Published in final edited form as:

Photodiagnosis Photodyn Ther. 2010 September ; 7(3): 158–161. doi:10.1016/j.pdpdt.2010.06.001.

Targeted Laryngeal Photodynamic Therapy with a Balloon Diffusing Light Source

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Abstract

Photodynamic therapy (PDT) has been used for premalignant mucosal lesions. In an attempt to treat a patient with recurrent high-grade dysplasia of the glottic larynx, we were faced with technical challenges leading us to abandon the classic microlens fiber for a 2-cm long translucent diffusing balloon catheter to deliver photoactivating light to the targeted lesion. Real-time measurements confirmed stable photobleaching with augmentation of the prescribed light fluence secondary to light scatter in regions not in contact with the balloon diffuser. We report a potential new application of the balloon catheter that may be more suitable for anterior glottic lesions associated with minimal acute toxicity.

Keywords

Photodynamic Therapy; Head and Neck Pre-Malignant Lesions; ALA; Levulan; Protoporphyrin IX; Balloon Catheter

Clinical Case

We present the case of a 67 year-old male with treatment-induced dysphonia enrolled on an approved Phase I clinical trial of escalating total light dose in combination with the oral photosensitizer, Levulan[®]. Despite multiply recurrent dysplasia over a 7-year period treated with CO₂ laser excisions and vocal fold strippings for his multiply recurrent dysplasia, the patient continued to smoke tobacco. Routine surveillance confirmed biopsy-proven high-grade dysplasia on the right anterior vocal cord and anterior commissure (Figure 1a), and its anatomical borders were approximated from digital photos obtained by direct laryngoscopy with narrow band imaging (NBI) capability. After 60 mg/kg Levulan[®] was administered 5

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Disclosures: none

Conflict of Interest: none

hours prior to light delivery, light precautions were maintained during the following 72-hours.

Intraoperative PDT, Light Fluence and PpIX Measurements

The patient was placed under general anesthesia and intubated with a reinforced intubation tube. White pledgets were placed above the endotracheal inflated cuff to facilitate scatter dose to the inferior glottic mucosa. Suspension laryngoscopy used a Storz anterior commissure scope. A standard silica fiber with a flat microlens at the distal tip was placed down the laryngoscope. We found that the illuminated field could not adequately cover the anterior located lesion. The limited ability to immobilize the distal microlens resulted in the risk of non-uniform light fluence especially for a small illuminated field (1). As such, we evaluated the merits of using a 2-cm long translucent diffusing balloon catheter (Model CDB-LB20, MedLight SA, Ecublens, Switzerland) previously described for PDT for dysfunctional uterine bleeding and Barrett's esophagus.

The inflated balloon was placed straddling the subglottic and supraglottic mucosa and anterior commissure (Figure 1b). After the stylet used to guide the catheter during passage into the larynx was removed, the 2-cm long cylindrical diffusing fiber (CDF; Model RD, Medlight SA, Ecublens, Switzerland) was introduced. This CDF has a core diameter of 500 μm and an active length of 2 cm. Insertion length of the fiber was premeasured in order to ensure that the diffuser was positioned in the center of the effective length of the cylindrical balloon. The balloon was inflated with normal saline to an 8 mm diameter adapting to the surrounding tissue. The CDF was attached to a Cerelas GaAlAs 4W diode laser emitting a peak wavelength of 632 nm. This resulted in a very stable light fluence rate and profile measured throughout treatment (Figure 2) using an isotropic detector placed within the treatment field. The fluence rate was prescribed to half of the maximum value, i.e. 50% of 180 mW/cm² in order to account for the inhomogeneity of the fluence rate within the treatment field.

Postoperatively, we observed glottic mucositis limited to the mucosa in proximity to the balloon with no patient reported side effects. Although mucositis completely resolved by postoperative day 22 (Figure 1e) where the balloon diffuser was juxtaposed to the mucosa, it was not until day 31 (Figure 1f) that complete healing of the posterior subglottis occurred. This spatiotemporal healing pattern was consistent with our fluence measurements that validated differences in fluence rate along the longitudinal axis of the balloon diffuser (Figure 2). We surmise that the higher dose to the posterior subglottic mucosa not in contact with the balloon resulted not only from back-scattering and surface reflection of light occurring when light is delivered to a hollow organ such as the larynx and from scattering off of the metallic endotracheal tube and white pledgets. A complete clinical response has been achieved six months from treatment, which is the time of his last follow-up.

ALA is metabolized to the photosensitizer protoporphyrin IX (PpIX). Quantifying the decline in PpIX concentration during treatment offers a surrogate assessing potential therapeutic efficacy with its photobleaching correlated with the extent of tissue injury. PpIX measurement confirmed target drug accumulation prior to light delivery (Figure 3) and was performed with a flat-cut optical fiber placed parallel to the axis of the balloon diffuser positioned with its field of view covering the treatment area (Figure 1c). The light collected was passed through a long-pass optical filter to remove the treatment light and collected by a CCD spectrograph at 15-second intervals analyzed using a singular value decomposition algorithm (2). The background spectrum was captured from the final measurement during treatment, at which point the PpIX and photoproduct contributions had been bleached away. To correct for variations in the positioning of the detection fiber and intensity of the light

source, we normalized PpIX and photoproduct emission intensities to background fluorescence. During treatment, the intensity of the fluorescence peak decreased until it was indiscernible from baseline (the discontinuity around 4.5 J/cm² was likely the result of a shift in the position of the probe, Figure 3).

Acknowledgments

Levulan[®] was kindly provided by DUSA Pharmaceuticals.

This study was supported in part by the National Institutes of Health (R01-CA-129554-01A2 and T32-CA-009677) and American Cancer Society (IRG-78-002-28). Its contents are solely the responsibility of the authors and do not necessarily represent the views of the National Cancer Institute.

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Figure 1. Photodynamic Therapy

Baseline examination demonstrated high-grade dysplasia of the right anterior vocal cord mucosa (red circle, A). Intraoperatively, a reinforced endotracheal tube and the balloon diffuser were introduced with the balloon apposed to the glottic mucosa and the probe measuring PpIX fluorescence on the right glottic mucosa (B). The optical fiber measuring the light intensity was placed on the left glottic mucosa ("x"). Postoperative day 3 (C), day 8 (D), day 22 (E) and day 31 (F) demonstrated mucositis healing first in the area in contact with the balloon.

Figure 2. Light Fluence During Photodynamic Therapy

A mean light fluence of 50 J/cm^2 was prescribed at a fluence rate of 90 mW/cm^2 (total treatment time of 556 seconds). The actual delivered fluence measured at the midpoint of the balloon ($x = 0$) is significantly greater than the planned prescription near the ends ($x = \pm 1 \text{ cm}$) due to the effects of light scattering and CDF uniformity. Fluence remains stable during the treatment.

Figure 3. Photobleaching of Protoporphyrin IX (PpIX)

Levels of PpIX decrease as administered light reaches the final prescription dose of 50 J/cm². A parallel decline was seen in the photoproduct of PpIX, which is produced as PpIX is consumed in the photoreaction.