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The effect of photodynamic therapy (PDT) on oesophageal motility and acid clearance in patients with Barrett's oesophagus

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Abstract

Background: Barrett's oesophagus is the major risk factor for oesophageal adenocarcinoma. It is proposed that long-term re-epithelialisation, which has been achieved following ablation using 5-aminolaevulinic acid (5-ALA) photodynamic therapy (PDT) may reduce the risk of malignant change. However, it is not known whether PDT modifies oesophageal motility.
Aim: To assess oesophageal pH and motility before and after PDT ablation in treated and untreated areas of the oesophagus.
Methods: Twelve patients (10 male) with Barrett's oesophagus, median segment length 4 cm, were treated with PDT ablation. Twenty-four hours pH assessment and oesophageal manometry were performed before and 4–6 weeks after ablation. PDT was carried out using 635 nm red light, 4–6 h after administration of 30 mg/kg 5-ALA. Proximal (untreated) and distal (treated) oesophageal resting pressure, wave amplitude, percentage peristalsis and percentage study time oesophageal pH < 4, were assessed. Proton pump inhibitors (PPI) were administered throughout the study.
Results: There were no significant differences in oesophageal motility in treated or untreated areas of the oesophagus after PDT compared to pre-treatment values. Patients who continued to experience oesophageal acid exposure required more treatments to achieve complete Barrett's ablation.
Conclusions: Oesophageal motility following ALA-PDT suggests a trend toward enhanced wave propagation however continued oesophageal acid exposure may affect PDT efficacy.

Keywords: Barrett's oesophagus; Oesophageal motility; Photodynamic therapy; ALA; Argon beam plasma coagulation

1. Introduction

Oesophageal motility is often impaired in Barrett's oesophagus, the level of impairment increasing with the Barrett's segment length [1,2]. Controversy exists as to whether pre-existing disturbed motility leads to metaplasia, or if it occurs in response to prolonged mucosal injury. Poor oesophageal clearance increases oesophageal exposure to the presence of any noxious refluxate, therefore any treatment that reduces oesophageal motility and the efficacy of clearance mechanisms may have the potential to increase the risk of adenocarcinoma.

Several different modalities are currently employed to treat Barrett's oesophagus including proton pump inhibitor (PPI) therapy, anti-reflux surgery and mucosal ablation. Gastric acid suppression using a variety of PPI's has been the predominant means of reducing both the volume and the acid content of reflux [3]. However, this fails to address the problem of duodeno-gastro-oesophageal reflux (DGOR), and the greatest complications have been seen to occur with concomitant acid and alkaline reflux [4]. Gastric acid suppression may reduce oesophageal clearance mechanisms resulting in prolonged oesophageal exposure to alkaline reflux [5], since the presence of acid within the

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oesophagus stimulates a number of receptors (mechanoreceptors, baroreceptors and chemoreceptors) to initiate both primary and secondary peristalsis to clear any refluxate [6–8]. Neither gastric acid suppression nor anti-reflux surgery has been shown to achieve regression of the Barrett's epithelium, or a reduction in the incidence of malignancy [9–11]. In contrast, mucosal ablation aims to reduce the risk of oesophageal adenocarcinoma by inducing squamous re-epithelialisation.

Several ablation therapies have been employed, including photodynamic therapy (PDT) and argon plasma coagulation (APC). Following randomised placebo controlled clinical trials using ALA-PDT [12] we have demonstrated long- term (5 years) mucosal re-epithelialisation in Barrett's Oesophagus [13]. However, evidence of the effect of ablation therapy on oesophageal motility appears to be contradictory. The only PDT study published to date suggested that this therapy may be detrimental to oesophageal motility in some patients, possibly due to mucosal inflammation, scarring and fibrosis, or to systemic effects such as cytokine activation [14]. However, this study selected a mixed group of patients, including those with Barrett's oesophagus and oesophageal carcinoma, and employed photofrin, a photosensitiser which accumulates both within the submucosa and muscularis mucosa, causing deeper tissue injury [15,16] when compared to ALA-PDT where the accumulation of the photosensitiser is restricted to the oesophageal mucosa [17,18]. A small study investigating the effects of APC on motility demonstrated that peristaltic amplitude may increase [19].

The choice of photosensitiser and the application of light during PDT can affect the depth of tissue injury due to photosensitiser accumulation and localisation, the wavelength required for activation (and therefore depth of treatment achieved) [20,21] and the degree of fibrosis that ensues; consequently, oesophageal contractility may also be affected by the same mechanism. It has been shown that mucosal injury resulting in oesophageal stenosis with the possible formation of stricture, may raise the oesophageal resting pressure [22]. Any reduction in the efficacy of oesophageal clearance mechanisms may prevent re-epithelialisation and promote further mucosal change.

The primary aim of this study was to investigate the effects of ALA-PDT (30 mg/kg) on oesophageal motility and acid clearance in Barrett's oesophagus, as there are no previously published studies. Motility was compared in treated (distal) and untreated (proximal) areas of the oesophagus, in addition to an assessment of 24 h pH, made prior to PDT treatment and after complete ablation was achieved, as identified by histological evaluation.

2. Materials and methods

Research ethics committee approval was gained (South Sheffield Research Ethics Committee; Reference number 00/031) for this study. Informed written consent was obtained from 12 patients (10 males and 2 females, median age 56 (range 51–81), all with biopsy proven metaplastic Barrett's oesophagus recruited from a cohort undergoing endoscopic ablation in a clinical trial comparing PDT with APC [23]. The median Barrett's segment length was 4 cm (range of 2–6 cm). All patients were administrated esomeprazole (Nexium, Astra Zeneca, UK) 40 mg daily throughout the trial. Prior to the study PPI therapy had been administered for at least 12 months and continued after the trial. Oesophageal manometry and 24-h pH studies were performed before the initial PDT treatment. PDT was repeated at 4–6 week intervals using 5-ALA 30 mg/kg and 635 nm red light until both macroscopic appearance and biopsies taken for histological assessment confirmed complete ablation. Assessment was carried out by a single experienced pathologist using modified Seattle criteria. Previous studies have shown that repeated treatments [23] with these parameters enhance Barrett's regression when compared to a single PDT treatment [12]. The oesophageal manometry and 24-h pH study were repeated 4–6 weeks after complete ablation was achieved and an assessment was made of any differences in motility.

2.1. Oesophageal manometry

A 9-lumen oesophageal catheter (Oakfield Instruments Ltd, Oxon, UK) was connected via transducers to water perfused manometry equipment (Albyn Medical, Dingwall, Ross-shire, Scotland – Phoenix system). Four radially spaced ports (90° apart) were positioned 5 cm from the catheter tip. Further ports were positioned longitudinally at 5 cm intervals along the catheter, which were also circumferentially orientated at 90° to adjacent ports.

The catheter was introduced via the nares with the patient seated. Initially all of the ports were placed into the stomach. The manometry continued with the patient recumbent and the mid-axillary line level with the pressure transducers. The catheter was pulled back at 1 cm intervals until the four level ports nearest to the tip were placed within the lower oesophageal sphincter (LOS). The catheter was held in this position with micropore tape while 10×10 ml boluses of water were given orally at approximately 30 s intervals. Oesophageal function in both the untreated proximal oesophagus and the treated distal oesophagus was assessed by oesophageal manometry both before the start of treatment and after PDT ablation was achieved. Measurements were taken from the proximal untreated area, approximately 15 cm above the area of the LOS showing the highest pressure, and from the distal, treated area of the oesophagus, approximately 5 cm above the highest pressure point of the LOS. Following complete ablation, 4–6 weeks later, a second manometry evaluation was carried out.

A standard oesophageal manometry protocol was used [24]. Mean mid-respiratory cycle pressure measurements were obtained (in cm H_2O) and the following parameters measured:

(1) Baseline lower oesophageal sphincter (LOS) pressure, (absolute pressure minus the gastric pressure); (2)