Analysis of Capacity of Novel, Antioxidant Toothpaste to Reduce Gingival Inflammation in Pilot, Small-population Clinical Study: Comparison to Levels of Gingival Inflammation Reduction Reported in Historical Control and Therapeutic Toothbrushing Studies.

Anita H. Daniels, R.D.H.†
Adjunct Clinical Instructor
University of Miami, School of Medicine
Department of Dental Implants

Steven R. Jefferies M.S., D.D.S.†
Temple University, School of Dentistry
Professor, Department of Restorative Dentistry
Dir. of Clinical Research & Biomaterials Research Laboratory

Background

Despite decades of effort, gingivo-perio dysfunction remains a significant threat to oral health, lifetime tooth retention and systemic health including effects on vascular endothelium and complications of pregnancy.1,2,3,4,6 Treatment of this spectrum of disorders typically involves oral hygiene measures designed to reduce plaque retention, antimicrobial therapy to suppress bacteria, scaling and root planing where indicated to remove mineralized bacterial colonies, and surgical approaches to debride inaccessible areas. At the basis for these therapies is an underlying assumption that plaque is fundamentally pathogenic and must be stripped away and disinfected as part of any long term strategy of managing this disease.

A new understanding of the oral environment is rapidly emerging that challenges this fundamental assumption. This new understanding constitutes a new science of oral health that has as its basis an ecologically based understanding of the oral plaque biofilm 6,7,8,9,10,11,12,13,14,15,16.

Simply put, the oral plaque biofilm refers to the organized, adherent layer that coats the oral hard and soft tissues, separate and distinct from free flowing saliva. The oral plaque biofilm exists on a continuum from an acquired pellicle on one end of the spectrum to a young or mature low film thickness biofilm (LFB), to an overgrown high film thickness biofilm (HFB) commonly termed ‘plaque’, to mineralized biofilms such as calculus. Each of these stages constitute an oral plaque biofilm—a structure that is natural and, in certain manifestations, is healthy and protective of oral soft and hard tissues.

Taking an ecological view, it is futile at best, and counterproductive at worst to base therapies on eliminating or disinfecting this structure, formed through millions of years of evolution with an inherent symbiosis amongst the resident flora, salivary proteins, minerals and cofactors, and the tissues of the oral cavity that form the scaffolding of this living entity. Rather, the new science points to an approach which recognizes the need to keep the oral biofilm in a state of balance, specifically, balanced towards the portion of its spectrum that is characterized by a mature LFB, lacking odor and inflammatory cofactors, and containing nutrients and other factors that favor and stabilize its presence in this stage.

† Editor in Chief, Journal of Practical Hygiene, 2003-2006
† This review and analysis was conducted independent of Dr. Jefferies’ parent institution, Temple University School of Dentistry.
None of the information or opinions expressed reflect those of Temple University or its affiliates. Dr. Jefferies conducted this review and provided this analysis at the request of CS Biosciences, and received no financial compensation for this work.
A novel approach to oral care based on this new science involves a topically applied complex engineered to balance and stabilize the oral biofilm within the range of its spectrum that clinically results in a healthy oral environment. Key to this approach is the avoidance of detergents and antimicrobials; elements that destabilize the biofilm and, according to the new science, thereby disrupt this key natural stabilizer of the oral environment.

Rather, this new complex consists of a balanced combination of antioxidants noted for their free radical scavenging and cell membrane stabilizing abilities including ascorbate, tocopherol, and ubiquione, herbal extracts noted for their physical properties in diminishing HFB plaque accumulation including stevioside and cranberry, and a proprietary blend of mineral cell salts noted for their actions in stabilizing and regulating all forms of gradient based ionic movement within the oral biofilm and the adjacent soft and hard tissues including methyl sulfonyl methane, Calc Phos HPUS, Calc Sulph HPUS, Calc Fluor HPUS, and Silica HPUS. The later four listed salts comprise a class of minerals formulated according to the Homeopathic Pharmacopeia of the United States (HPUS) and having a track record of safety and efficacy dating back over one hundred years. Homeopathy, a system of medicine that works in harmony with the body's natural immune responses, is practiced widely in Europe and Asia and, while discredited early in the twentieth century in America, has gained increasing favor owing to positive clinical trials published in the mainstream medical literature.

The purpose of this report is to analyze pilot clinical data utilizing Revitin™ Oral Care Paste with NuPath® Complex formulation, in a short-term, seven day toothbrushing regimen, to reduce gingival inflammation (GI) using a widely employed measurement index for gingival inflammation (Loe & Silness). This data will then be compared (in a non-statistical fashion) to historical literature reports concerning levels of reduction of gingival inflammation demonstrated by conventional manual toothbrushing with standard fluoride toothpaste and also novel oral hygiene formulations and devices. While such comparisons can not directly substitute for prospective, controlled clinical comparative studies; indirect comparison of GI reduction levels could provide preliminary insight into the potential validity of this novel and alternative approach to oral hygiene and gingival health care.

**Review of Selected Literature Concerning Levels of Gingival Inflammation Reduction Using Conventional and Advanced Oral Hygiene Therapeutics**

A PubMed literature review was conducted searching the topic, "reduction of gingival inflammation by toothbrushing". This search yielded 112 references for review. A sub-group of these papers was selected based on available data concerning gingival inflammation reduction, and with the additional condition that sufficient level of detail was reported to determine levels of gingival inflammation reduction by both control and experiment groups. It should be noted that not all publications incorporated gingival inflammation measurement using the Loe & Silness index as a clinical parameter endpoint, therefore only those papers utilizing this specific clinical measurement index (see Appendix A) were considered for review. Four published research reports appeared to give sufficient baseline and control data on gingival inflammation measurement (utilizing the Loe & Silness index), and were included in this retrospective data review. The specific data of interest from these four published research reports has been organized and summarized in Table 1. Levels of gingival inflammation reduction, utilizing more conventional methods, i.e.; manual toothbrushing with a standard, fluoride toothpaste; are described in all four cited studies. The timeframes for these studies range from two week to three months assessment of gingival inflammation changes.
The range of percent reduction of gingival inflammation from baseline levels, using a standard manual toothbrush and standard fluoride toothpastes, ranged from 9.7% to 15%. The values that are represented within this range are depicted in the left four vertical bars (light blue) in Figure 1. Using a liberal estimation of this therapeutic effect, the mid-range of these values, approximately 12.5%, could be used for comparative purposes as a general control, reference value (i.e., percent reduction of gingival inflammation by usual oral hygiene procedures). This value will be utilized in this analysis as a historical reference value for reduction of gingival inflammation; and will be compared to the gingival inflammation reduction values for Revitin™.

The literature also reports reductions in gingival inflammation for some of the newer oral hygiene devices and toothpaste formulations. Three of these therapeutic approaches are also depicted in Table 1. Tritten, et al.⁹⁹, measured a 15% reduction in gingival inflammation (L-S index) with the use of a sonic toothbrush (Sonicare) for 4 weeks. Cronin, et al.⁷⁰, demonstrated a 10.7% reduction in gingival inflammation using the oscillating Oral-B 3D Plaque removing brush with standard fluoride toothpaste. A fluoride, anti-plaque, anti-inflammatory toothpaste, formulation containing triclosan was evaluated over a three month period by Triaratana, et al.⁷². Levels of gingival inflammation reduction reached approximately 22.4% over a three month period. These values are depicted as the three colored bars on the far right-hand side of Figure 1.

**Reduction In Gingival Inflammation By Revitin – Limited Pilot Study**

Ten patients were included in this study and evaluated at baseline and then seven (7) days after use of Revitin toothpaste. Total numerical values for gingival inflammation per patient mouth (using the L-S index) were determined from the average of the sum of all buccal and lingual tooth surfaces measured; resulting in an average gingival inflammation value per each patient. This computation then resulted in a baseline and 7 day gingival inflammation value for each patient. The average difference in the values, divided by the average baseline score, multiplied by 100, gave the percentage reduction in gingival inflammation for the ten patient group. Table 1 provides the standard statistical analysis of this data, including a single factor Analysis of Variance (ANOVA) to evaluate statistical significance from the baseline to the 7 day data. The analysis indicates a 25% reduction in gingival inflammation from the average baseline value over the seven day period using Revitin toothpaste. The single factor ANOVA analysis indicated a statistically significant difference in the change in gingival inflammation scores comparing baseline to 7 day recall data, with a *p value*<0.0005. Additionally, the 25% gingival inflammation reduction value for Revitin compares favorably with levels of gingival inflammation reduction cited in the literature (approximately 12.5% by the above literature analysis) for manual brushing with a standard fluoride toothpaste. The reduction in gingival inflammation measured in the Revitin treatment group also compares favorably with energy-assisted toothbrushes, as well as with an anti-microbial, anti-inflammatory fluoride toothpaste. Figure 1 depicts the reduction in the Revitin group (purple bar) as well as the visual comparison to historical values of standard oral hygiene procedures in light blue bars. Again, while caution must be used in any comparison between historical literature values and those found in this pilot study (in the absence of a specific prospective clinical study with appropriate control groups); this data may suggest, with caution, a potentially significant enhancement of gingival health by the anti-oxidant toothpaste, Revitin. As such, Revitin use may be a highly useful adjunctive modality in reducing gingival and periodontal inflammation. Further support of the technology and further expanded clinical evaluations appear warranted, and may result in the demonstration of a potentially novel and useful addition to the oral hygiene product armamentarium.
References Cited


Appendix A

Loe and Silness Gingival Index

1 = Normal gingiva

1 = Mild inflammation; slight change in color, slight edema, no bleeding upon probing

2 = Moderate inflammation; redness, edema, and glazing, bleeding upon probing

3 = Severe inflammation; marked redness and edema, ulceration, tendency for spontaneous bleeding
Fig. 1: Reduction in Gingival Inflammation vs. Various Oral Hygiene Therapeutic Modalities

<table>
<thead>
<tr>
<th>Reduction in Gingival Inflammation (%)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revitin™, 1 week</td>
<td>1 week</td>
</tr>
<tr>
<td>Colgate Total</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Oral-B</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Sonicare</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Revitin™, 1 week
- Paste, Manual, 2 weeks
- Paste, Manual, Floss, 2 weeks
- Paste, Oral-B, 2 weeks
- Paste, Manual, Floss, 4 weeks
- Paste, Sonicare, 4 weeks
- Paste, Manual, 12 weeks
- Colgate Total, Manual, 12 weeks

Confidential
Table 1: LITERATURE REFERENCES WITH RESPECT TO REDUCTION IN GINGIVAL INFLAMMATION (LOEW-SILNESS INDEX) ACHIEVED WITH VARIOUS STANDARD AND THERAPEUTIC (in bold) TOOTHBRUSHING REGIMENS

<table>
<thead>
<tr>
<th>STUDY SOURCE</th>
<th>TREATMENT METHOD</th>
<th>TIME PERIOD</th>
<th>PERCENT REDUCTION IN GI (L-S INDEX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tritten CB, Armitage GC. Comparison of a sonic and a manual toothbrush for</td>
<td>Manual Toothbrush</td>
<td>Four (4) weeks</td>
<td>Baseline: 1.41 (0.16) 4 Weeks: 1.20 (0.17) 15% Reduction (Significant difference from baseline, p&lt;0.001).</td>
</tr>
<tr>
<td>efficacy in supra-gingival plaque removal and reduction of gingivitis. J</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clin. Periodontol, 23(7), July 1996, 641-646.</td>
<td>Sonicare Toothbrush</td>
<td>Four (4) weeks</td>
<td>Baseline: 1.40 (0.10) 4 Weeks: 1.16 (0.19) 17% Reduction (Significant difference from baseline, p&lt;0.001).</td>
</tr>
<tr>
<td>Cronin M, Dembling W, Warren PR, King DW. A 3-month clinical investigation</td>
<td>ADA reference manual toothbrush; Colgate Regular (std. F') toothpaste</td>
<td>Two week data</td>
<td>Baseline: 1.14 (0.10) 2 Weeks: 1.03 (0.09) 9.7% Reduction (Significant difference from baseline p&lt;0.005).</td>
</tr>
<tr>
<td>comparing the safety and efficacy of a novel electric toothbrush (Braun</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral-B 3D Plaque Remover brush; Colgate Regular (std F') toothpaste</td>
<td>Oral-B 3D Plaque Remover brush; Colgate Regular (std F') toothpaste</td>
<td>Two week data</td>
<td>Baseline: 1.12 (0.13) 2 Weeks: 1.00 (0.12) 10.7% Reduction (Significant difference from baseline p&lt;0.005).</td>
</tr>
<tr>
<td>Barnes CM, Russell CM, et.al. Comparison of irrigation to floss as an</td>
<td>Manual Toothbrush plus Floss</td>
<td>Two (2) weeks</td>
<td>Facial Surfaces: 11.3 % Lingual Surfaces: 12.4% Aver. Red. = 11.85%</td>
</tr>
<tr>
<td>adjunct to tooth brushing: effect on bleeding, gingivitis, and supragingival plaque. J Clin Dent 16(3):71-77, 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual Toothbrush plus Floss</td>
<td>Four (4) weeks</td>
<td>Facial Surfaces: 9.9% Lingual Surfaces: 9.4% Aver. Red. = 9.65%</td>
<td></td>
</tr>
<tr>
<td>Triratana T, Rustogi KN, Volpe AR, et.al. Clinical effect of a new liquid</td>
<td>Manual Toothbrush using &quot;control&quot; dentifrice containing 0.243% NaF in a silica</td>
<td>Three months (12</td>
<td>Baseline: 1.72 (0.20) 12 Weeks: 1.54 (0.22) 10.5% Reduction (Significant difference from baseline, p&lt;0.01).</td>
</tr>
<tr>
<td>dentifrice containing triclosan/copolymer on existing plaque and</td>
<td>base</td>
<td>weeks</td>
<td></td>
</tr>
<tr>
<td>gingivitis. JADA, Vol. 133, Feb 2002. 219.</td>
<td>Manual Toothbrush using &quot;experimental&quot; dentifrice containing 0.243% NaF, 0.3%</td>
<td>Three months (12</td>
<td>Baseline: 1.70 (0.19) 12 Weeks: 1.32 (0.16) 22.4% Reduction (Significant difference from baseline, p&lt;0.01).</td>
</tr>
<tr>
<td></td>
<td>triclosan, 2.0% PVM/MA copolymer in silica base (Colgate Total Toothpaste).</td>
<td>weeks</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: BASELINE, 7 DAY GINGIVAL INFLAMMATION DATA FOR REVITIN

(Full mouth average, paired, GI (L-S) index scores for 10 patients at baseline and 7 days Revitin use)

<table>
<thead>
<tr>
<th>Patient Gingival (L-S) Index Data</th>
<th>Baseline Statistical Summary</th>
<th>7 Day Statist Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 7 Day Post</td>
<td>Mean 2.221</td>
<td>Mean 1.664</td>
</tr>
<tr>
<td>2.25 1.7</td>
<td>Standard Error 0.073416</td>
<td>Standard Error 0.108045</td>
</tr>
<tr>
<td>2.18 1.32</td>
<td>Median 2.175</td>
<td>Median 1.685</td>
</tr>
<tr>
<td>2.57 1.78</td>
<td>Mode 2.17</td>
<td>Mode 1.74</td>
</tr>
<tr>
<td>2.23 1.74</td>
<td>Standard Dev. 0.232161</td>
<td>Standard Dev. 0.341669</td>
</tr>
<tr>
<td>2.17 1.13</td>
<td>Sample Vari. 0.053899</td>
<td>Sample Vari. 0.116738</td>
</tr>
<tr>
<td>2.66 2.43</td>
<td>Kurtosis 0.348106</td>
<td>Kurtosis 2.723461</td>
</tr>
<tr>
<td>2 1.65</td>
<td>Skewness 0.958628</td>
<td>Skewness 0.880042</td>
</tr>
<tr>
<td>2.05 1.74</td>
<td>Range 0.73</td>
<td>Range 1.3</td>
</tr>
<tr>
<td>2.17 1.67</td>
<td>Minimum 1.93</td>
<td>Minimum 1.13</td>
</tr>
<tr>
<td>1.93 1.48</td>
<td>Maximum 2.66</td>
<td>Maximum 2.43</td>
</tr>
<tr>
<td></td>
<td>Sum 22.21</td>
<td>Sum 16.64</td>
</tr>
<tr>
<td></td>
<td>Count 10</td>
<td>Count 10</td>
</tr>
</tbody>
</table>

Anova: Single Factor

SUMMARY

<table>
<thead>
<tr>
<th>Groups</th>
<th>Count</th>
<th>Sum</th>
<th>Average</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column 1</td>
<td>10</td>
<td>22.21</td>
<td>2.221</td>
<td>0.053899</td>
</tr>
<tr>
<td>Column 2</td>
<td>10</td>
<td>16.64</td>
<td>1.664</td>
<td>0.116738</td>
</tr>
</tbody>
</table>

ANOVA

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>1.551245</td>
<td>1</td>
<td>1.551245</td>
<td>18.1815</td>
<td>0.000467</td>
<td>4.413873405</td>
</tr>
<tr>
<td>Within Groups</td>
<td>1.53573</td>
<td>18</td>
<td>0.085318333</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3.086975</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>