Report

Efficacy Evaluation of a Chlorine Dioxide Toothpaste (DioxiBrite™) on Plaque and Gingivitis

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Introduction

Periodontal disease presence in adults.

The term periodontal disease is not easily defined, but what is universally found in its definition is that patients with periodontal and epithelial attachment loss around the root structure of teeth suffer from periodontal disease. The American Academy of Periodontology defines periodontal disease as gingivitis, gingival inflammation without the loss of periodontal attachment, and periodontitis, gingival inflammation accompanied by the loss of connective tissue attachment (Guidelines for Periodontal Therapy, 1998).

The prevalence of periodontal disease in the adult population varies considerably according to the individual published study. For example, according to Soder (1994), it can be as low as 17% in patients with periodontal pockets $\geq$ 5 mm in depth or according to Horning et al (1990), as high as 99% in patients with similar pocket depth criteria. In this latter study, gingivitis prevalence was 37% and early, moderate and advanced stages were 33, 14 and 15%, respectively. A variety of risk factors have been implicated to be involved in the development of periodontal disease. A partial list would include age, smoking, diabetes mellitus, education level, gender, presence of certain subgingival microorganisms and plaque accumulation to name a few (Ismail, 1990; Haffajee, 1991; Brown, 1994; Papapanou, 1996).

Measurement of gingival inflammation and periodontal disease.

The most common method utilized by the dental clinician to measure the level of periodontal disease is the hand-held periodontal probe. To assess gingival inflammation (GI), which is a visual and tactile assessment, the same or similar probe is utilized. The periodontal

probe, with a limited degree of accuracy, is used to measure the depths of pockets (PD) and assess clinical attachment loss (AL). Neither method, PD or GI measurements, are sufficiently objective, sensitive or accurate enough alone to be able to conduct satisfactory longitudinal studies. It is necessary to standardize the observations.

The establishment of the Loe-Silness Gingival Index (Loe, 1963) enabled the quantification of inflammation at a dentition site. This includes assessment of the tissue visual redness, and level of bleeding. A value usually 0 - 3 is assigned where 0 is no inflammation, 1 is slight, 2 is moderate and 3 is severe. The use of the periodontal probe to measure PD is critical to identify sites with periodontitis (sites with clinical attachment loss). These sites serve as a habitat for pathogens that are difficult for the patient or dental professional to maintain in a hygienic condition (Armitage, 1996). Pocket depth, as a stand alone prognostic test, is not sufficient for predicting the progression of periodontitis (Halazonetis, 1989), but a change in pocket depth does serve as an effective means of monitoring disease progression. Plaque scores, as described by Loe (1967) have served as a means for quantifying effectiveness of a patient's dental hygiene and for product effectiveness in plaque removal. Although, plaque removal alone is not an indicator or prognosticator of disease progression (Armitage, 1996) it may be critical for the prevention of periodontal disease.

Gingival crevicular fluid (GCF) flow rates serve as a sensitive measure of the inflammatory status surrounding a gingival sulcas/pocket (Hancock, 1979). GCF is a serum transudate that leaks into the sulcas from the underlying connective tissue at an increasing rate with an increasing inflammatory status (Brill, 1959; Egelberg, 1964; Borden, 1973). This can be measured by use of either filter paper strips or fine capillary tubes inserted into or placed at the orifice of the crevice. Golub and Kleinberg (1976; 1986) described the use of the Periotron™ micro-moisture meter as a means of measuring GCF flow rate and as a means of monitoring gingivitis and periodontal disease status quantitatively. Hinrichs et al. (1984) and others have

confirmed that the Periotron gives an accurate measure of GCF/Periodontal Pocket Fluid volumes and that elevated crevicular fluid flow levels are directly related to greater disease activity in the gingival sulcas. Lindhe et al. (1973) demonstrated in beagle dogs that increases in GCF and clinical evidence of gingival inflammation are early signs of eventual increases in pocket depth. Lee et al. (1997) demonstrated that GCF flow was directly related to the amount of tissue destructive enzyme collagenase and the breakdown of alpha-1 proteinase inhibitor (a regulator of elastase activity) in patients with periodontitis.

Chlorine dioxide

Chlorine dioxide (ClO_2) is a powerful oxidant with potent bactericidal (Harakeh 1988), viricidal (Alvariz 1982), sporicidal (Foegeding 1986), cysticidal (Korich 1990), algicidal, and fungicidal (Takahashi 1979) properties and has found much use as a deodorizing and bleaching agent. For instance, it is used in municipal water supplies and in the paper pulp industry (Massenchelein 1979). It is approved by the Food and Drug Administration (FDA) as a disinfectant on meat, poultry, fruits, vegetables and seafood (FDA Federal Register 21 Part 173-section 173.325 revised April 1, 2001; 21 CFR Part 173 revised June 13,2001). Biocidal actions of ClO_2 are more effective and safer than those of chlorine, and do not give rise to chlorinated organic products (e.g. chlorophenol and chloroform) which pose a major hazard to human health. In addition to exerting powerful antimicrobial activity, formulations containing ClO_2 have been shown (Chapek 1994) to 1) oxidatively consume volatile sulfur compounds (VSCs) responsible for halitosis, 2) elevate the O_2 tension in both saliva and plaque, 3) remove residual organic solutes, and 4) suppress the activity of bacterial proteolytic enzymes. Therefore therapeutic application of ClO_2 containing oral healthcare products would appear to serve as an effective means of preventing or combating periodontitis and maintaining a high level of oral hygiene.

In the last 15 years, only two compounds have been approved by the FDA for treating plaque and gingivitis, chlorhexidine and triclosan. Similar to ClO_2, these two chemicals act on microorganisms by cell wall disruption, but they are slow acting and only have a limited spectrum of action. A chlorine dioxide mouthrinse (Goultschin et. al. 1989) has been evaluated for plaque reduction. The study showed that over a 5-day period a significant reduction of dental plaque was observed. Yates *et. al.*(1997) investigated the persistence of antimicrobial action and plaque inhibitory properties of ClO_2 mouthrinses by comparison with a positive control, chlorhexidine 0.12%. The results indicated that the ClO_2 rinses have equivalent plaque inhibitory action to chlorhexidine. So far there have been isolated reports in the literature of improved periodontal parameters in gingivitis and periodontitis patients using "stabilized" chlorine dioxide. DioxiBrite™, on the other hand, contains "active" chlorine dioxide, and is expected to have a dramatic effect on both plaque and gingivitis.

Purpose and Study Design

The purpose of this double blind placebo controlled clinical study was to compare the efficacy of a chlorine dioxide toothpaste (DioxiBrite™ Toothpaste manufactured by Frontier Pharmaceutical, Inc.), with an active control (commercially available toothpaste containing triclosan, Total®, manufactured by Colgate Palmolive) and a vehicle control (DioxiBrite™ toothpaste minus the active ingredient), on plaque inhibition and gingivitis. DioxiBrite™ contains 30-50 ppm chlorine dioxide.

Subjects were randomly assigned to receive one of three study products (mentioned above). All participants were instructed to brush 2 times daily with their assigned toothpaste over a 6-week period. Gingival inflammation and dental plaque accumulation were assessed at

baseline, 3 and 6 weeks by gingival index, gingival crevicular fluid flow, bleeding on probing and plaque index. Enrollment in the study was designed to complete 54 compliant subjects.

Materials and Methods

Screening and Enrollment

Subjects (≥18 years of age) were solicited through an IRB approved advertisement and scheduled for a screening visit. They were instructed not to brush within two hours of their screening visit. At that time, subjects were given an IRB approved consent form and had questions related to the study answered. Subjects were asked to complete a comprehensive medical history. Only subjects in good health were enrolled. Upon completion of the consent and history, subjects received an intra-oral examination to determine the presence of the inclusion criteria and the absence of the exclusion criteria. Teeth with extensive caries, heavy calculus, crowns, orthodontic bands or moderate to advanced periodontitis (pockets >5mm) were eliminated. All remaining teeth (providing the subject has ≥ 20 teeth available to study) were evaluated for plaque index (PI) using the criteria described below. The 20 teeth with the highest average PI were included for subsequent evaluation (and study), provided that the mean PI per surface was ≥ 1.00 (subjects with < 1.00 were disqualified). The 20 teeth were evaluated for Gingival Index (GI) and Bleeding on Probing (BI). Mean values for GI had to be ≥1.5 and BI had to be >0 at ≥5% of the sites for a subject to qualify for the study.

Subjects were excluded from this study if they:

1) had taken any antibiotics within one month or used any chemical antiplaque products (Peridex or Colgate Total) within two weeks prior to study initiation;

2) had a history of hypersensitivity to dentifrices or triclosan;

3) were unable to comply with the follow up visits

4) had untreated caries or periodontitis requiring prompt treatment;

5) had undergone any oral hygiene program within the month, had any dental treatment in the week prior to study initiation, or were undergoing an extensive oral hygiene program;

6) were pregnant or planning to be pregnant, or nursing.

7) had any metabolic condition that might have affected gingival health or required antibiotic premedication prior to examination.

Experimental Design

Three groups of subjects were to be enrolled expecting a total of 54 subjects to complete the study:

Group A: Chlorine dioxide toothpaste (Treatment group) – [DioxiBrite™]
Group B: Triclosan toothpaste (Active Control) – [Total®]
Group C: Fluoride toothpaste (Vehicle Control)–[DioxiBrite™ with the active ingredient removed]

After baseline evaluations, subjects were randomized to one of the three above groups based upon the severity of their gingival index (to assure equal distribution of the worst cases). Subjects were instructed to use their assigned study toothpaste twice daily only, using their normal brushing technique. DioxiBrite™ is a two-part product. In order to maintain the blind, all 3 toothpastes were visually similar and packaged in identical dual dispensers. These dispensers dispel both parts simultaneously upon pressing a pump. The patients were instructed to dispense equal amounts of both parts onto the toothbrush (supplied by Frontier) and brush his or her teeth for 60 seconds. During brushing, the patient ensured that the two parts were mixed by utilizing all of the dispensed toothpaste (no clumps remain in the mouth). This procedure was

demonstrated to the patient by the research team to improve patient compliance and subjects were asked to brush prior to leaving baseline visit.

Subjects were asked to record the time of day that they used the study product in a Product Use Diary, which was collected by the investigator at the conclusion of the study. Product samples were collected and reweighed at the final follow-up visit.

Clinical Indices

Clinical evaluation scoring was carried out by one investigator, experienced in the use of the Loe Plaque index (Loe 1963), the Lobene *et al.* (1986) modification of the Löe and Silness (1963) gingival index, and bleeding upon probing (BOP) methodology. As a measure of gingival inflammation, the Gingival Crevicular Fluid Flow (GCF) was assessed on the mesial surface of the 20 examined teeth, as described by Bordon, et. al.(1973), utilizing filter paper strips (Periopaper™) inserted into the sulcus for 5 seconds after gently drying the sulcus with air. Fluid volumes were determined utilizing a Periotron 8000™ and recorded. Bleeding upon probing (BOP) was assessed by gently inserting a 25 g controlled force Florida™ probe into the sulcus to the base of the pocket. After removal of the probe, the presence or the absence of blood was noted using a 5-point scale from 0 to 4 (see below). All indices were assessed at baseline, 3 and 6 weeks. These four indices were assessed in the following order:

Scoring Methods

Plaque Index (PI)

Plaque was scored on six surfaces (mesiobuccal, buccal, distobuccal, lingual, mesiolingual and distolingual) of all teeth by the Löe plaque index.

0 = No plaque in the gingival area.

1= A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may only be recognized by running a probe across the tooth surface.

2 = Moderate accumulation of soft deposit is within the gingival margin, which can be seen by the naked eye.

3= Abundance of soft matter within the gingival pocket and/or on the gingival margin.

Crevicular Fluid Flow (GCF)

Collection of gingival crevicular fluid involved isolating the mesial surface of the tooth to be measured, removing any remaining supra-gingival plaque with an instrument or cotton roll, gently drying the sulcas with a three second transverse air stream, the careful insertion of a Periopaper™ strip to the base of the sulcas for five seconds and quantification performed using a Periotron 8000™. Data were reported in microliters of fluid accumulated in a 5 second collection. A decreasing flow rate is indicative of a decrease in gingival inflammation.

Gingival Index (GI)

Gingival inflammation was scored on the marginal and papillary gingival units associated with scorable teeth, using the Lobene Gingival Index:

0 = Absence of inflammation.

1 = Mild inflammation; slight change in color, little change in texture of any portion of but not the entire marginal or papillary gingival unit.

2 = Mild inflammation, criteria as above, but involving the entire marginal or papillary gingival unit.

3 = Moderate inflammation; glazing, redness, edema, and/or hypertrophy of the marginal papillary gingival unit.

4 = Severe inflammation; marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

Bleeding on Probing (BOP)

The presence or absence of bleeding on probing was evaluated on six areas per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) utilizing a 25 g controlled force Florida™ probe.

0 = No bleeding present.
1 = Pinpoint bleeding present without flow along gingival margin.
2 = Bleeding with flow along gingival margin.
3 = Profuse bleeding immediately on probing.
4 = Spontaneous bleeding in the absence of probing.

Soft Tissue Examination

Intra-oral soft tissue examination was performed on each subject at each visit and abnormalities were recorded.

Adverse Events

Adverse events were to be recorded at each clinic visit on an Adverse Event report form, including date of onset and cessation, intensity, relationship to study product, action and outcome.

Efficacy Analysis*

Products were evaluated for effectiveness compared to baseline values at both three and six weeks. A change in a clinical parameter (PI, GI, BI and GCF) was considered statistically significant if it had a probability value of $p \leq 0.05$. Changes in a clinical parameter (PI, GI, BI and GCF) with a $p > 0.05$ and < 0.10 were interpreted as reflecting tendencies toward statistical significance. SAS™ PROC Mixed was utilized to implement ANOVA models which utilized all available data from subjects' tooth sites. The models included error terms reflecting inter- and intra-subject variance. Least-squares mean estimates were adjusted for intercorrelations among tooth sites within patients. Changes from baseline values were analyzed for differences between pairs of treatment groups utilizing appropriate mixed-model analysis of variance models adjusted for relevant covariates such as baseline parameter values as appropriate.

Results

One hundred and fifty subjects were telephone and or clinically screened for eligibility for participation. Sixty subjects with acceptable parameters at screening were enrolled in the study for initial stratification. Three subjects failed to appear for their baseline appointment and two subjects were lost to recall after baseline. Attempts to contact and reenroll the subjects lost to recall failed despite written and telephone messages (subjects failed to return product). The age, gender and ethnic distribution of subjects completing the study are presented in Table I. Mean PI, GI, BI and GCF and their change from baseline for 3 and 6 week assessments are presented in Tables II and III and Figures I and II respectively. Statistical significance was determined for differences from baseline for each product. Probability values ≤ 0.05 are considered significant and values >0.05 but <0.10 are considered trends worthy of further investigation. At the three

week analysis, DioxiBrite™ displayed significant improvement in PI, GI and BI; Total® displayed significant improvement in PI, GI and GCF; and Placebo displayed significant improvement in GI and a trend toward improvement in PI. At the six week analysis, DioxiBrite™ displayed significant improvement in PI, GI and BI; Total® displayed significant improvement in PI, GI, BI and GCF; Placebo displayed significant improvement in GI and BI. In addition, data was also analyzed to determine if either DioxiBrite™ or Total® was statistically superior to placebo or one another for the measured indices and values are reported in Tables II and III. DioxiBrite™ displayed a tendency toward statistical significance for PI at 3 and 6 weeks when compared to Placebo. Total® displayed significant improvement over Placebo in GCF at 6 weeks. When compared to DioxiBrite™, Total® displayed a tendency toward significant improvement for GCF at 3 weeks, and significant improvement at 6 weeks. Since a portion of the tooth sites evaluated had no disease, and therefore had no room for improvement, a more refined analysis was performed on the diseased sites only. Diseased sites are defined as having baseline values of PI > 1, GI > 1 and BI > 1. These analyses included the mean change from baseline, as well as the percent improvement and percent worsening at 3 and 6 weeks. Analysis revealed no evidence of evaluable trend at any time point for GI and BI as well as no significant changes for plaque at 3 weeks. When reviewing PI at 6 weeks only 3% of the sites ≤ 1 got worse for DioxiBrite™ while 6% and 10% got worse for Total® and Placebo respectively. Differences between placebo and DioxiBrite™ were significantly different ($p<0.009$). Further, as for evaluation of the sites improving, DioxiBrite™ demonstrated a greater trend (7%) towards reducing the number of sites with plaque than placebo ($p<0.067$). Reducing the amount of plaque on problem sites by 7% and preventing the development of sites with more plaque (7%) can result in significantly less plaque on a subject's teeth. A larger/longer study may demonstrate a significantly better plaque removal and prevention of plaque accumulation than placebo.

Eight subjects suffered nine adverse events ranging from minor apthi (possibly related to products) to the common cold and ear infections (probably unrelated to products). Of the possibly related adverse events, all resolved on their own without additional treatment. For the possibly related adverse events, none were unblinded during the study (one subject was utilizing DioxiBrite™, two subjects were utilizing Colgate Total® and one subject was utilizing the placebo). The distribution of subjects with minor apthi indicates that this event was not related to the product.

A review of subject diaries revealed good compliance with product usage according to protocol instructions.

Discussion

It is well accepted that the accumulation of plaque and calculus on teeth leads to the development of periodontal disease. Loe et. al. (1965) and later Theilade et. al. (1966) demonstrated that with the cessation of home care a cascade of events occurs that will lead to gingivitis. As plaque accumulates, a complex bacteriologic environment develops. Initially the population involves gram positive cocci and rods. As the plaque thickens (and oxygen is depleted) the plaque microflora has a greater proportion of gram negative cocci and rods. Fusiforms, filaments and spirochetes eventually appear and a transepithelial exudate (GCF) develops. Today, it is well understood that the toxic by-products of the bacteria damage the epithelium, leukocytes leak into the sulcas and the clinical signs of gingival inflammation develop. Loe et. al. (1965) demonstrated that crevicular fluid flow increased days before the clinical signs of inflammation are present. Lindhe et. al. (1973) demonstrated, on beagle dogs, that gingivitis progressed to periodontitis and as this occurred crevicular fluid flow increased. In the current study, plaque

index (PI), gingival index (GI), bleeding index (BI) (which is an extension of the gingival index) and gingival crevicular fluid flow (GCF) were measured. Subjects received home care instruction and their study toothpaste after baseline data was collected. They were shown how to utilize the dual dispensing chamber and how to brush twice per day.

Subjects were randomized into the three toothpaste groups. This randomization was based upon the gingival index at baseline. Though close in values, slight differences in the baseline values for the PI, GI, BI and GCF were obtained. Use of change from baseline data, however, corrects for differences in these baseline values. At both three and six weeks, the DioxiBrite™ and Total® reduced the plaque score significantly when evaluating all tooth sites. The decrease in PI for the placebo group did not reach statistical significance at the $p \leq 0.05$ level. Tables II and III indicate that DioxiBrite™ demonstrated a trend ($p<0.09$) for reduction of plaque better than placebo, whereas the improvement with Colgate Total® did not. The mechanism of action of the two products may explain this. Colgate Total®, a product approved for reducing plaque and gingivitis by both the American Dental Association and U.S. Food and Drug Administration, contains 0.3% triclosan, an antibacterial agent. An oxidizing agent, such as DioxiBrite™, in addition to its claimed antimicrobial properties, may be more effective at disrupting the biofilm that allow the adherence of plaque to the tooth than a pure germicidal agent. Chlorine dioxide, in particular, is known to attack biofilms. The continued presence of plaque on the teeth after brushing with DioxiBrite™ may indicate that the paste may not be entering the sulcas in high enough concentration to disrupt the plaque attachment. Better tooth brushing instructions may be indicated. This may explain why DioxiBrite™, in the short period of this study, did not have the effect on GCF flow. The anti-microbial triclosan may work to reduce the number of viable bacteria, but not act to dislodge the plaque as well. Over a longer period of time, the decreased bacterial load may reduce the volume of plaque (as demonstrated in

Colgate sponsored efficacy studies). For GI and BI neither product was better than placebo though for PI, DioxiBrite™ was the only product that demonstrated a trend to better improvement over baseline values compared to placebo (Tables I and II). When reviewing the changes in GI, all three products showed statistically significant improvement over baseline, but it is important to remember that the magnitude of the improvement (<0.2) probably is not demonstrating any clinical significance (1.88 to 1.68 for placebo). The mean values at six weeks still represents significant levels of gingival inflammation.

The Task Force on Design and Analysis in Dental and Oral Research (Imrey et. al. 1994), recommended that clinical studies to prove efficacy involve several items including that the study be at least six months in duration. In addition, the study must be large enough in size to provide for adequate data analysis. As an example, the Allen et. al. (2002) study had at least 36 subjects per group to complete the study. The study here was ¼ the duration and half the panel size. Even with this as the case, there was a trend toward significant improvement in the PI for DioxiBrite™. All three products demonstrated a significant decrease in the BI over the short time. Total® demonstrated a significant decrease in the GCF flow. These findings for Total® indicate that this product is operating as previously reported (qualifying as a plaque reducing and gingivitis reducing product). DioxiBrite™ results appear similar in trend to the Total® results (and may even be better for plaque reduction).

Figures I and II demonstrate the changes from baseline in PI, GI, BI and GCF over three and six weeks respectively. The magnitude of the change in plaque index for DioxiBrite™ over a short period of time should be noted. The substantial magnitude of the placebo improvement (though not significant) might be due to the short term effect that the initial oral hygiene instruction had on all pastes. Over a longer study period, the effect of oral hygiene instructions may have been less and the change of the placebo group might not have been as dramatic. It

must also be remembered that the placebo was the same paste as DioxiBrite™ without the chlorine dioxide. The effectiveness of many anti-plaque formulas may reside in the abrasives and wetting agents utilized in the paste. The effectiveness of this base paste remains untested. It too may possess therapeutic value.

Conclusion

If considered as a preliminary evaluation, DioxiBrite™ shows promise in producing a clinically significant reduction in plaque accumulation and gingivitis. Throughout this study, the DioxiBrite™ appeared safe with no greater incidence of adverse events than either placebo or Total®. In view of the small study size and short duration, the drop in the plaque index is extremely promising. Larger studies of greater duration are required to prove its effectiveness.

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* All data efficacy analyses completed by Mark Bradshaw, PhD.
Global Biometrics Data Management, IT Covance, Inc.

Table I.

SUBJECT DEMOGRAPHICS

	Number of Subjects	MEAN AGE*	RACE (W/B/A)
DioxiBrite			
Male	6	39.5 (±2.0)	4/2/0
Female	13	39.3 (±2.6)	11/1/1
Total	19	39.4 (±1.9)	15/3/1
Total			
Male	5	29.6 (±4.0)	5/0/0
Female	14	41.2 (±3.4)	13/1/0
Total	19	38.2 (±2.9)	18/1/0
PLACEBO			
Male	5	39.8 (±4.5)	4/1/0
Female	12	35.8 (±3.5	11/1/0
Total	17	37.0 (±2.8)	15/2/0

*(±S.E.)

Table II. Mean Plaque, Gingival, Bleeding and Crevicular Fluid Flow at Baseline and 3 Weeks and their Change from Baseline for All Tooth Sites

Visit:		Baseline		Week 3		Change from Baseline		
Parameter:	N	Mean	Std. Error	Mean	Std. Error	Mean	p-Value	% Change from Baseline
Plaque Index								
DioxiBrite	19	1.470	0.053	1.156	0.092	-0.314	**<.0001**	-21.36%
Total	19	1.363	0.052	1.157	0.084	-0.207	**0.0004**	-15.15%
Placebo	17	1.625	0.080	1.389	0.117	-0.236	0.0953	-14.54%
DioxiBrite v. Placebo		-0.155		-0.233		-0.078	0.0871	
Total v. Placebo		-0.262		-0.232		0.030	0.1778	
DioxiBrite v. Total		0.107		0.000		-0.107	0.6993	
Gingival Index								
DioxiBrite	19	1.728	0.054	1.615	0.072	-0.113	**0.0079**	-6.52%
Total	19	1.766	0.082	1.625	0.071	-0.141	**0.0083**	-7.99%
Placebo	17	1.876	0.048	1.647	0.062	-0.229	**0.0069**	-12.19%
DioxiBrite v. Placebo		-0.148		-0.032		0.116	0.8873	
Total v. Placebo		-0.110		-0.022		0.087	0.8783	
Bleeding								
DioxiBrite	19	0.453	0.040	0.327	0.058	-0.126	**0.0107**	-27.81%
Total	19	0.370	0.047	0.383	0.054	0.013	0.2233	3.51%
Placebo	17	0.536	0.070	0.405	0.062	-0.131	0.2844	-24.50%
DioxiBrite v. Placebo		-0.084		-0.078		0.005	0.3051	
Total v. Placebo		-0.167		-0.022		0.144	0.9504	
GCF								
DioxiBrite	19	0.304	0.027	0.304	0.037	0.000	0.8764	-0.05%
Total	19	0.295	0.027	0.257	0.022	-0.039	**0.014**	-13.11%
Placebo	17	0.325	0.038	0.296	0.029	-0.029	0.4711	-9.05%
DioxiBrite v. Placebo		-0.021		0.008		0.029	0.6766	
Total v. Placebo		-0.030		-0.039		-0.009	0.2271	
DioxiBrite v. Total		0.008		0.047		0.039	0.0974	

Figure I. Change in Indices at 3 Weeks

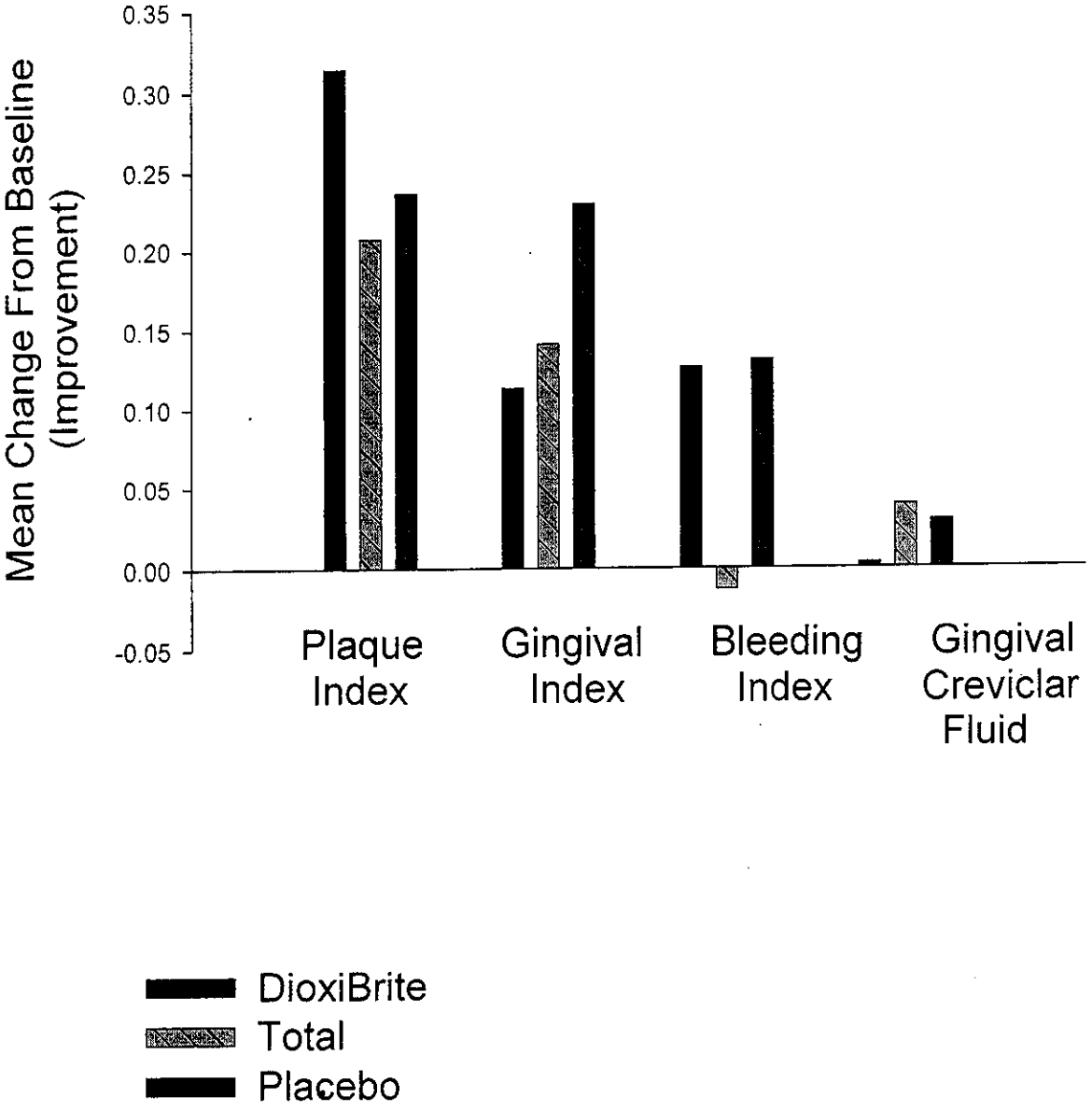

Table III. Mean Plaque, Gingival, Bleeding and Crevicular Fluid Flow at Baseline and 6 Weeks and their Change from Baseline for All Tooth Sites

Visit:		Baseline		Week 6		Change from Baseline		
Parameter:	N	Mean	Std. Error	Mean	Std. Error	Mean	p-Value	% Change from Baseline
Plaque Index								
DioxiBrite	19	1.470	0.053	1.145	0.088	-0.325	**<.0001**	-22.11%
Total	19	1.363	0.052	1.132	0.062	-0.231	**0.0001**	-16.92%
Placebo	17	1.625	0.080	1.377	0.132	-0.248	0.0719	-15.23%
DioxiBrite v. Placebo		-0.155		-0.232		-0.077	0.0876	
Total v. Placebo		-0.262		-0.245		0.017	0.1448	
DioxiBrite v. Total		0.107		0.013		-0.094	0.7899	
Gingival Index								
DioxiBrite	19	1.728	0.054	1.659	0.064	-0.069	**0.0464**	-3.99%
Total	19	1.766	0.082	1.664	0.078	-0.102	**0.0300**	-5.76%
Placebo	17	1.876	0.048	1.684	0.072	-0.191	**0.0281**	-10.20%
DioxiBrite v. Placebo		-0.148		-0.026		0.122	0.8122	
Total v. Placebo		-0.110		-0.020		0.090	0.9151	
Bleeding								
DioxiBrite	19	0.453	0.040	0.320	0.042	-0.133	**0.0046**	-29.36%
Total	19	0.370	0.047	0.286	0.037	-0.084	**0.0021**	-22.78%
Placebo	17	0.536	0.070	0.362	0.077	-0.175	**0.0422**	-32.54%
DioxiBrite v. Placebo		-0.084		-0.042		0.042	0.6026	
Total v. Placebo		-0.167		-0.076		0.090	0.4807	
GCF								
DioxiBrite	19	0.304	0.027	0.276	0.027	-0.027	0.1149	-9.04%
Total	19	0.295	0.027	0.215	0.016	-0.080	**<.0001**	-27.25%
Placebo	17	0.325	0.038	0.285	0.031	-0.040	0.2145	-12.30%
DioxiBrite v. Placebo		-0.021		-0.009		0.013	0.8495	
Total v. Placebo		-0.030		-0.070		-0.041	**0.0220**	
DioxiBrite v. Total		0.008		0.061		0.053	**0.0300**	

Figure II. Change in Indices at 6 Weeks