ABSTRACT

Background: Chronic recurrent sinusitis (CRS) is one of the most common chronic conditions in the United States. There is a significant subpopulation of CRS patients who remain resistant to cure despite rigorous treatment regimens including surgery, allergy therapy and prolonged antibiotic therapy. Antimicrobial photodynamic therapy (aPDT) is a non-invasive non-antibiotic broad spectrum antimicrobial treatment. Our previous in vitro studies demonstrated that aPDT reduced CRS polymicrobial biofilm and planktonic bacteria and fungi by >99.9% after a single treatment.

Prior to human treatment however, aPDT treatment must be demonstrated to not result in histologic damage to the sinus ciliated respiratory epithelium. The objective of this study was to demonstrate the safety of aPDT treatment on a living human ciliated respiratory mucosa model (EpiAirway™).

Methods: Treatment groups included a non-treatment control, laser light alone, photosensitizer alone and therapeutic photosensitizer and light combination (aPDT). In all, seven study groups, each with four specimens, were evaluated in order to assess the effect of various treatment conditions on the EpiAirway™ ciliated respiratory mucosal grafts. The optimal aPDT treatment conditions for CRS therapy have been previously determined to be MB 0.03% incubated for 3.5 minutes at 37°C. After completion of treatment, the EpiAirway™ tissue was fixed in 10% formalin, paraffin-embedded, sectioned, H & E stained and mounted. All samples were blinded and microscopically examined by a human pathologist to assess any effect of aPDT on the tissue, cilia or mucosal epithelium. The results were correlated with the treatment parameters.

Results: The EpiAirway™ histologic study demonstrated no histologic alteration of the respiratory cilia or mucosal epithelium in any of the treatment groups.

Conclusions: aPDT is a safe treatment for CRS resulting in no histologic alteration of ciliated respiratory epithelium.

REFERENCES


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The Effect of Antimicrobial Photodynamic Therapy on Human Ciliated Respiratory Mucosa

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INTRODUCTION

Chronic recurrent sinusitis (CRS) is one of the most common chronic conditions in the United States affecting an estimated 37 million Americans and is a significant subpopulation of patients with CRS remain resistant to cure despite rigorous treatment regimens including surgery, allergy therapy and prolonged antibiotic therapy. One of the major causes of recurrent CRS is the polymicrobial biofilm colonization of the sinuses resulting in a local inflammatory response, edema and chronic infection. The failure of standard therapies to control and cure CRS, other novel non-antibiotic therapies that are able to destroy biofilms and antibiotic resistant bacteria and fungi which contribute to the chronic recurrence of CRS are needed.

RESULTS

The histomorphological evaluation of the EpiAirway™ human ciliated respiratory epithelium demonstrated no histological evidence of epithelial damage when compared to untreated controls. The epithelium was intact with normal-appearing cilia and mucosal epithelium. There was no histological evidence of epithelial injury or morphologic changes.

CONCLUSIONS

The present study demonstrated that MB PDT is highly effective in the photoreactivation of pathogenic Candida and various antibiotic resistant gram positive and gram negative bacteria that are commonly associated with chronic recurrent sinusitis. Importantly, in in vitro biofilm studies demonstrate a greater than 6.5 log reduction of antibiotic-resistant multi-species bacterial biofilms after a single PDT treatment. Using a higher MB concentration and lower light parameters achieved greater than 7 logs of bacteria kill using two PDT light treatments. These results demonstrated that MB PDT results in a significant reduction in antibiotic-resistant multi-species bacterial biofilms that are commonly found in CRS. These studies therefore indicated that MB PDT may be an effective treatment method for the control or eradication of bacterial biofilms from the sinuses.

DISCUSSION

CRS is one of the most common chronic conditions in the United States affecting an estimated 37 million Americans and a significant number of patients with CRS remain resistant to cure despite rigorous treatment regimens including surgery, allergy therapy and prolonged antibiotic therapy. One of the major causes of recurrent CRS is the polymicrobial biofilm colonization of the sinuses resulting in a local inflammatory response, edema and chronic infection. Due to the failure of standard therapies to control and cure CRS, other novel non-antibiotic therapies that are able to destroy biofilms and antibiotic resistant bacteria and fungi that are a major contributing cause of CRS. However, prior to human clinical use, MB aPDT treatment must be demonstrated to not result in histologic damage to the normal sinus ciliated epithelium.

The photodynamic mechanism of bacterial and fungal cell destruction is by perforation of the cell membrane or wall by PDT induced singlet oxygen and oxygen radicals thereby allowing the bacteria, viruses, allergies, fungi, superantigens, exotoxins and microbial biofilms. Importantly, CRS is also considered to be a significant factor that can exacerbate asthma, chronic lung diseases, eczema, otitis media and chronic fatigue. Failure to effectively treat CRS not only results in prolonged illness but can also result in significant complications including osteomyelitis of the facial bones, meningitis and brain abscesses.

In clinical practice there is a significant subpopulation of patients with CRS who remain resistant to cure despite rigorous treatment regimens including surgery, allergy therapy and prolonged antibiotic therapy. The reason for treatment failure is thought to be the destruction of the sinus mucosal defense by the chronic sinus infection resulting in the development of secondary antibiotic resistant microbial colonization of the sinuses and biofilms forming in the sinus mucosa. Methicillin resistant Staphylococcus aureus (MRSA) and multidrug resistant Pseudomonas aeruginosa are found in the clinical isolates of CRS patients and are a cause of antibiotic treatment failures. Numerous investigators have reported the presence of biofilms in the sinuses of patients with CRS and consider biofilm as a cause of the recurrent nature of persistent CRS. CRS with its chronic indolent course, resistance to antibiotics and acute exacerbations has a clinical course that parallels that of chronic recurrent sinusitis.

The present study of the effect of MB alone and MB aPDT treatment on a validated living human ciliated respiratory mucosa model (EpiAirway™) demonstrated intact ciliated respiratory epithelium without necrosis or destruction of cilia.

METHODS AND MATERIALS

EpiAirway™

EpiAirway™ ciliated respiratory mucosal tissue, each entire specimen was fixed in neutral buffered 10% formalin, processed, paraffin-embedded, sectioned, H & E stained and mounted. All samples were blinded and microscopically examined by a human pathologist to assess any effect of aPDT on the tissue, cilia or mucosal epithelium. The results were correlated with the treatment parameters.

RESULTS: The EpiAirway™ histologic study demonstrated no histologic alteration of the respiratory cilia or mucosal epithelium in any of the treatment groups.

Conclusions: aPDT is a safe treatment for CRS resulting in no histologic alteration of ciliated respiratory epithelium.

Figure 1. EpiAirway Untreated Control (H&E, HPF 20X) demonstrating intact ciliated respiratory epithelium with intraepithelial vesicles.

Figure 2. EpiAirway exposed to MB 0.3%, 10X therapeutic concentration, (H&E, HPF 20X) demonstrating intact ciliated respiratory epithelium.

Figure 3. EpiAirway exposed to full PDT treatment, MB 0.03% and 670nm light at 150mW/cm², (H&E, HPF 20X) demonstrating intact ciliated respiratory epithelium without necrosis or destruction of cilia.

Figure 4. MB PDT demonstrated histomorphological evaluation of the EpiAirway™ human ciliated respiratory mucosa model (EpiAirway™).