Localized Reduction of Gingival Inflammation Using Site-specific Therapy with a Topical Gingival Patch

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Abstract

• Objective: The purpose of this pilot study was to examine the effects of a topical patch on gingival inflammation.

• Methods: Sites of inflammation were identified on subjects with moderate-to-severe chronic periodontitis, and were allocated to either patch placement or untreated controls, both for 24 hours. Conventional treatment with scaling and root planing was postponed during the study period. Inflammation was evaluated measuring neutrophilic activity using gingival crevicular fluid (GCF) β-glucuronidase (β-glu) levels, and clinical response was evaluated using the gingival index (GI).

• Results: A total of 26 patients were recruited and 36 sites examined, with 22 sites on which the patch was placed and 14 controls. GCF β-glu levels at 24 hours were reduced following patch placement, significantly more so than with controls (17/22 vs. 3/14 sites, respectively; p = 0.002). The patch placement resulted in a significant reduction in mean b-glu levels (–2.52 ± 1.62), with a reduction from baseline of 29.7%. This compared to untreated controls, for whom the mean b-glu levels and percent change from baseline increased (2.14 ± 0.89, and 33%, respectively). At 24 hours, GI response rate for treated sites was better than for control sites (18/21 vs. 7/14; p = 0.053). No adverse events were reported in either group.

• Conclusion: This pilot study indicates that a topical gingival patch promotes reduction of gingival inflammation. Further clinical testing of this novel treatment of gingival inflammation is warranted.

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Introduction

Chronic periodontitis is initiated by bacterial infiltration of the gingival mucosa which results in an inflammatory process which, if left untreated, can progress to more serious and destructive periodontal disease. Chronic periodontitis has been linked to systemic inflammatory conditions such as atherosclerosis and macrovascular complications associated with diabetes mellitus. Current treatments for this condition are geared toward reducing periodontal bacterial load through local techniques such as scaling and root planing (SRP), as well as the use of local and systemic antibiotic medication. Yet despite the use of these treatments, clinical and biochemical manifestations of gingival disease often persist or even progress. Systemic modulation of the host inflammatory response using NSAIDs has been shown to effectively control periodontal inflammation; however, issues of safety limit the long-term use of these agents. There is thus a need to find other approaches, preferably local, which will be both safe and effective in enabling the reduction of gingival inflammation in the patient with chronic periodontitis.

Topical treatment of inflamed skin and mucosal wounds using hydrogel and hydrophilic bandages and dressings has been described extensively in the literature. The mechanism of action of this treatment is believed to result from the absorption of surface inflammatory exudates. The study patch is a hydrogel-based topical patch with two layers; an inner layer composed of a hardened hydrophilic gel designed to absorb exudates from the tissue, and an outer occlusive layer which supports the adhesive layer and facilitates application of the hydrogel to inflamed tissue. The outer layer also provides additional protection and coverage of the affected site. The inner layer of the patch contains the herbs Centella asiatica, Echinacea purpurea, and Sambucus nigra, as well as polyacrylic acids which can absorb moisture. These components become “sticky,” adhering to the tissue for up to six hours. The outer layer is made of common ingredients such as ethyl cellulose and acacia gum, among others. Once the inner gel layer is fully adherent to the tissue, the outer layer dislodges after approximately two hours.

The three herbal components of the study patch are considered safe for human consumption. Whereas the herbs have a history of anti-inflammatory benefits, the primary mechanism of activity in the patch is local hydrodynamic changes to the inflammatory exudate. The first herb, Centella asiatica, reduces inflammatory
mediators such as IL-1β in animal models, and improves clinical signs of chronic periodontitis when used in conjunction with SRP.9–13 The second compound, Echinacea purpurea, reverses stress-delayed wound healing in mice14 and pro-inflammatory cytokines in infected epithelial cells.15,16 This herb has been shown to be of benefit in mixed periodontopathies.17,18 Finally, the compound Sambucus nigra (elderberry) inhibits pro-inflammatory activity of major periodontal pathogens,19 and promotes a healthy cytokine-mediated immune response.20,21

The purpose of this proof-of-concept study was to evaluate the immediate (24 hours) effect of these patches on local gingival inflammation as assessed by the enzymatic activity of gingival crevicular fluid (GCF) β-glucuronidase (β-glu), a glycohydrolase marker of neutrophil activity in the gingival sulcus. Clinical response was evaluated using the gingival index (GI).

Materials and Methods

Subject Population

The study population included subjects aged 18–75 years with a history of moderate to severe chronic periodontitis and a GI of ≥ 2 on the buccal side of the selected teeth (no minimum number of teeth required). Subjects who were pregnant, had a history of recent (within the previous month) antibiotic treatment (systemic or in a mouthrinse), or those who were currently using salicylate-based medication were excluded from the trial. Informed consent was obtained from all subjects according to a protocol approved by the Shaare Zedek Medical Center Institutional Review Board.

Clinical Procedure

Upon evaluation of eligibility for participation in the study, potential subjects underwent a periodontal examination with the selection of one or two sites (mandibular or maxillary premolars and molars). Those fulfilling the inclusion criteria (GI ≥ 2) with none of the exclusion criteria were deemed eligible for recruitment. After receiving an explanation of the study proceedings and signing an informed consent form, GCF was sampled from the affected area. Patients with two involved sites used the patch for one site, with the second site used as a control. In the patch placement arm of the study, the patches were placed over the designated site by the study periodontist and subjects were instructed to replace the patch every eight hours for 24 hours (for a total of three patches). For control sites, no patches were administered. At the end of the 24-hour period, subjects underwent a second examination which included a re-sampling of the GCF and a second measurement of GI. At the end of the study, each subject underwent a complete conventional treatment with scaling and root planing.

GCF Collection, β-glu Determination, and GI Scoring

GCF samples were collected using precut filter paper strips, as described elsewhere.22,23 The fluid on the strip was then eluted into 0.9% saline, and the levels of β-glu activity were assayed by a time-dependent fluorometric procedure using a synthetic substrate of β-glu (4-methylumbelliferyl β-D glucuronide, Calbiochem) based on the method describe by Lamster, et al.24 When enzymatically cleaved by β-glu the reaction emits a fluorescent signal (Ex 360, Em 455), reported as kIU/ml. Laboratory procedures were performed in a blinded fashion with the technician unaware of the identity of the patients. GI was measured at the four involved sites that the patch covered using the method developed by Löe, et al.25 prior to collection of the GCF. The scores for all four sites were averaged for a single mean GI score.

Statistical Analysis

Both response rates and reduction in β-glu values at 24 hours were used as outcome measures. A positive response for a site was defined as a lower β-glu activity value after 24 hours among those sites treated with a patch. This was compared to the number of untreated sites with a spontaneous lowering of β-glu activity after 24 hours. Comparison was made using the non-parametric Fisher exact test (two-tailed). Both the average and percent average change in β-glu were calculated, with a negative number indicating a lower (i.e., improved) β-glu value after 24 hours. The average changes in absolute and percent values for β-glu were compared for treated and control sites using a paired t-test (two-tailed). To ensure that the significance reached with the t-test was not the result of a skewed data set, we used the non-parametric Mann-Whitney test to compare the groups. The mean GI scores for the treated and control sites were compared using the paired t-test statistic.

Results

A total of 26 subjects were deemed eligible and recruited, and 36 gingival sites evaluated: 22 sites were treated and 14 sites served as controls. No serious adverse events were noted in patients receiving patches at the end of the 24-hour study period. Site response rate (defined as a reduction in GCF β-glu compared to baseline) was 77.3% (17/22) for the treated sites, while 27.2% (3/14) of the control sites had a spontaneous reduction in β-glu (p = 0.002; χ², two-tailed test, Figure 1). For treated sites, there was an absolute reduction in mean GCF β-glu levels from baseline, while the control site group showed an increase in β-glu values after 24 hours when compared to baseline values (Figure 2). When comparing β-glu levels after 24 hours (delta β-glu) at treated and control sites, the patch-treated group showed a

![Figure 1. Response rate for treated sites compared to control sites (after 24 hours).](URL)
In previous studies, GCF levels of b-glu have been shown to correlate with the degree of gingival inflammation and neutrophil influx. Site-specific GCF b-glu levels complement the GI scale in terms of assessing gingival inflammation, and even offer several advantages. GI is an operator-based ordinal clinical measure, and the four-point scale does not allow for assessing subtle changes in gingival inflammation. In contrast, b-glu level as an interval ratio measurement is more precise and avoids the problem of inter-observer variability. Changes in b-glu can identify early responses to the reduction of inflammation more effectively than the limited clinical GI score.

There are a number of limitations to this pilot study, such as the short duration (24 hours), small sample size, and the fact that the GI measurements were not performed by a blinded examiner. Treated and control sites were not chosen in a randomized or blinded fashion, and the number of treated and control sites were not balanced. However, GCF b-glu was the primary measure, and it was sampled in a blinded fashion. GI was used as a secondary measure in order to support the clinical implications of our results. Future research will address these limitations in a larger double-blinded and randomized control clinical trial.

The purpose of this pilot study was to determine feasibility and safety, and to obtain preliminary efficacy data for future research. This is the first clinical study to evaluate the use of a topical patch to promote control of localized inflammation. The patch was found to be both safe and easy to use, and our preliminary findings demonstrate that it induced a rapid and significant reduction in the inflammatory marker b-glu. While this is an important first step in demonstrating a rapid decrease in the gingival inflammation associated with periodontitis, further research is required to determine the long-term benefits of the patch as an adjunct to standard periodontal therapy.

### Acknowledgment and Disclosure
The study product was provided free of charge by Izun Pharma (Israel), who funded the statistical analysis of the data as well. Aron Saffer is senior vice president for research and development and Isaiah D. Wexler is a scientific consultant for Izun Pharma (Israel).

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### References

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Table I

<table>
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*Patch vs. control, two-tailed t-test.

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**Figure 2.** Baseline and 24-hour levels of gingival crevicular β-glucuronidase.


