Canine Periodontal Disease Control Using a Clindamycin Hydrochloride Gel

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Summary:
Stabilizing or reducing periodontal pocket depth can have a positive influence on the retention of teeth in dogs. A topical 2% clindamycin hydrochloride gel (CHgel) was evaluated for the treatment of periodontal disease in dogs. The CHgel formulation provides for the sustained erosion of the matrix, but also flows into the periodontal pocket as a viscous liquid, and then rapidly forms a gel that has mucosal-adhesive properties and also may function as a physical barrier to the introduction of bacteria. A professional teeth cleaning procedure including scaling and root planing was done in dogs with one group receiving CHgel following treatment. Periodontal health was determined before and after the procedure including measurement of periodontal pocket depth, gingival index, gingival bleeding sites, and number of suppurating sites. There was a statistically significant decrease in periodontal pocket depth (19%), gingival index (16%), and the number of bleeding sites (64%) at 90-days in dogs receiving CHgel. Additionally, the number of suppurating sites was lower (93%) at 90-days for the group receiving CHgel. The addition of CHgel effectively controlled the bacterial burden (e.g., Fusobacterium nucleatum) at both day 14 and 90. Gingival cells in culture were shown to rapidly incorporate clindamycin and attain saturation in approximately 20-minutes. In summary, a professional teeth cleaning procedure including root planning and the addition of CHgel improves the gingival index and reduces periodontal pocket depth. J Vet Dent 28(4); 224 - 229, 2011

Introduction
Dental disease is the number one disease diagnosed in adult dogs and cats1 with more than 80% of dogs and 70% of the cats developing oral disease by age three.1 Periodontal disease is a potentially serious condition that threatens most dogs and is among the most common seen in veterinary medicine. In an observational study of 31,484 dogs at private veterinary clinics, 20.5% had dental calculus, 19.5% had gingivitis, and 2.2% had periodontal disease.1

Untreated, periodontal disease in the dog is a potentially progressive condition, often beginning with halitosis (oral malodor) as the first detectable sign.2 Periodontal disease progresses through stages, including plaque formation, calculus or tartar accumulation, inflammation of the gingiva, periodontal pocket formation, alveolar bone resorption, tooth mobility, and tooth loss.3 The presence and severity of periodontal disease commonly increases with the age of the dog if treatment intervention is not pursued. Because periodontitis is complex, progressive and has been associated with diseases of other vital organs, such as the kidney, liver, and heart4, delaying the progression (as assessed by either no change, or reduced pocket depth) would logically be expected to contribute to improved general oral health of the canine patient. Presently, periodontal disease is treated frequently by scaling and root planning (periodic removal of plaque), with or without concurrent oral or topical antibiotic therapy.

Acquired pellicle, a film of salivary proteins, starts to form on the exposed dental surfaces within hours of a professional dental cleaning. Bacteria, food particles, and other cells colonize this pellicle leading to plaque formation, the first step in the cascade of events leading to tooth loss. Most subgingival organisms associated with gingivitis in both dogs and cats have been shown to be aerobic gram-positive (Staphylococcus or Streptococcus species) or anaerobic gram-negative bacteria.4-5 Antimicrobials used to suppress subgingival plaque accumulation should be effective against gram-positive aerobes, as well as gram-negative anaerobes, which are the initiators of gingival inflammation and destruction.4

Clindamycin hydrochloride has been used in conjunction with dental procedures because it is active against staphylococcal, anaerobic (gram-positive and gram-negative), and polymicrobial dental infections.6-7 Its wide spectrum of activity, excellent tissue and bone penetration, and efficacy in purulent environments makes it well-suited for this use.7-8

In the United States, clindamycin is approved for use in treating dental infections caused by susceptible bacteria in both dogs and cats.3 Clindamycin has been shown to have in vitro activity against canine isolates of aerobic gram-positive cocci (Staphylococcus aureus, S. epidermidis, and streptococci, except Streptococcus faecalis), anaerobic gram-negative bacilli (Porphyrmonas, Bacteroides, and Fusobacterium species), anaerobic gram-positive bacilli (Propionibacterium, Eubacterium, and Actinomyces species), and microaerophilic gram-positive cocci (Peptococcus and Peptostreptococcus species and microaerophilic streptococci), and most Clostridium perfringens.7,9,11

As mentioned above, current therapy includes scaling, root planing, and polishing under anesthesia with subgingival curetage and oral antibiotics. There are other commercially available treatments for early and late-stage periodontitis.12 Some of these treatment modalities require practice to administer.11 The product evaluated here is a recently introduced new and unique 2% clindamycin hydrochloride gel (CHgel) designed to undergo liquid-to-gel transition at body temperature, stay in periodontal pockets by adhering to its walls, and dissolve in saliva and other fluids over a period of time. This study was conducted to determine the benefit, if any, of combining the CHgel with scaling, root planing, and polishing (professional teeth cleaning procedure) over professional teeth cleaning alone as determined by improvements in gingival index and pocket depth measurements.
Materials and Methods

**Animals**

Forty-eight client-owned dogs with signs of periodontal disease were randomly assigned to the professional teeth cleaning with scaling, root planning, and polishing (cleaning only) (16 dogs) or to the cleaning + CHgel group (32 dogs) [Table 1]. Dogs were considered to be healthy and able to undergo multiple anesthetic procedures, and had early (stage 2) periodontal disease or a periodontal pocket depth > 3-mm and < 6-mm of attachment loss based on dental radiographic assessment. Any dog with a current history of cancer, uncontrolled metabolic disease (e.g., diabetes), autoimmune, or immunosuppressive disease; receiving a dental professional cleaning within the last 75-days; receiving oral or parenteral antibiotics within the past 60-days; receiving oral or parenteral short-acting steroids within the past 14-days; receiving oral or parenteral long-acting steroids within the past 30-days; and, any female intact dog in estrus within the past 30-days was ineligible to participate in the study. During the initial oral examination with dogs under general anesthesia, any dog with more than 3 pockets of > 6-mm in any quadrant, a tooth mobility index of 2 to 3 for the treated tooth, or a dog considered to require oral antimicrobial therapy was excluded.

Twice as many dogs were in the CHgel treatment group, relative to the control group, to maximize experience and practice using this new product. All dogs had a CBC and serum chemistry evaluation 7-days prior to enrollment in the study. None of the dogs had any obvious underlying disease based on physical and laboratory examinations.

In addition, the CHgel (periodontal filler) was applied in all dogs with periodontal pockets > 3-mm and < 6-mm in depth for the cleaning + CHgel group on day 0. Differences in groups were compared at day 0 versus day 90. The depth of the periodontal pocket was measured using a constant electronic probe with a computer automatically capturing all measurements. No other oral antibiotics were used during the course of this 90-day study. Owners of the dogs agreed to cooperate with the investigations required to complete the study over the 90-day period.

**Experimental Design**

A member of the clinic staff assigned treatments and discussed administration of the protocol with the dog owners. The principal investigators remained blinded throughout the study period. The CHgel was applied topically (filled) in the pockets until the gel was seen at the free gingival margin as described in the manufacturer’s instructions. Data were recorded by one of the two clinical investigators. The study was blinded, with (SM) performing the treatment, and (SC) scoring the indices.

On initial assignment to the study, each of the following procedures was performed: anesthesia (premedicated with either morphine and atropine, or morphine, atropine, and dexmedetomidine, induction with propofol (3.0 mg/lb IV), maintained on isoflurane, subgingival and gingival plaque removal, scaling and curettage, polishing, full-mouth periodontal charting, gingival indexing, and full-mouth radiographs. Follow-up assessments were done at days 14 and 90. On day 14, physical examinations were conducted and oral evaluations (no measurements) were done in non-sedated dogs. On day 90, dogs were anesthetized as described previously for gingival indexing and recording of periodontal pocket depths. In addition, periodontal pockets were sampled on day 14 and day 90 in 10 dogs from each group for the purpose of determining the trend in bacterial load using a commercially available test kit. This test involves introducing the manufacturer’s paper probe or point (size #50) into the periodontal pocket for 10-seconds. Colonized bacteria adhere to the test probe and then DNA, which identify a specific bacterium, are subsequently quantified. The probes were tested for eleven periodontopathogenic species. All paper probes were transported in sterile vials to a testing facility and screened for bacterial species in the red complex.

**Periodontal Disease Assessment**

The primary outcome measures in the present study were measurement of pocket depth and gingival index. Secondary outcome assessments of overall periodontal health included determination of the number of bleeding and suppurating sites and the temporal trend in bacterial load following either professional teeth cleaning alone or professional teeth cleaning plus the CHgel.

Periodontal disease stage 1 was defined as gingivitis with inflammation of the gingival tissue characterized by changes in color (red), gingival form, position, surface appearance, and the presence of bleeding and/or exudates. Pocket depth may be minimal (< 2 mm). Periodontal disease stage 2 was defined as early periodontitis with progression of the gingival tissue inflammation into the deeper periodontal structures and alveo-

**Table 1**

Breeds, gender, and age of client-owned dogs used in this study.

<table>
<thead>
<tr>
<th>Breed</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Bernard</td>
<td>1</td>
</tr>
<tr>
<td>German Shepherd</td>
<td>4</td>
</tr>
<tr>
<td>Australian Shepherd</td>
<td>1</td>
</tr>
<tr>
<td>Boxer</td>
<td>5</td>
</tr>
<tr>
<td>Schnauzer</td>
<td>1</td>
</tr>
<tr>
<td>Pembroke</td>
<td>2</td>
</tr>
<tr>
<td>Poodle</td>
<td>3</td>
</tr>
<tr>
<td>Terrier</td>
<td>11</td>
</tr>
<tr>
<td>Welsh/Corgi</td>
<td>1</td>
</tr>
<tr>
<td>Beagle</td>
<td>2</td>
</tr>
<tr>
<td>Chihuahua</td>
<td>1</td>
</tr>
<tr>
<td>Labrador Retriever</td>
<td>2</td>
</tr>
<tr>
<td>Bicho Frise</td>
<td>1</td>
</tr>
<tr>
<td>Border/Collie</td>
<td>1</td>
</tr>
<tr>
<td>Chow Chow</td>
<td>1</td>
</tr>
<tr>
<td>Afghan Hound</td>
<td>1</td>
</tr>
<tr>
<td>Golden Retriever</td>
<td>1</td>
</tr>
<tr>
<td>Collie</td>
<td>1</td>
</tr>
<tr>
<td>Basenji</td>
<td>1</td>
</tr>
<tr>
<td>Shih Tzu</td>
<td>3</td>
</tr>
<tr>
<td>American Eskimo</td>
<td>1</td>
</tr>
<tr>
<td>Dachshund</td>
<td>1</td>
</tr>
<tr>
<td>Italian Greyhound</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 3.69 SEM 0.15</td>
<td>F 26  M 22</td>
</tr>
</tbody>
</table>

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lar bone crest, with slight bone loss. Pocket depths up to 4-mm with less than 25% loss of attachment level. Irreversible, but arrestable, destruction. Periodontal disease stage 3 was defined as moderate to severe periodontitis with increased destruction of periodontal structures with pocket depths of 4 to 6-mm and beyond; 25-50% loss of attachment level with varying degrees of furcation involvement. Tooth mobility is evident.15,16

The gingival index assigned gingival scores of 0 to 3 to buccal, lingual, mesial, and distal areas of all the teeth. Scores for the four areas were added and then divided by four to equal the gingival index for a tooth. Then scores for all the examined teeth were added and divided by the number of teeth to give the gingival index for the mouth. Scores were assigned according to the following criteria: 0 = absence of inflammation; 1 = mild inflammation; slight change in color and little change in texture; no bleeding on probing; 2 = moderate inflammation; moderate glowing, redness, edema and hypertrophy; bleeding on probing; 3 = severe inflammation; marked redness and hypertrophy; tendency for spontaneous bleeding; ulceration.17

Pocket depth, as mentioned above, was measured in millimeters (mm) using the constant electronic probe connected to a computer, which automatically captured all of the measurements when a foot switch was depressed. The probe was gently inserted at the free gingival margin until resistance was encountered. Six sites (mesial-buccal, mid-buccal, distal-buccal, mesial-lingual, mid-lingual, and distal-lingual) around the circumference of each tooth were measured.2 Scores from sites with greater > 3-mm, but < 6-mm depth, were averaged to produce a mean pocket depth. The pocket depth measurement was done while dogs were under anesthesia on days 0 and 90.

Professional teeth cleaning was performed using ultrasonic scaling for supragingival cleaning. A combination of ultrasonic scaling and hand scaling were used for subgingival scaling. The technique used the lateral edge of the thin tip, beginning the stroke at the gingival margin. Vibrations broke the deposit and dislodged it from the tooth surface. Scaling was performed with light pressure, and the tip was moved over every square millimeter of the root surface to remove bacteria, plaque, and calculus. This procedure was performed on both days 0 and 90.

Gingival Cell Uptake Study of Clindamycin Hydrochloride

Uptake studies were conducted on confluent HGF-cell monolayers grown on 12 well plates. In the uptake experiments, cell monolayers grown on 12 well plates were rinsed with Dulbecco’s modified phosphate buffer saline (DPBS containing 110 mM NaCl, 0.03 mM KCl, 7.5 mM Na₂HPO₄, 1.5 mM KH₂PO₄, 1 mM CaCl₂, 0.5 mM MgSO₄, 20 mM HEPES and 5 mM glucose; pH 7.4) three times over the course of 10-min. Two mL of [³H]-clindamycin in DPBS (1 μCi/mL) was placed in each well (initially containing 8.3 x 10⁴ cells per well) and incubated for an appropriate time period (5 to 30-min) at 37°C. Following incubation, the cell monolayer was rinsed 3 times with ice-cold stop solution (210 mM KCl and 2 mM HEPES buffer) to terminate the cell uptake experiment. Cells were lysed overnight with 1 mL of 0.1% (w/v) Triton X-100 in 0.3 N NaOH per well at room temperature. A 500 μL sample from each well was then transferred to scintillation vials containing 5 mL scintillation cocktail. The rest of the samples were used

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### Table 2
Results of periodontal pocket depth measurements and gingival index scores in dogs treated with 2 % clindamycin hydrochloride gel (CHgel).

<table>
<thead>
<tr>
<th>Day</th>
<th>Cleaning</th>
<th>Cleaning + CHgel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pocket Depth (mm) ± SEM</td>
<td>Gingival Index ± SEM</td>
</tr>
<tr>
<td>0</td>
<td>3.69 ± 0.05</td>
<td>1.44 ± 0.13</td>
</tr>
<tr>
<td>90</td>
<td>3.57 ± 0.08</td>
<td>1.13 ± 0.09</td>
</tr>
<tr>
<td>0</td>
<td>3.58 ± 0.07</td>
<td>1.56 ± 0.10</td>
</tr>
<tr>
<td>90</td>
<td>2.92 ± 0.26*</td>
<td>1.31 ± 0.08*</td>
</tr>
</tbody>
</table>

*P < 0.05 when compared with the corresponding day 0 value.

### Table 3
Results of the number of bleeding and suppuration sites in dogs treated with 2 % clindamycin hydrochloride gel (CHgel).

<table>
<thead>
<tr>
<th>Day</th>
<th>Cleaning</th>
<th>Cleaning + CHgel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bleeding sites ± SEM</td>
<td>Suppurating sites ± SEM</td>
</tr>
<tr>
<td>0</td>
<td>12.19 ± 3.53</td>
<td>0.25 ± 0.19</td>
</tr>
<tr>
<td>90</td>
<td>6.13 ± 1.48*</td>
<td>0.13 ± 0.13</td>
</tr>
<tr>
<td>0</td>
<td>8.59 ± 2.55</td>
<td>0.44 ± 0.34</td>
</tr>
<tr>
<td>90</td>
<td>3.06 ± 0.55*</td>
<td>0.03 ± 0.03</td>
</tr>
</tbody>
</table>

*P < 0.05 when compared with the corresponding day 0 value.

### Table 4
Periodontal pocket depth changes in dogs treated with 2 % clindamycin hydrochloride gel (CHgel).

<table>
<thead>
<tr>
<th>Type of Improvement</th>
<th>Cleaning</th>
<th>Cleaning + CHgel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (&lt; 0.2 mm)</td>
<td>69 %</td>
<td>66 %</td>
</tr>
<tr>
<td>Medium (0.2 - 0.5 mm)</td>
<td>31 %</td>
<td>28 %</td>
</tr>
<tr>
<td>High (&gt; 0.5 mm)</td>
<td>0 %</td>
<td>6 %</td>
</tr>
</tbody>
</table>

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...
for protein estimation. Samples were then analyzed by liquid scintillation spectrophotometry and the rate of uptake was normalized to the protein content of each well. The amount of protein from the ‘best-fit’ regression line drawn through the data points prior to the attainment of saturation associated with cell uptake.

For each dog, overall pocket depth and gingival index scores were recorded on days 0 and 90. The gingival margin of each tooth was scored at the buccal, lingual, mesial, and distal locations. Scores were then converted to a gingival index for a specific tooth by taking the average of these four sites. At each time point, these scores were averaged to provide an overall gingival index for the mouth of each dog. For pocket depth, although the whole mouth was charted, only measurements with a reading > 3-mm, but < 6-mm, were averaged to represent the mean pocket depth. Gingival index and pocket depth served as the primary decision variables for the analysis in the current investigation.

Presence of bleeding on probing and suppuration were noted during the charting procedure for the whole mouth as a “yes” or “no” response at the same locations as the pocket depth. These responses for each location were then coded (1 for yes and 0 for no) and summed to convert them to number of bleeding and suppurating sites per tooth, which were then averaged to represent the mean number of bleeding and suppurating sites for the mouth.

Bacterial load was determined on pooled probe samples for each dog. The results were semi-quantitative and categorized as (-), (+), (++) , (+++) , and (++++) , to represent <10⁴, 10⁴, <10⁵, <10⁶ and >10⁷ pathogen concentrations, respectively. The categories were then coded (0, 0.5, 1, 2, and 3, respectively), normalized for the number of sites sampled, and averaged to obtain the bacterial load/site. The results were then expressed as a percentage of total pathogen concentration for each bacterial species at each time point.

Statistical Analysis

All analyses were performed using either the statistical software package or the data analysis software. Measurements collected at the time of enrollment (day 0) provided an indication of baseline levels in each group. Therefore, day 90 measurements in each group were compared with their respective day 0 measurements using a paired t-test. P-values of < 0.05 were considered significant.

Results

The analysis indicated that using CHgel, after professional teeth cleaning and drying of the whole mouth, produced a significant reduction in pocket depth (19 %), gingival index (16 %), and the mean number of bleeding sites (64 %). In addition, using CHgel after professional teeth cleaning also lowered the mean number of suppurating sites (93 %) at day 90, however not significantly different from the control group. Results are summarized in the Tables 2 and 3, and Fig. 1.

An analysis of the type of improvement in pocket depths of the entire mouth showed that adding CHgel to professional teeth cleaning shifts the improvement more towards the high type (Table 4). The greatest improvement, as defined by > 0.5-mm reduction in the pocket depth, occurred in the professional teeth cleaning + CHgel group. Professional teeth cleaning (including scaling and root planning) only for periodontal pockets consistently produced < 0.2-mm reduction in pocket depth.

The trend in bacterial load in these two groups indicated Treponema denticola and Fusobacterium nucleatum were most prevalent. The remaining bacteria, due to their sporadic occurrence, were included in the ‘other’ group (Fig. 2). Although not significant, there was a trend for the professional teeth cleaning + CHgel group to have a lower bacterial burden at day 14 and...
90 (as evidenced by the smaller band widths). Colonization of *Fusobacterium nucleatum*, bacteria found in the plaque associated with dental disease, was controlled with the inclusion of CHgel (smaller band widths compared with the band widths of the professional teeth cleaning only group) [Fig. 2].

The *in vitro* gingival cell uptake study indicated that gingival cells very rapidly incorporate sufficient amounts of clindamycin and reach saturation in approximately 20-min (Fig. 3). The rate of clindamycin uptake by cultured gingival cells was 77 pmol/min/mg of protein (Fig. 3). This suggests that gingival cells may act as a reservoir and assist with maintaining gingival crevicular levels of clindamycin for limiting bacterial colonization.

Discussion

This study evaluated whether the addition of a slowly eroding preparation of CHgel to a standard professional teeth cleaning procedure for periodontal disease in dogs was more efficacious than professional teeth cleaning alone. CHgel may have the added advantage of potentially acting as a physical barrier to bacterial colonization in the periodontal pocket, since the formulation exists as a mobile viscous gel shortly after placement in the pocket. This thickened ‘gelatinous-type’ matrix may impede bacterial translocation since the three-dimensional polymer gel matrix would represent a significant hindrance or barrier to the diffusion of bacteria (0.2 to 2.0 μm diameter). A single drug molecule has a much smaller overall hydrodynamic radius than does a bacteria, and yet the drug molecule’s diffusion is severely hampered or restricted through the polymer network.19 This restriction to free diffusion of a drug molecule through the polymer matrix is partly responsible for the protracted release of clindamycin from the gel.19

Results of the present investigation would seem to suggest that the CHgel treatment, in conjunction with a professional teeth cleaning procedure, may slow the progression of periodontal disease by more effectively eliminating the bacterial burden than professional teeth cleaning alone. CHgel may have the added advantage of potentially acting as a physical barrier to bacterial colonization in the periodontal pocket, since the formulation exists as a mobile viscous gel shortly after placement in the pocket. This thickened ‘gelatinous-type’ matrix may impede bacterial translocation since the three-dimensional polymer gel matrix would represent a significant hindrance or barrier to the diffusion of bacteria (0.2 to 2.0 μm diameter). A single drug molecule has a much smaller overall hydrodynamic radius than does a bacteria, and yet the drug molecule’s diffusion is severely hampered or restricted through the polymer network.19 This restriction to free diffusion of a drug molecule through the polymer matrix is partly responsible for the protracted release of clindamycin from the gel.19

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More recently, a different antimicrobial was evaluated to treat periodontitis in canines.25 A commercial product containing doxycycline was placed in the periodontal pockets of beagle dogs and assessment of gingivitis index, gingival crevicular fluid, probing depth, and attachment loss was done at 6 and 12-weeks after the treatment. However, these authors did not evaluate the topical treatment of doxycycline alone, because all dogs in both the treatment and control groups were pre-treated with oral clindamycin prior to the start of the investigation. Moreover, in addition to pre-treatment with oral clindamycin, pre-selected teeth in all dogs contained in both groups underwent cleaning, scaling, polishing, and curettage prior to assessing the therapeutic efficacy of doxycycline.26 It was concluded that the local application of doxycycline complements traditional curettage therapy in a reasonable and effective way and can significantly improve treatment success, especially in regard to pocket depth reduction and attachment gain.26 While we did not assess attachment gain in the present study, we did find a significant reduction in the pocket depth, gingival index, bleeding sites, and a lower number of suppurating sites at day 90.

Finally, in another study using doxycycline in beagle dogs with severe periodontitis, it was demonstrated that the clinical
response from a biodegradable polymeric system containing 10 % doxycycline hyclate (treatment group) was superior to the non-drug-loaded polymer system alone (control group) in terms of bleeding on probing and probing depth.27 The probing depth reduction was suggested to have occurred primarily due to a gain in clinical attachment.27 Although these authors followed the periodontal health of the beagle dogs for 4-months following the 7-day doxycycline treatment period, they continued periodontal maintenance by toothbrushing the treated sites three times each week. Therefore, it would appear speculative to conclude the effect(s) of doxycycline treatment alone at various times (1, 2, 3, and 4-months) following application of the doxycycline drug delivery system. Although the system employed was biodegradable, the authors elected to remove the residual polymer at day 7 following the 1-week treatment period.27 The CHgel used in this study does not require removal from the application site as it is biodegradable and biocompatible.

The CHgel used in this study has benefits that include gelation (solution to gel transition); mucoadhesive properties; a potential physical barrier to minimize the initial intrusion and migration of diffusing bacteria; sustained erosion of the matrix over 7 to 10-days; ease of application; biocompatibility, bioreabsorption, and nontoxicity; and efficacy in the control of the periodontal pocket bacterial burden at both day 14 and day 90. This clinical study demonstrates improved periodontal disease control in dogs.

References

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