

Topical enrofloxacin solution delays tympanic membrane epithelial migration in healthy dogs

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Abstract

Tympanic membrane epithelial migration (TMEM) is essential for homeostasis and self-cleaning function of the tympanic membrane and external ear canal. Otitis externa is common in small animal practice, and topical preparations are widely used for management. Although several treatments have been reported to alter TMEM rates in dogs, evidence on the effects of topical antibiotics on TMEM is limited. This study evaluated the effect of topical enrofloxacin on TMEM in healthy dogs. TMEM was assessed in both tympanic membranes of three healthy dogs (six ears) using a within-subject design with control and experimental conditions. In the experimental condition, enrofloxacin (5 mg/mL) was administered topically into the ear canal every 12 hours for 14 days, with sterile saline as the control. A 1-week washout period separated the control and experimental conditions. The TMEM rate was evaluated on days 0, 7, 14, 21, and 28 using video otoscopy under sedation. Ink migration distance was measured three times in pixel units from each image, and the mean value was converted to micrometers using a calibration ratio to calculate TMEM rates. The TMEM rates between the control and experimental conditions were compared using both a paired t-test and a Wilcoxon signed-rank test. Repeated measurements of ink migration distances demonstrated excellent intra-observer reliability (average-measures ICC = 0.999). The mean TMEM rate was lower in the enrofloxacin-treated ears ($97.25 \pm 36.54 \mu\text{m}/\text{day}$) than in the control ears ($126.0 \pm 42.07 \mu\text{m}/\text{day}$), representing an approximately 23% reduction. The paired t-test suggested a lower TMEM rate in the enrofloxacin-treated ears (95% CI, -57.12 to $-0.46 \mu\text{m}/\text{day}$; $P = 0.0476$; Cohen's $d_z = 1.066$), whereas the Wilcoxon signed-rank test did not reach statistical significance ($P = 0.0625$). No significant differences were observed between left and right ears in either condition ($P > 0.05$). These preliminary findings suggest that topical enrofloxacin may delay TMEM in healthy dogs. Further studies with larger sample sizes and under different clinical conditions are warranted to clarify these findings.

Keywords: dog, enrofloxacin, epithelial migration, tympanic membrane

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Introduction

Tympanic membrane epithelial migration (TMEM) refers to the outward movement of keratinizing squamous epithelial cells from the tympanic membrane toward the external auditory meatus (Tabacca *et al.*, 2011; Kim *et al.*, 2025). Most epithelial migration on the tympanic membrane proceeds radially from the malleus toward the annular region of the external ear canal (Cole, 2009; Tabacca *et al.*, 2011). This process is essential for maintaining homeostasis and the structural integrity of the tympanic membrane and external ear canal by facilitating the removal of cellular debris and keratin (Tabacca *et al.*, 2011).

Otitis externa is a common dermatologic condition in small animal practice, affecting approximately 7–20% of dogs (Hill *et al.*, 2006; Miller *et al.*, 2012; O'Neill *et al.*, 2021). Although it is often associated with underlying conditions such as allergic skin disease, it is frequently complicated by secondary bacterial infections, most commonly caused by *Staphylococcus pseudintermedius* and *Pseudomonas aeruginosa* (Miller *et al.*, 2012; Tesin *et al.*, 2023; Rosales *et al.*, 2024; Tanveer *et al.*, 2024; Garcias *et al.*, 2025). Topical therapy is generally preferred because it provides high local drug concentrations with minimal systemic adverse effects (Morris, 2004; Bajwa, 2019). These formulations typically contain antibiotics, antifungal agents, and corticosteroids, either alone or in combination. While corticosteroids have been reported to influence the TMEM rate in dogs, the effects of antibiotic agents on TMEM remain unclear (Kim *et al.*, 2025).

Enrofloxacin is one of the most commonly used fluoroquinolone antibiotics in dogs, and it is included in several commercially available topical formulations used in clinical practice (e.g., Baytril Otic®) that contain only antimicrobial components without corticosteroids (U.S. Food and Drug Administration, 2001; Vingopoulou *et al.*, 2018; Lees *et al.*, 2021). Clarifying how antibiotic-only components affect TMEM is clinically important because alterations in TMEM may influence tympanic membrane healing and treatment decision-making. Despite the widespread clinical use of these agents, studies evaluating the effects of enrofloxacin on TMEM in dogs are limited (Dirain *et al.*, 2018).

Therefore, the aim of this study was to evaluate the TMEM rates following topical application of enrofloxacin in dogs and to compare them with those observed in control ears.

Materials and Methods

Animals: Three healthy 2-year-old male Beagle dogs were used in this study. Throughout the study period, the dogs received no medications other than routine heartworm prophylaxis and the topical agents used for the study. All dogs were confirmed to be clinically healthy before the experiment based on physical examination findings, complete blood counts, and serum chemistry profiles.

Before initiating the experiment, the external ear canal and tympanic membrane were assessed using cytology and otoscopic examination (SMART Multiscope, CMS Medical, Korea). Cytology samples collected from the vertical ear canal revealed no

inflammatory cells or bacterial infection in any dog. The external ear canal was scored using the Otitis Index Score (OTIS-3); all dogs scored ≤ 1 throughout the study period, indicating normal findings (Nuttall and Bensignor, 2014). Otoscopic examination confirmed intact, translucent tympanic membranes in all dogs. No signs of otitis externa or adverse reactions related to the topical agent were observed during the study period.

Study design: This study was approved by the Institutional Animal Care and Use Committee (IACUC) of our institution (Approval No. 2025-0353). Six tympanic membranes from three dogs were evaluated, and each tympanic membrane served as its own control in a within-subject crossover design. The control testing was conducted first in all dogs, followed by a 1-week washout period before experimental testing was performed in the same animals. To minimize potential interference between ears, the experimental procedures were initiated only after completion of the control procedures in both ears.

For the control condition, 0.3 mL of 0.9% normal saline (JW NS inj., JW life science, Korea) was instilled into the external ear canal every 12 hours for 14 days. For the experimental condition, injectable enrofloxacin (50 mg/mL; Baytril 50®, BayerKorea, Korea) was diluted with 0.9% normal saline to a final concentration of 5 mg/mL and instilled on the same schedule.

On day 0, animals were sedated intravenously with medetomidine hydrochloride (Domitor®, Zoetis, Finland; 10 µg/kg) and alfaxalone (Alfaxan Multidose®, JUROX, Australia; 1.5–2 mg/kg) for ink placement on the tympanic membrane. A custom-made device consisting of a syringe, needle, and polytetrafluoroethylene (PTFE) Teflon tube (inner diameter 0.5 mm, outer diameter 1 mm, Uxcell, Hong Kong) was used to apply waterproof tattoo ink (Tana Lee Temporary Coloring Tattoo Ink, Oyecoskorea, Korea) to the posterior quadrant of the pars tensa under video otoscopy (Karl Storz Veterinary Endoscopy, USA) (Fig. 1). Tympanic membrane images were recorded using the AIDA-vet video capture system (Karl Storz Veterinary Endoscopy, USA) on days 0, 7, 14, 21, and 28 (± 1 day) to track the migration of the ink. If the ink mark migrated beyond the posterior quadrant during the observation period, only images obtained up to that time point were included in the analysis.

Subsequent imaging sessions were performed under sedation using the same drug combination. During follow-up imaging, previous recordings were displayed simultaneously to ensure consistent angles and fields of view across all time points.

Calibration and evaluation of the TMEM rate:

Tympanic membrane images obtained at each time point were aligned based on the malleus using Adobe Photoshop 7.0 (Adobe Systems, USA). A 2.0 × 2.0 mm piece of 3M index tape was used as a calibration reference to convert pixel distances to actual length measurements. Under sedation, the index tape was placed near the short process of the malleus, and the pixel widths of both the malleus and the index tape were measured to calculate the ratio (Fig. 2).

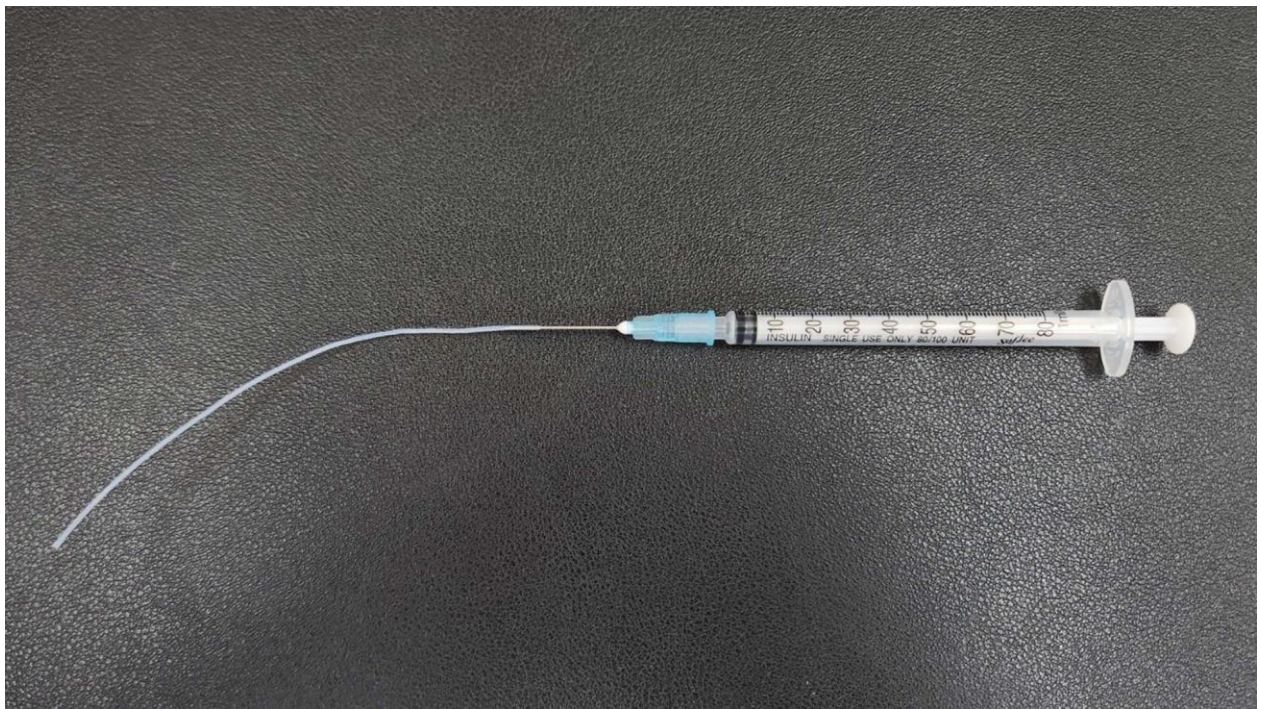


Figure 1 Custom-made device. Constructed using a 1 mL syringe, a 23-gauge needle, and a PTFE (Teflon) tube (0.5 mm inner diameter, 1 mm outer diameter).

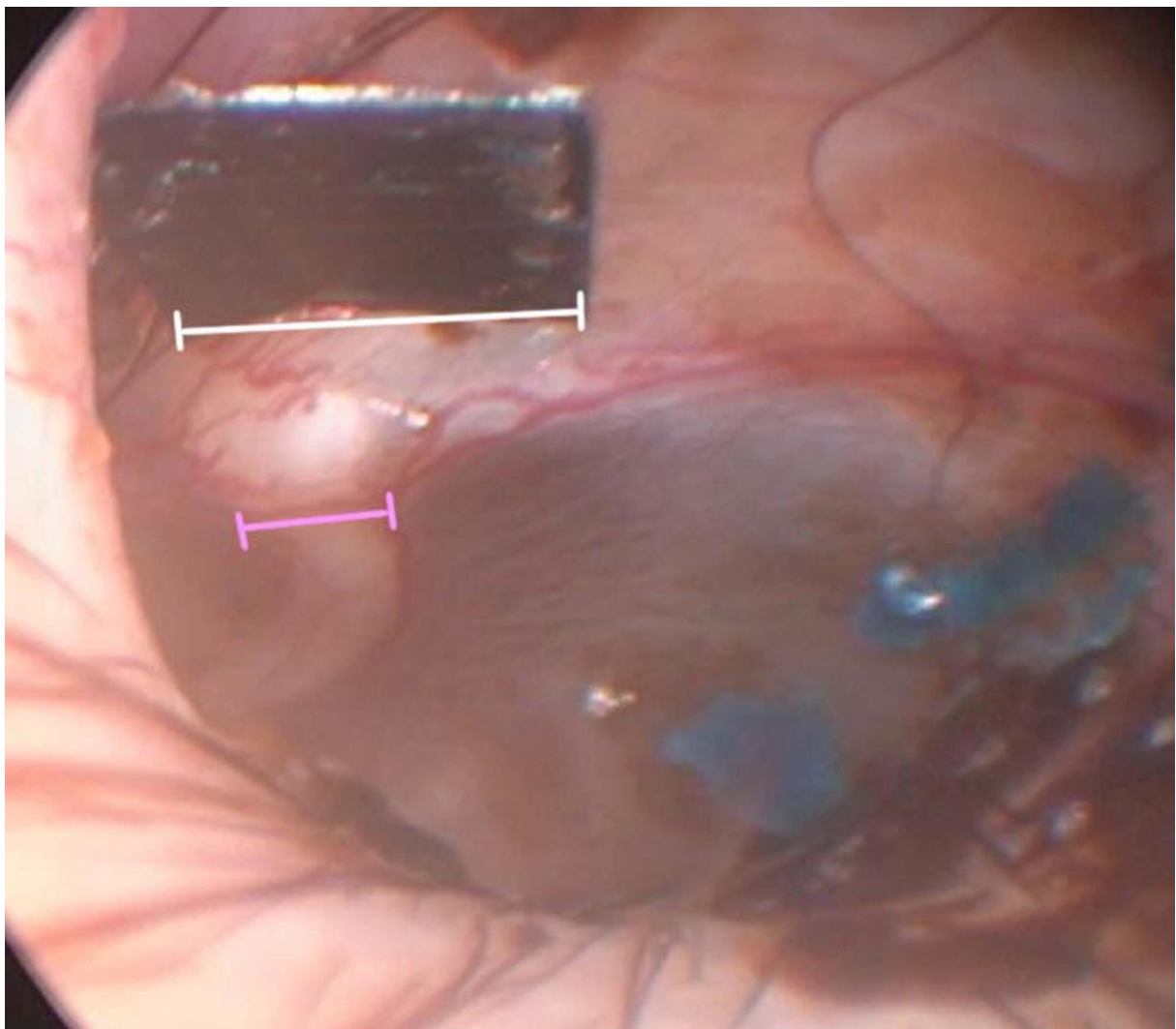


Figure 2 Comparison of pixel widths between the 2.0 × 2.0 mm 3M index tape and the malleus. The 3M index tape is highlighted in white, whereas the malleus is marked in pink.

At each imaging time point, the boundary of the migrated ink was outlined, and the central points of the ink marks were connected to determine the migration distance relative to the malleus. To assess intra-observer reliability, the migration distance was measured three times in pixel units for each image, and the mean pixel distance was converted to micrometers using the calibration ratio. The daily TMEM rate was calculated as total migration distance divided by the observation period and compared between the control and experimental conditions.

Statistical analysis: Statistical analyses were performed using GraphPad Prism version 11.0.1 (GraphPad Software, Boston, MA, USA). To minimize measurement variability associated with subjective assessment, ink migration distances were measured three times from each image in pixel units. Intra-observer reliability of repeated measurements was assessed using the intraclass correlation coefficient (ICC), calculated using the Real Statistics Resource Pack (Release 9.8) implemented in Microsoft Excel for Microsoft 365 (Microsoft Corp., Redmond, WA, USA), based on a two-way mixed-effects model with absolute agreement for average measurements. ICC values were interpreted according to previously published guidelines, with values <0.50 indicating poor reliability, 0.50–0.75 moderate reliability, 0.75–0.90 good reliability, and >0.90 excellent reliability (Koo and Li, 2016). The mean of the three repeated measurements was then used to calculate TMEM rates after conversion to micrometers using the calibration ratio described above. TMEM rates were presented as mean $\pm$ standard deviation (SD). The individual tympanic membrane ($n = 6$) was considered the experimental unit for statistical analysis because each tympanic membrane served as its own control in the crossover design. Given the small sample size, both a

paired t-test and a Wilcoxon signed-rank test were used to compare TMEM rates between the control and experimental conditions. Left-right comparisons within each condition were also analyzed using both tests. Effect sizes for paired comparisons were expressed as Cohen's d_z . $P < 0.05$ was considered statistically significant.

Results

In vivo TMEM was evaluated in six tympanic membranes from three healthy dogs. Throughout the study period, all dogs remained clinically normal, and OTIS-3 scores remained within the normal range (≤ 1). No local hypersensitivity reactions associated with topical administration or any other systemic adverse effects were observed.

Representative ink migration patterns are shown in Figure 3, and TMEM measurements are summarized in Table 1. Intra-observer reliability of repeated pixel measurements of ink migration distances was excellent, with an average-measures ICC of 0.999 (95% confidence interval [CI], 0.998–1.000), indicating excellent intra-observer agreement (Table 2). The mean TMEM rate was lower in the experimental condition ($97.25 \pm 36.54 \mu\text{m}/\text{day}$) than in the control condition ($126.0 \pm 42.07 \mu\text{m}/\text{day}$), representing an approximately 23% reduction. The paired t-test indicated a lower TMEM rate in the experimental group, with a mean difference of $-28.79 \mu\text{m}/\text{day}$ (95% CI, -57.12 to $-0.46 \mu\text{m}/\text{day}$; $P = 0.0476$; Cohen's $d_z = 1.066$). However, the Wilcoxon signed-rank test did not reach statistical significance ($P = 0.0625$).

No significant differences in TMEM were detected between the left and right ears in either condition using both a paired t-test and a Wilcoxon signed-rank test ($P > 0.05$) (Fig. 4).

Table 1 Comparison of calculated daily TMEM rate ($\mu\text{m}/\text{day}$; mean $\pm$ SD) between control and experimental groups.

Side of ear	TMEM rate ($\mu\text{m}/\text{day}$)		
	Control group	Experimental group	Mean difference (95% CI)
Total	126.0 ± 42.07	97.25 ± 36.54	-28.79 (-57.12 to -0.46)
Left ears	112.3 ± 46.95	79.55 ± 31.62	-
Right ears	139.8 ± 40.68	114.9 ± 37.41	-

Table 2 Intra-observer reliability of repeated measurements of ink migration distance

Variable	ICC model	ICC	95% CI	Interpretation
Ink migration distance	Two-way mixed absolute agreement average measures	0.999	0.998–1.000	Excellent

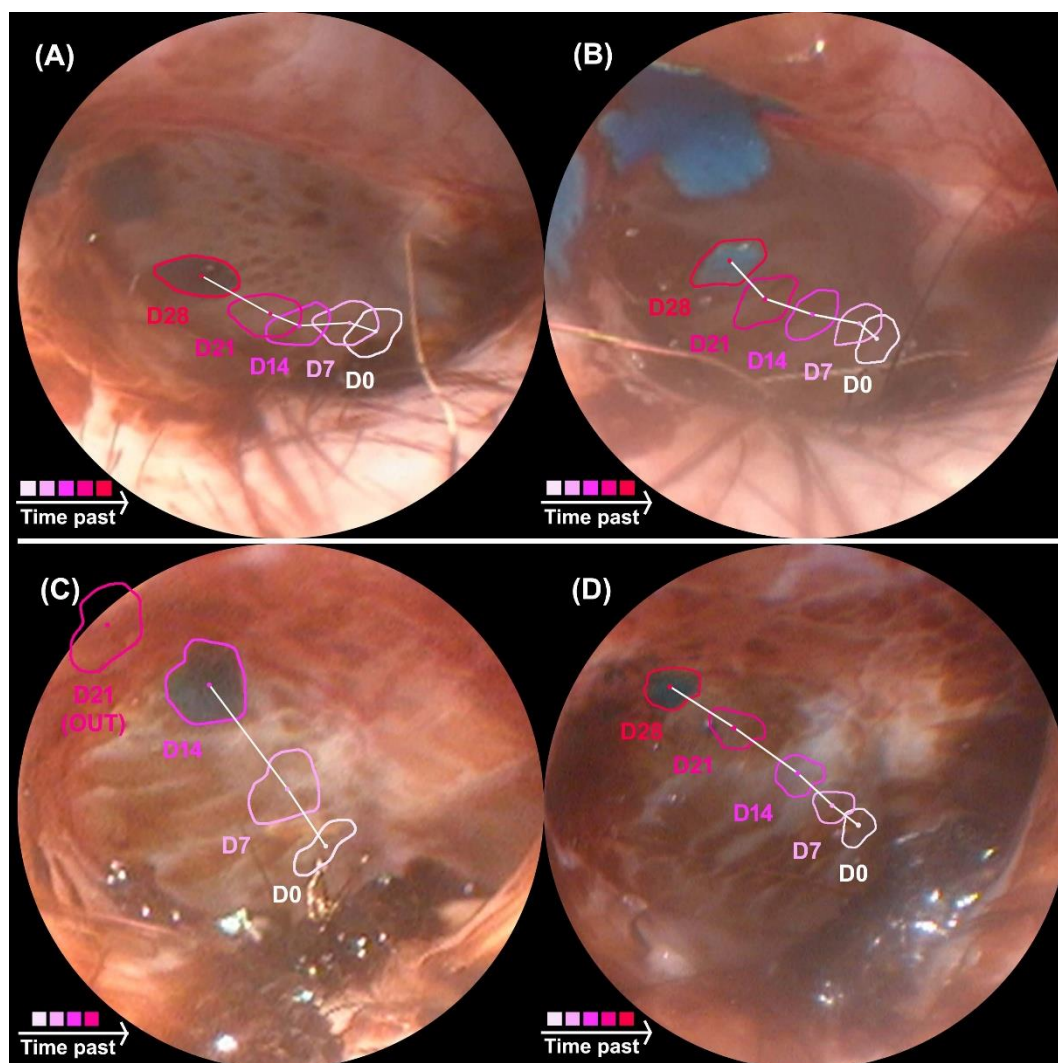


Figure 3 Otoscopy-based gross comparison of TMEM in two individuals. Panels A and B show the control and experimental groups, respectively, in the same ear of one individual; panels C and D show the corresponding comparison in another individual. D indicates day; D0, D7, D14, D21, and D28 denote ink migration on days 0, 7, 14, 21, and 28 after application.

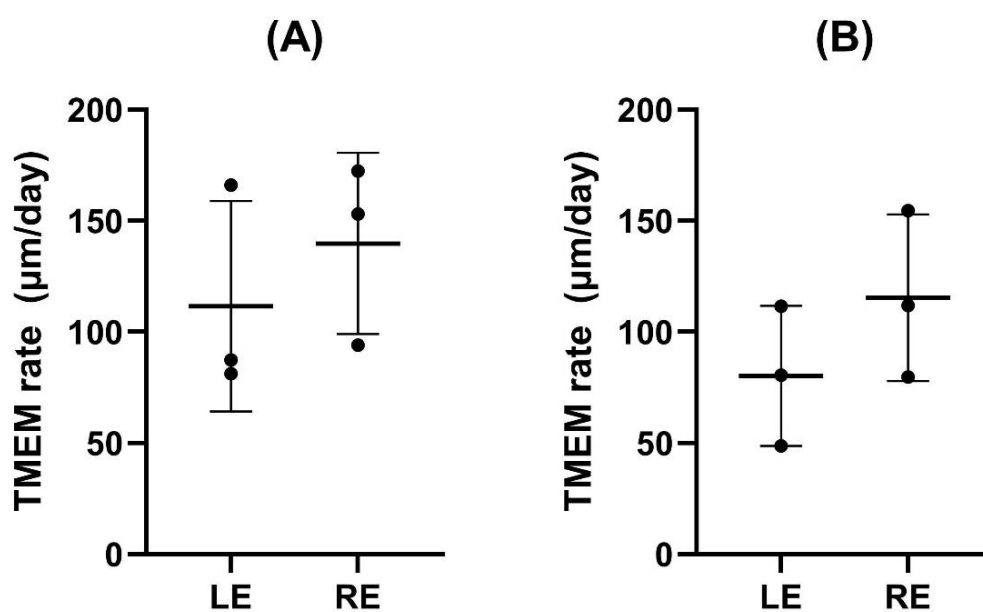


Figure 4 Comparison of the TMEM rate between left and right ears. No significant difference was detected between left ears (LEs) and right ears (REs) in either the control group (A) or the experimental group (B), as determined by both a paired t-test and a Wilcoxon signed-rank test.

Discussion

Several studies have examined the effects of various components, including drugs, adipose tissue-derived mesenchymal stem cell-conditioned media, and epidermal growth factor (EGF), on TMEM (Suh *et al.*, 2022; Kutbi *et al.*, 2024; Kim *et al.*, 2025; Lee and Bae, 2025). However, despite the frequent use of topical antibiotics in clinical practice, evaluations of their effects on epithelial migration and tympanic membrane healing remain limited.

Enrofloxacin was selected for this study because it is one of the most widely used fluoroquinolone antibiotics in veterinary practice (Vingopoulou *et al.*, 2018; Lees *et al.*, 2021). Before commercial topical products such as Baytril Otic® were available, diluted injectable enrofloxacin was used off-label in clinical practice (Vingopoulou *et al.*, 2018).

However, no studies have evaluated TMEM in dogs following topical application of this compound. Furthermore, previous research has reported that solutions prepared by diluting injectable enrofloxacin with sterile normal saline remain stable and retain their antimicrobial efficacy for up to 28 days at room temperature (25°C) (Park *et al.*, 2023). Accordingly, sterile normal saline was used as the diluent, and its application to control condition allowed direct comparison of outcomes with and without enrofloxacin. While previous studies evaluated a higher concentration (10 mg/mL), the concentration used in the present study (5 mg/mL) corresponds to that of Baytril Otic®, which is approved by the U.S. Food and Drug Administration (FDA) as appropriate for topical therapy (U.S. Food and Drug Administration, 2001; Park *et al.*, 2023). This concentration was selected to evaluate the effects of enrofloxacin on TMEM within a clinically relevant dosage range while minimizing potential epithelial toxicity or exaggerated responses that may occur at higher concentrations.

In this study, the application volume for both control and experimental conditions was standardized at 0.3 mL. This volume was selected based on a previous study in which 0.3–0.5 mL was applied according to body weight (Clegg *et al.*, 2023). In addition, the commercially available Baytril Otic® recommends administering 5–10 drops for dogs weighing less than 16 kg (U.S. Food and Drug Administration, 2001). Because the dogs in the present study weighed approximately 10 kg and 0.3 mL corresponds to 7–8 drops, this volume was considered clinically appropriate for the enrofloxacin concentration used.

Previous studies have reported that fluoroquinolone antibiotics may affect TMEM and the healing process (Dirain *et al.*, 2018; Kutbi *et al.*, 2024). Ciprofloxacin has been reported to potentially delay TMEM in rats, whereas ofloxacin has been shown to promote tympanic membrane healing (Dirain *et al.*, 2018; Kutbi *et al.*, 2024). These findings suggest that the effects on TMEM may differ among individual fluoroquinolone agents, highlighting the need for agent-specific evaluation (Dirain *et al.*, 2018).

Fibroblasts and collagen are essential components of the lamina propria of the tympanic membrane and

play key roles in the healing process (Redula *et al.*, 2018). Ciprofloxacin reduced fibroblast viability and collagen expression in mouse tympanic membranes, suggesting potential interference with both epithelial migration and the structural fibroblast–collagen layer that is essential for tympanic repair (Orobello *et al.*, 2016; Dirain *et al.*, 2018; Redula *et al.*, 2018). Enrofloxacin and ciprofloxacin share structural and functional similarities because enrofloxacin is partially metabolized to ciprofloxacin following systemic administration (Cester and Toutain, 1997; Lees *et al.*, 2021). Based on this relationship, it may be hypothesized that enrofloxacin could exert effects on TMEM similar to those reported for ciprofloxacin.

The present study did not directly evaluate tympanic membrane healing after injury. However, the reduced TMEM rate observed with enrofloxacin treatment raises the possibility that similar effects could occur during tympanic membrane repair. Although the underlying mechanism remains unclear, the similarities between enrofloxacin and ciprofloxacin suggest that they may influence the tympanic membrane through related biological pathways (Lees *et al.*, 2021). Further studies are needed to elucidate these mechanisms.

This study evaluated the *in vivo* effects of topical enrofloxacin on TMEM in dogs. In contrast to previous studies in which no solution was applied to control ears, the present study used normal saline as a control, allowing differentiation between pharmacologic effects and mechanical effects associated with topical application (Kim *et al.*, 2025; Lee and Bae, 2025). In addition, TMEM was assessed using indirect indicators, enabling repeated evaluation of the same animals without the need for euthanasia or tissue collection.

The magnitude of TMEM reduction observed in this study should be interpreted in the context of previous reports. Previous studies have demonstrated marked changes in TMEM, including approximately 60% increase following adipose tissue-derived mesenchymal stem cell-conditioned media or EGF application, and a 54% reduction following dexamethasone treatment (Kim *et al.*, 2025; Lee and Bae, 2025). In contrast, the present study showed a more modest reduction of approximately 23% in the experimental ears relative to controls. Although the present findings suggest that topical enrofloxacin may delay TMEM, they do not necessarily indicate a pronounced biological inhibitory effect. Furthermore, the difference between the paired t-test and the Wilcoxon signed-rank test may be related to the small sample size and the conservative nature of non-parametric tests. Therefore, caution against overinterpretation is warranted. Rather, the present results should be regarded as preliminary evidence suggesting that enrofloxacin may reduce TMEM.

This study has several limitations. The small sample size and evaluation of only a single concentration of enrofloxacin (5 mg/mL) limit the generalizability of the findings. Larger studies assessing multiple concentrations are needed to better characterize dose-dependent effects on TMEM. In addition, because both ears originated from the same dogs, they may not be fully independent biological

replicates. Although each tympanic membrane served as its own control in the crossover design, the possibility of pseudoreplication should be considered when interpreting the statistical results. An evidence-based optimal washout interval for TMEM studies has not been formally established. Although a total of 3 weeks elapsed without exposure to any new topical agent before initiation of the experimental phase, including an additional 1-week washout period, this interval was selected as a conservative measure based on pragmatic considerations of the crossover design. Furthermore, the topical solution was prepared by diluting an injectable formulation rather than using a commercial otic product. Differences in formulation characteristics, such as excipients or additives, may have influenced TMEM in a manner that differs from an otic preparation. Finally, this study was conducted in healthy dogs with intact tympanic membranes. Therefore, the effects of topical enrofloxacin on TMEM in patients with structural abnormalities or perforations of the tympanic membrane, as well as in patients with concurrent inflammation or infection of the ear canal, were not evaluated. As these conditions may influence TMEM and local drug exposure, the present findings should be interpreted with caution when applied to these patients. Further studies involving dogs with these pathological conditions are warranted.

In conclusion, in this study, topical application of 5 mg/mL enrofloxacin was associated with lower TMEM rates in healthy dogs. These preliminary findings suggest that topical enrofloxacin may delay TMEM. However, given the small sample size, these findings should be interpreted cautiously and require confirmation in larger studies under various clinical conditions.

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Declaration of artificial intelligence use: During the preparation of this work, the authors used ChatGPT (OpenAI) for language editing and formatting assistance. The authors take full responsibility for the integrity, accuracy, and originality of the work.

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