Breed	Jindo	1
	Maltese	1
	Pomeranian	2
	Shih tzu	2
	Bichon Frise	1
	Mixed	2
	Golden retriever	1
	French bulldog	1
Type of the operation	Splenectomy	3
	Ovariohysterectomy	1
	Partial gastrectomy	1
	Enteroanastomosis	1
	Nephrectomy	1
	Liver lobectomy	1
	Cystotomy	1
	Exploratory laparotomy	1
Bodyweight (kg)		9.2 ± 7.12
Age (years)		9.7 ± 3.95

Study design and ethical approval

This prospective study was approved by the Institutional Animal Care and Use Committee of Jeju National University. Informed consent was obtained from all the owners of the included dogs.

Perioperative anesthesia and analgesia

All included dogs underwent the same premedication and perioperative analgesia protocol. Before premedication, maropitant (1 mg/kg, intravenously; Cerenia®, Zoetis Inc., NJ, USA) and cefazolin (22 mg/kg, intravenously; Cefazoline Injection 1g, Chongkundang, Republic of Korea) were administered. Premedication was performed using midazolam (0.2 mg/kg, intravenously; Bukwang Midazolam Inj., Bukwang Pharmaceutical Co.,Ltd., Republic of Korea) and remifentanil (Remiva Inj®, Hana Pharm Co., Republic of Korea), lidocaine (Daihan Lidocaine HCl Hydrate Inj®, Daihan Pharmaceutical Co.,Ltd., Republic of Korea), and ketamine (Ketamine 50 Inj®, Yuhan Corporation, Republic of Korea) mixed solution (RLK, 0.2 ml/kg, loading dose, intravenously). Preoxygenation was performed using 100% oxygen for at least 5 min, and propofol (Anepol Inj®, Hana Pharm Co., Korea) was administered intravenously at a rate of 1 mg/kg/min up to 2 mg/kg. Upon the disappearance of the palpebral reflex and a decrease in jaw tone, endotracheal tube intubation was performed. In cases where the anesthesia induction was insufficient, additional propofol was administered at a rate of 1 mg/kg/min to achieve the desired effect. All dogs were successfully induced before receiving 4 mg/kg of propofol. Intraoperative and postoperative analgesia were managed using an RLK continuous rate infusion (CRI).

Preparation of infiltration solution

The lyophilized TRH powder (ez:AP®, TGel Bio, Co., Ltd., Republic of Korea) was mixed with 0.5% bupivacaine (Myungmoon Bupivacaine Hydrochloride 0.5% Inj., Myungmoon Pharm Co.,Ltd, Republic of Korea) at least a day before use and stored according to the manufacturer's guidelines. Bupivacaine was stored in its commercially available form and kept in a vial until needed.

Infiltration anesthesia

At the final stage of the operation, before suturing the subcutaneous tissue, the length of the incision line was measured using a sterile medical ruler. The area located 0.5 cm away from the starting point of the cranial midline incision was indicated as site 1. Subsequently, sequential numbering was assigned in a caudal direction with intervals of 1 cm each. Then, the incision line was divided into two sections, with the upper half indicated as the upper zone and the lower half indicated as the lower zone. The person administering the injection was blinded to the procedure and injected 0.12 ml (0.6 mg bupivacaine) of TRH combined with bupivacaine or bupivacaine alone into the left and right subcutaneous tissues, centered on the incision line at each site, using a 1-ml integrated needle. The needle was inserted parallel to the subcutaneous tissue at the incised area, 1 cm in length, and the injection was administered after regurgitation according to general subcutaneous injection techniques. The total bupivacaine dosage injected was dependent on the patient's body weight and incision length and did not exceed 2 mg/kg. The point at which infiltration anesthesia was completed in all cases was set as 0 h. TRH combined with bupivacaine or bupivacaine alone was randomly administered to the upper and lower zones, defined as the TRH and Bup zones, respectively. The evaluator was blinded to which area was the TRH or Bup zone

until the evaluation was completed.

Pain assessment and data collections

All dogs in the intensive care unit (ICU) received continuous nursing care for at least 24 h post operation. Assessments were performed at 2-h intervals from 2 h up to 24 h. Pain assessment was conducted using the short form of the Glasgow Composite Measure Pain Scale (CMPS-SF), and additional items were created for evaluation purposes (Appendix 1). The additional items focused on the evaluation of local anesthetic-induced sensory block in the incision area rather than systemic pain response. The patients maintained a natural and comfortable standing posture with their hind limbs placed on the floor and their line of sight naturally obstructed to prevent anticipation of the evaluator's actions. Subsequently, the incision line was divided into four quadrants, and stimulation was applied using a needle. The response criteria were as follows: 0 points indicate no response or indifference, 1 point indicates a mild response (contraction of abdominal muscles, vocalizing, or turning the head), and 2 points indicate a strong response (strong contraction of abdominal muscles, avoidance, or aggression). Based on the incision line, the mid-point of the upper zone was identified, with 1 cm to the right indicated as quarter 1 and 1 cm to the left indicated as quarter 2. Similarly, in the lower zone, 1 cm to the right was indicated as quarter 3, whereas 1 cm to the left was indicated as quarter 4. Subsequently, stimulation was applied to these indicated parts using needles (Fig. 1). The needle used for stimulation was a fine insulin syringe (BD Ultra-Fine® II Insulin Syringe, 31G, Becton, Dickinson and Company, NJ, USA). The 8 mm length of the needle ensured consistent stimulation and minimized the possibility of iatrogenic skin damage during repeated stimulation tests.

Appendix 1. Modified short form of the Glasgow Composite Measure Pain Scale

A. Look at dog in Kennel **Is the dog** **Q1.**		**Q2.**	
Quiet	**0**	**Ignoring any wound or painful area**	**0**
Crying or whimpering	**1**	**Looking at wound or painful area**	**1**
Groaning	**2**	**Licking wound or painful area**	**2**
Screaming	**3**	**Rubbing wound or painful area**	**3**
		Chewing wound or painful area	**4**
B. Put a lead on dog and lead it out of the kennel **Q3. When the dog rises/walks is it?**		**C. If it has a wound or painful area, such as abdomen, apply pressure gently 2 inches around the site** **Q4-1. (TRH zone), Q4-2. (Bup zone)**	
Normal	**0**	**Do nothing**	**0**
Lame	**1**	**Look round**	**1**
Slow or reluctant	**2**	**Flinch**	**2**
Stiff	**3**	**Growl or guard area**	**3**
It refuses to move	**4**	**Snap**	**4**
		Cry	**5**
Q5. Is the dog?		**Q6. Is the dog?**	
Happy and content or happy and bouncy	**0**	**Comfortable**	**0**
Quiet	**1**	**Unsettled**	**1**
Indifferent or non-responsive to surroundings	**2**	**Restless**	**2**
Nervous or anxious or fearful	**3**	**Hunched or tense**	**3**
Depressed or non-responsive to stimulation	**4**	**Rigid**	**4**
D. When stimulating quadrants with a needle **Q7-1. (TRH zone), Q7-2. (Bup zone)**			
No response or indifference	**0**		
Mild response (contraction of abdominal musecles, vocalizing, turning the head)	**1**		
Strong response (Strong contraction of abdominal muscles, avoidance, aggression)	**2**		

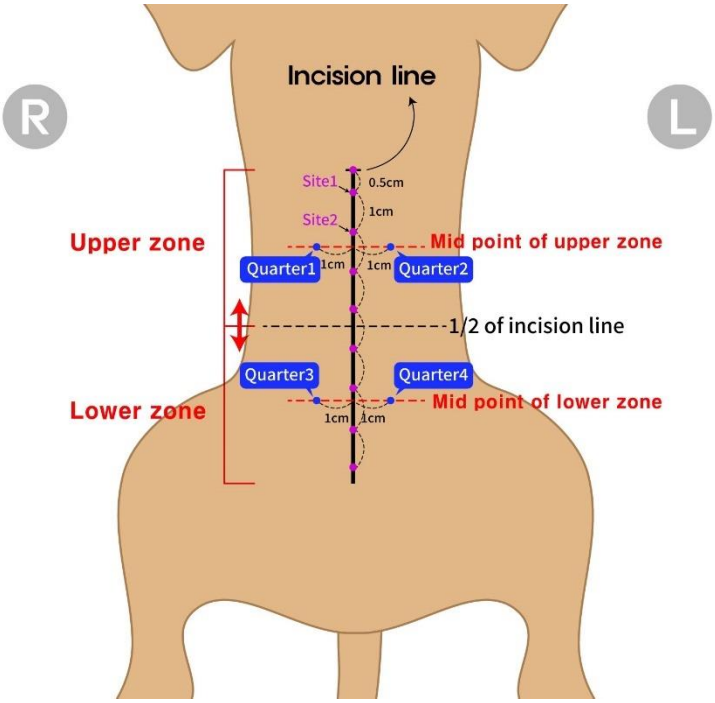

Figure 1. Schematic diagram showing a division of the area around the incision line. Sites were demarcated at 1-cm intervals, starting from a point 0.5 cm away from the cranial end of the incision line. These sites were then divided into two halves: the cranial and caudal parts. Infiltration anesthesia was performed randomly using either bupivacaine combined with a temperature-responsive hydrogel or bupivacaine alone. Touch and needle stimulations (TS and NS, respectively) were performed in the quarters indicated in blue.

Statistical analysis

All statistical analyses were performed based on the scores of items in Appendix 1, which were modified based on CMPS-SF. The mean and standard error of the mean of all values were calculated. Using IBM SPSS, the Mann–Whitney U test and repeated measures analysis of variance (ANOVA) were performed for testing, and the area under the curve (AUC) was calculated. Statistical significance was set at $P < 0.05$.

Ⅲ. Results

Degree of systemic pain during 24 h post operation

The total score of the modified CMPS-SF was 33 points, and the average score for 11 dogs was 8.6 ± 0.19 points for 2–24 h. No statistically significant difference was confirmed using repeated measures ANOVA (p > 0.05). The systemic analgesic effect in all dogs was at a similar level between the end of the operation and 24 h post operation, when assessments were completed (Fig. 2).

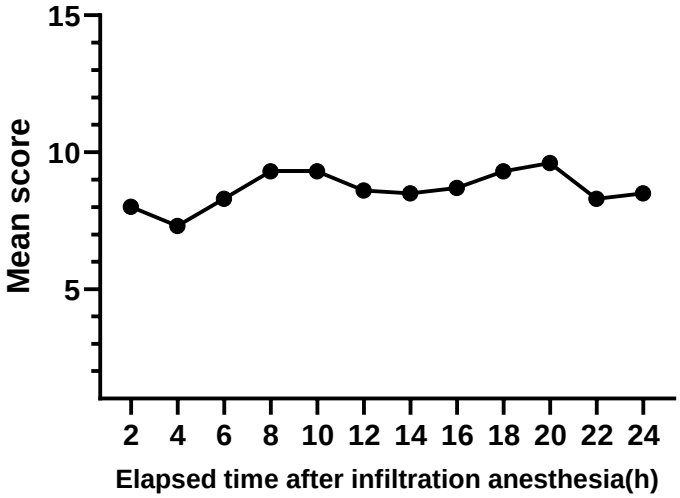

Figure 2. Mean score for 11 dogs during 24 h. The score was measured using a modified version of the Glasgow Composite Measure Pain Scale. No statistical significance was found when comparing each set of values (p < 0.05).

Onset of local sensory recovery after infiltration anesthesia

In modified CMPS-SF, questions 4 and 7 are about touch and needle stimulations (TS and NS, respectively) in the TRH and Bup zones, respectively. The average time of response onset owing to TS was 16.6 ± 2.57 and 8.9 ± 1.65 h in the TRH and Bup zone, respectively. The average time of response onset owing to NS was 22.2 ± 1.28 and 8.9 ± 1.25 h in the TRH and Bup zones, respectively. According to the Mann–Whitney U test, the onset time of sensory recovery owing to TS and NS in both the TRH and Bup zones are significantly different ($p < 0.05$) (Fig. 3).

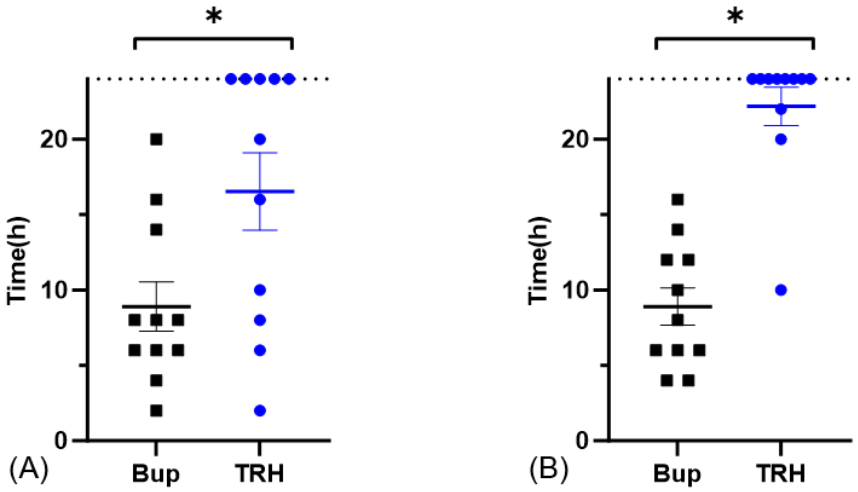

Figure 3. Graph showing the onset time of sensory recovery during touch stimulation (TS) and needle stimulation (NS) in the areas where infiltration anesthesia was performed using bupivacaine combined with temperature-responsive hydrogel (TRH zone) and or bupivacaine alone (Bup zone). (A) Comparison of the onset time of sensory recovery during TS showed significant differences between the TRH and Bup zones ($p < 0.05$). (B) Comparison of the onset time of sensory recovery during NS showed significant differences between the TRH and Bup zones ($p < 0.05$).

Duration of local analgesic effect

The scores of TS and NS were analyzed using repeated measures ANOVA to determine the duration of the local analgesic effect of bupivacaine alone and bupivacaine combined with TRH. For both TS and NS, the TRH zone showed no statistically significant difference between 2 h, when evaluation started, and 24 h, when evaluation ended. During TS, the average score at 2 h was 0.2 ± 0.19 in the Bup zone, and statistical significance was observed at 8 h, with an average score of 1.4 ± 0.32 ($p < 0.05$). During NS, the average score at 2 h was 0, and statistical significance was observed at 6 h, with an average score of 0.6 ± 0.26 ($p < 0.05$) (Fig. 4).

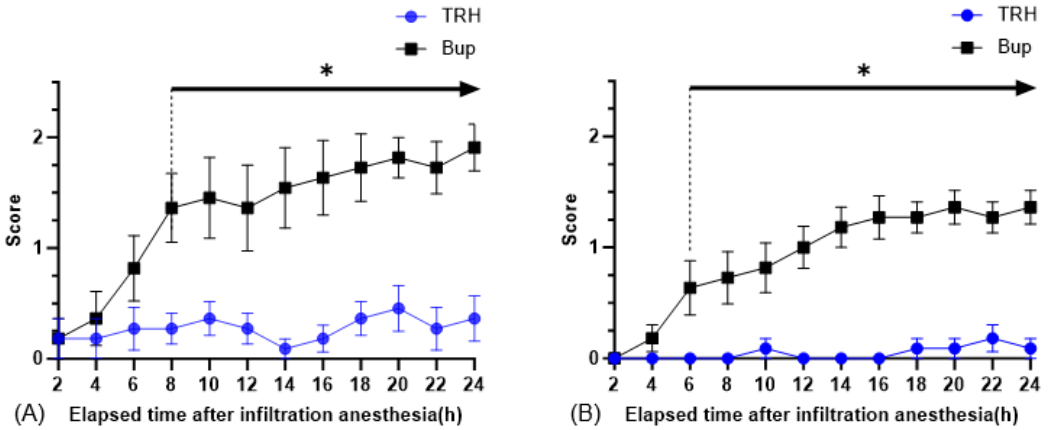

Figure 4. Graph illustrating the changes in scores over the evaluation period during touch stimulation (TS) and needle stimulation (NS) in the areas where infiltration anesthesia was performed using bupivacaine combined with temperature-responsive hydrogel (TRH zone) or bupivacaine alone (Bup zone). (A) During TS, the TRH zone showed no statistically significant difference, whereas the Bup zone showed statistical significance at 8 h after the start of the evaluation ($p < 0.05$). (B) During NS, the TRH zone showed no statistically significant difference, whereas the Bup zone showed statistical significance at 6 h after the start of the evaluation ($p < 0.05$).

Overall degree of local pain

To assess pain severity based on the scores obtained using the CMPS-SF during TS and NS, the mean AUC values for the Bup and TRH zones in 11 dogs were calculated. For TS, the average AUC value in the Bup zone was 14.9 ± 2.52, whereas that in the TRH zone was 3.0 ± 1.09, indicating a significant difference ($p < 0.05$). For NS, the average AUC value in the Bup zone was 10.4 ± 1.51, whereas that in the TRH zone was 0.5 ± 0.26, indicating a significant difference ($p < 0.05$) (Fig. 5).

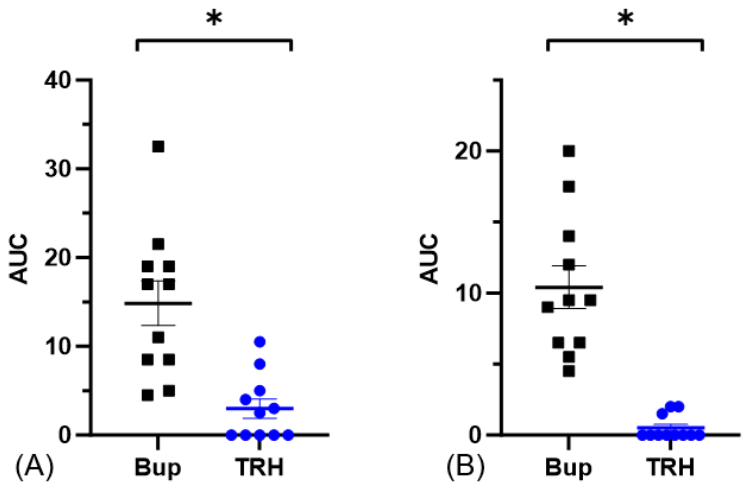

Figure 5. Comparison of the average values of the area under the curve (AUC) for scores obtained during touch stimulation (TS) and needle stimulation (NS) in areas of infiltration anesthesia performed using bupivacaine combined with temperature-responsive hydrogel (TRH) or bupivacaine alone in 11 dogs. (A) During TS, the average AUC value in the Bup zone was 14.9 ± 2.52, whereas that in the TRH zone was 3.0 ± 1.09, indicating a statistical significance ($p < 0.05$). (B) During NS, the average AUC value in the Bup zone was 10.4 ± 1.51, whereas that in the TRH zone was 0.5 ± 0.26, indicating statistical significance ($p < 0.05$).

IV. Discussion

In the present study, systemic pain, measured using the scores obtained during the 24-h evaluation period, in 11 dogs showed no statistical significance, suggesting that postoperative pain management was maintained at a similar level. During the 24-h evaluation period, all dogs in the present study presented with mild systemic pain, possibly greatly influenced by the RLK CRI used in postoperative pain management. A study comparing pain in dogs undergoing postoperative pain management using various drugs, including fentanyl, after ovariohysterectomy (OHE) reported that the group that received fentanyl CRI exhibited the greatest analgesic effect [20]. The efficacy of opioid CRI has been proven in several studies and is regarded as the cornerstone of postoperative pain management in small animal practice [35, 53]. Well-maintained postoperative pain management could minimize the side effects caused by postoperative pain in patients, help maintain stable vital signs, and expedite patient recovery by encouraging early voluntary eating, drinking, and urination. In human medicine, recovery according to pain duration and degree is a factor that affects the development of chronic pain [3, 5, 10, 23, 41, 52]. Therefore, owing to the similarity of the mammalian pain pathway across species, reducing the degree of pain and supporting rapid recovery is important in veterinary medicine [19].

Regarding the onset of local sensory recovery after infiltration anesthesia, the first response in the TRH zone began at 16.6 ± 2.57 and 22.2 ± 1.28 h for TS and NS, respectively, whereas that in the Bup zone began at 8.9 ± 1.65 and 8.9 ± 1.25 h for TS and NS, respectively. The duration of action between the two drugs significantly differed, indicating a significant extension of the effect of TRH for infiltration anesthesia. The onset of local sensory recovery in the Bup zone, where

bupivacaine alone was administered, began much later than the commonly known onset of the effect of bupivacaine. According to previous studies, drugs such as opioids (fentanyl) and NSAIDs manage systemic pain and induce synergistic pain-relieving effects when combined with local anesthetics for multimodal analgesia [6, 24].

The duration of the local analgesic effect was analyzed using repeated measures ANOVA, based on when statistical significance was observed several hours after the evaluation began at 2 h. No statistically significant difference in pain response was observed in the TRH zone during TS and NS between 2 and 24 h. In contrast, statistical significance was observed in the Bup zone at 8 h after the start of TS and at 6 h after the start of NS. These findings suggest that TRH significantly extends the duration of the analgesic effect of bupivacaine. Regarding the onset of local sensory recovery, response onset was observed much earlier during TS than during NS. Regarding the duration of the local analgesic effect, pain response was observed much earlier during TS than during NS. When designing the present study, initially, the sharp stimulation of a needle was assumed to be greater than that of an examiner's finger. However, this assumption was not reflected in the actual results. This could be considered one of the limitations of the present study, indicating the challenge in managing the intensity of the stimulus using the finger each time even if the evaluation was conducted by the same examiner or that the insulin syringe used during NS, being very fine and short in length, could have a very low intensity of stimulation. In a study evaluating pain responses in dogs that underwent OHE after infiltration anesthesia was performed at the incision site using bupivacaine, von Frey filament was used to control these variables [17]. Von Frey filament, bending naturally at certain intensities, can provide a consistent stimulus regardless of the evaluator's strength and has been validated as an

objective measurement in numerous species, both in clinical and laboratory settings [7, 15].

The overall degree of local pain indicated more discomfort in the Bup zone than in the TRH zone during the 24-h evaluation period, possibly due to the extended local analgesic effects of TRH, as previously described, resulting in less pain being felt in the TRH zone over 24 h. In contrast, sensory recovery and pain responses in the Bup zone began as the evaluation progressed into the latter half.

In dogs undergoing local or regional anesthesia as part of multimodal analgesia, the required minimum alveolar concentration of inhalational anesthetics during surgery is reduced [2, 29, 36]. This minimizes common side effects of inhalational anesthetics, such as dose-dependent respiratory depression [49], and less common effects, such as the potential for inhalational anesthetics to partially suppress the cell-mediated immune system, which could otherwise allow for cancer cell proliferation [26, 30]. In addition, it can enhance the safety of anesthesia during surgery and serve as a foundation for successful surgical outcomes. Notably, performing local or regional anesthesia in dogs reduces the need for opioids for perioperative rescue analgesia [11, 18, 38]. This can decrease common side effects caused by opioids, such as nausea, vomiting, constipation, and respiratory depression [4]. Opioid sparing reduces these side effects in patients and is useful in clinical applications in countries or facilities where opioid use is restricted due to strict regulations [19].

Liposome-encapsulated bupivacaine, known as Nocita®, was developed and approved in the United States for commercial use in veterinary medicine and is known to relieve postoperative pain for up to 72 h in dogs and cats [32]. Nocita® has been officially approved for local anesthesia and peripheral nerve block during cranial cruciate ligament surgery and onychectomy in dogs and cats, and

additional research is needed on its pain-relieving effect and safety in procedures such as celiotomy, in which an incision is made in the abdominal wall. In Korea, where Nocita® is unapproved, no options for extending the duration of local anesthesia exist. Therefore, based on the results of the present study, TRH combined with bupivacaine could be beneficial when performing procedures where local infiltration anesthesia is recommended.

In humans, self-reporting pain is the gold standard for assessing pain levels [34]. Compared to human research, in small animal practice, direct communication with the patient is impossible, rendering the accurate and reliable differentiation of pain difficult. Furthermore, pain is regarded as an abstract construct, and there is no established gold standard for its assessment in dogs. Therefore, in small animal practice, many tools have been developed and are being utilized based on composite-based pain scales [8, 16, 21, 37]. The recently published 2022 World Small Animal Veterinary Association The Global Pain Council recommends the use of CMPS-SF, for which validity has been reported [22, 43]. Based on the above evidence, additional items were added to the CMPS-SF in the present study. However, there may be limitations in using CMPS-SF as an absolute indicator because it relies heavily on the subjectivity of the evaluator. Therefore, one of the items in the CMPS-SF used in the present study, “whether or not the animals walked voluntarily when a leash was put on them,” had significantly different responses among animals hospitalized postoperatively. Therefore, many dogs exhibited fear and reluctance towards the medical staff, hospital environment, and ICU cages, even in preoperative stages without significant pain. However, some dogs, despite presenting with local sensation and pain during postoperative pain assessment, were friendly towards the medical staff by wagging their tails and voluntarily walking when a leash was put on them. Therefore, we excluded this

item because it was deemed unsuitable for accurately indicating pain severity. Furthermore, considering the characteristics of the companion dog population in Korea, where approximately ≥88% are small breeds and mostly live indoors [54], these dogs are assumed to be less social and may have a greater fear of unfamiliar people and environments.

Every dog underwent different procedures, and the duration of the operation and instruments used during the operation also varied according to each procedure. A study reported that even within the same surgical procedure, the degree of pain experienced by patients can vary depending on the surgical device used [40]. In addition, in the present study, due to the varying expected duration of each dog's procedure, we standardized the experimental time by setting the point at which all operations were completed and the abdominal muscles were sutured as 0 h. The essence of local anesthesia is to relieve pain by blocking sensory nerves before their action potential is generated and conducted; however, because preemptive pain relief was not achieved physiologically, central sensitization is believed to have occurred and affected the experimental results. In addition, each dog may have varying thicknesses of the skin, subcutaneous tissue, and muscle, which could generate variability due to the different locations of pain receptors. Physiologically, pain is unique to each individual; therefore, the degree of pain that can be felt in response to the same stimulus and the analgesic effects from identical drug metabolism can all vary, possibly due to factors such as individual genetic differences in the number of inherent opioid receptors [31]. In a human study comparing pain after laparoscopic surgery between patients administered PF-72® combined with 0.75% ropivacaine and those administered 0.75% ropivacaine alone for local anesthesia, a method to evaluate visceral pain was lacking [13]. Pain that can occur in dogs undergoing celiotomy can be broadly

categorized into visceral and somatic pain. Notably, somatic pain is described as a sharp pain that arises when nociceptors in the skin and muscle layers are stimulated, whereas visceral pain is evaluated as the moderate-to-severe degree of dull pain resulting from peritoneal traction, diaphragm irritation, and organ incision or resection during the operation. In the present study, despite the dogs receiving considerable relief from somatic pain through a sensory block of the incision site using TRH combined with bupivacaine and systemic analgesic effects of opioids CRI, the possibility that local somatic pain was dulled cannot be ruled out, making visceral pain more prominent within the complex pain mechanism. In human medicine, distinct evaluation methods for somatic and visceral pain are still being studied, and as observed in the present study, evaluating which pain is more prominent between somatic and visceral pain in dogs is impossible. In future studies, conducting various tests under the same surgical and incision length conditions with a larger number of experimental subjects in a clinical setting will be beneficial.

V. Conclusion

Bupivacaine combined with TRH for local infiltration anesthesia during celiotomy can extend the duration of local analgesic effects. According to the results of our study, sensory recovery commences 16–22 h after a single administration of bupivacaine combined with TRH for infiltration anesthesia, and the analgesic effect lasts for more than 24 h. Therefore, when planning a multimodal analgesic strategy specific to a patient, performing infiltration anesthesia using bupivacaine combined with TRH can induce significant benefits in postoperative pain management.

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정중개복술을 시행한 개에서 온도감응형 하이드로겔을 이용한 부피바카인 침윤 마취의 효과

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요약

수술 후 통증 관리는 임상수의학에서 매우 중요하다. 효과적인 통증 완화를 위해 일반적으로 다중 진통 전략이 사용되며, 절개 부위의 국소마취도 그 중 일부이다. 약물 전달 시스템에 대해 많은 연구가 진행되고 있으며, 그 중 ez:AP® (TGel Bio, Co., Ltd., Republic of Korea)는 온도 감응형 하이드로겔 (Temperature-responsive hydrogel, TRH) 로서 저온 (2-8°C)에서는 액체 상태, 고온(30°C 이상)에서 겔 상태로 전환되는 독특한 특성을 나타낸다. 본 연구에서는 이 하이드로겔과 일반적으로 사용되는 국소마취제인 부피바카인을 병용하면 부피바카인 단독 투여에 비해 정중개복술을 받은 개에서 진통 효과가 연

장될 수 있는지 조사하였다. 본 연구에서는 총 11마리의 개에서 정중개복술을 진행하였으며 부피바카인 단독 혹은 TRH와 혼합한 부피바카인을 이용하여 국소 침윤 마취를 실시하였다. 이후 24시간 동안 2시간 간격으로 the short form of the Glasgow composite measure pain scale을 이용하여 통증을 평가하였다. 결과적으로, TRH와 부피바카인을 사용한 한 번의 국소 침윤 마취 후 16-22시간 이내에 감각 회복이 시작되며, 진통 효과는 24시간 이상 지속되었다. 본 연구에서는 개에서 정중개복술 시 부피바카인과 TRH를 혼합하여 국소 침윤 마취 시 국소 진통 효과의 지속 시간을 연장시킬 수 있는 것으로 생각되며, 이는 수술 후 통증 관리에 다양하고 중요한 이점을 가져다줄 수 있다.

중심어: 침윤 마취, 온도감응형 하이드로겔, 부피바카인, 개, 정중개복술