Effect of adjuvant Pentoxifylline and Vitamin E on compliance of pharyngoesophageal junction after endoscopic dilatation.

Version Number: 3.0

Date of Protocol: 13/08/2018

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2 BACKGROUND

2.1 Disease Background

Head and neck cancer (HNC) is the 6th most common cancer, accounting for an estimated 650,000 newly diagnosed cancers each year worldwide [1]. The advent of concurrent chemoradiotherapy (CRT) led to an excellent 5-year cancer free survival of >70% [2, 3]. However, normal tissues are inevitably exposed to high radiotherapy doses leading to a range of acute and late treatment toxicities.

Swallowing dysfunction (dysphagia), primarily due to fibrotic stricturing at the pharyngo-oesophageal junction (POJ), often in conjunction with nerve and muscle damage, is the most common and the most devastating [4, 5] of the long-term complications in survivors. Fibrosis is a common consequence of RT in many organs. Post-RT strictures of the pharyngoesophageal junction (POJ) have an incidence of 20% in radiographic studies[6]. However, in our cohort (n=35) of HNC patients with dysphagia (approx. 60% of all our HNC survivors[7]) who underwent empiric dilatation, 80% had reduced POJ compliance on direct measurement at endoscopy[8]. Hence, the true prevalence of reduced POJ compliance contributing to dysphagia is approximately 45% of all HNC survivors. Traditionally, stricturing was believed to be a delayed complication.

Pentoxifylline (PTX) is currently used to improve circulation in peripheral vascular disease. Although its exact mechanism of action as an anti-fibrotic agent has not been fully elucidated, in-vivo, it has been shown to increase red blood cell flexibility, dilate blood vessels and inhibit inflammatory reactions. In-vitro studies have indicated that Pentoxifylline inhibits cells that synthesize the structural framework of animal tissues and increase activity of enzymes which break down collagen [9].

The role of Vit E as a scavenger of the reactive oxygen species generated during oxidative stress protecting membrane lipid components is well documented [10]. In addition to its antioxidant properties, many of Vit E activities are mediated by a non-antioxidant mechanism involving regulation of genes known to be involved in fibrotic process[10].

Interestingly, Pentoxifylline and Vit E display drug synergy with the effect of the combination being more potent than that of either of the individual treatments, even at much higher concentrations[11]. Pentoxifylline combined with Vit E has been demonstrated in both in-vitro and animal studies[12] as well as clinical studies[11] to reverse chronic RT-induced fibrosis. Several controlled and uncontrolled trials in women with breast cancer after RT demonstrated reversal of RT-induced fibrosis in the treated group [13-15]. In HNC, data is also encouraging but currently limited to uncontrolled studies. In one study, Pentoxifylline alone achieved reversal of painful iscarring in 4/6 patients[16]. In a larger cohort, an objective response to treatment

at 12 months was recorded in 23/28 (83%) RT-induced fibrosis areas, with a mean decrease of 67% in their surface areas [12].

2.2 Rationale for performing study

Strictures of the POJ, are traditionally managed by endoscopic dilatation imposing a significant burden on patients and the healthcare budgets as it requires sedation, operating theatre staff and multiple dilatation sessions. While the response rate is good (75%) it is not durable with a relapse rate of 50% at 19 months. Multiple sessions are often required, firstly to achieve a safe and satisfactory response and secondly to maintain remission. In a review of 54 consecutive patients in our department, 203 dilatations were required over 5yrs (average of 4 per person). With this ongoing burden of maintenance therapy, there is an urgent need for a safe but more effective and durable method to manage this problem.

Up to date there is a paucity of proven anti-fibrotic pharmacological approaches. Pentoxifylline (PTX) and Vitamin E (Vit E) combination, which is today available for clinical use, shows promising results and may be clinically useful in the management of established POJ strictures currently managed by endoscopic dilatation, however, this efficacy needs to be established in a rigorous RCT

3 AIMS AND HYPOTHESES

This is preliminary pilot study, conducted in order to evaluate feasibility, time, cost, and effect size, and consequently provide information to predict an appropriate sample size and improve the study design prior to developing a full scale randomised controlled trial (RCT).

The specific aims of the full scale RCT are tudy is to determine whether combination of Pentoxifylline and Vitamin E prevent symptom relapse and improve compliance of pharyngoesophageal junction after endoscopic dilatation.

Primary Hypothesis: Patients treated with Pentoxifylline and Vitamin E have a more compliant POJ, 12 months after endoscopic dilatation when compared with placebo treatment.

Secondary Hypothesis: Following endoscopic dilatation of POJ, the dysphagia relapse rate is reduced in patients treated with Pentoxifylline and Vitamin E compared with placebo.

4 STUDY DESIGN

4.1 Approach

The study design mimics the design of a RCT however it is not powered to show unequivocal proof of treatment's efficacy. Its purpose is to test the design of the full-scale trial which then can be adjusted if problems are identified in the pilot study to improve the likelihood of a clear outcome later.

4.2 Design

Pilot double-blind randomised controlled trial

4.3 Study Groups

Patients with dysphagia symptoms undergoing dilatation for a stricture of a pharyngo-oesophageal junction.

Subjects will be randomised into 2 groups:

1) Receiving Pentoxifylline + Vite. E treatment

2) Receiving placebo

4.4 Treatment

1) Compounded tablets of Pentoxifylline and Vitamin E, three times a day for 12 weeks, combined daily dose of 1,200mg of Pentoxifylline and 1,000IU Vitamin E Succinate

Or

2) Identical placebo tablets

Active and placebo drugs will be supplied by STENLAKE compounding chemist.

4.5 Number of participants

40 participants (20 per group)

4.6 Number of centres

This is a single centre study (St George Hospital)

4.7 Duration

2 years from the time of ethics approval.

5 PARTICIPANT SELECTION

5.1 Inclusion criteria

- Age ≥18
- Completion of radiotherapy with or without adjuvant chemotherapy and dysphagia symptoms defined as Sydney Swallow Questionnaire > 234 (upper limit of normal).
- Clinical indication for endoscopic dilatation demonstrating a pharyngo-oesophageal junction stricture confirmed by EndoFLIP (see 6.3.2 below) defined as POJ compliance below the established lower limit of normal (CSA < 4.0 mm^2/mmHg) [8].
- No Vitamin E supplementation at least 2 weeks* before commencement on study medication and willingness to abstain from Vitamin E supplements including multivitamin formulations containing Vitamin E for the duration of the study. * (Plasma half-life of alpha-tocopherol is ~ 44hrs)

5.2 Exclusion criteria

- Individuals who cannot provide informed consent due to any reason (language barrier, impaired cognitive function)
- Recurrence or persistent disease following head and neck cancer treatment.
- Pre-existing disorder known to cause pharyngeal dysphagia such as: MVA, MND, Parkinson's, inflammatory myopathy.
- Pre-existing oesophageal disease known to cause dysphagia such as eosinophilic oesophagitis, achalasia, oesophageal cancer.
- Either current pregnancy, intended pregnancy or breastfeeding during the study
- History of severe haemorrhage, e.g. massive retinal haemorrhage, cerebral haemorrhage, acute myocardial infarction or recent history of peptic ulcer.
- Concomitant or recent use of Warfarin or impaired blood clotting.
- Previous intolerance to Pentoxifylline or other methylxanthines such as caffeine, theophylline, and theobromine.
- Significant impairment of renal or hepatic function or other co-morbid conditions which in the opinion of the investigators preclude inclusion in the study

5.3 Clinician screening guideline

Refer to Screening Guideline v1.0 document to flag participants with increased risk of adverse events and drug interaction for close monitoring.

6 STUDY OUTLINE

6.1 Study Flow Chart

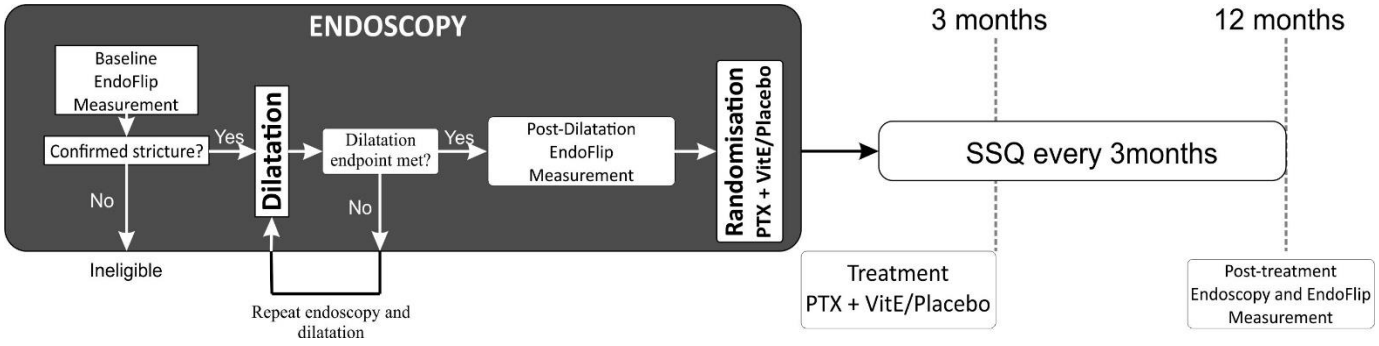

Figure 1. Study Flow Chart

6.2 Study Plan

Following informed consent, but prior to randomisation, participants will undergo a baseline diagnostic endoscopy as per 'standard of care'. While sedated the compliance (elasticity) of their pharynx will be assessed using EndoFLIP (see 6.3.2 below) and they will undergo an endoscopic dilatation procedure. If baseline compliance of the POJ is reduced ie: a fibrotic stricture is present, the EndoFLIP assessment will be repeated after dilatation and participants will be randomised to receive either 1) PTX + VitE or 2) Placebo after the dilatation. Endoscopy and dilatation is part of routine care and is indicated regardless whether a patient is participating in the study.

NOTE: In case when dilatation endpoint is not met during the first dilatation (see 6.3.3 below), endoscopy will be repeated until one of the endpoints is met and then post-dilatation EndoFLIP assessment will be performed and participant will be randomized and commence study medication. Repeated incremental dilatation are part of routine care (see 6.3.3 below).

Following discharge, patients will be followed-up by a monthly phone call while on study medication for 3 months (see telephone script in appendix). From 3 to 12 months participants will have the option to attend a 'Swallow clinic' every 3 months where they will return unused medication and their swallowing function will be assessed by SSQ. Otherwise medication and SSQs will be returned by posting ad reply-paid envelopes to the participants.

Repeat endoscopy with EndoFLIP will be performed at 12 months to assess the change in POJ compliance from the immediate post-dilatation assessment.

6.3 Component measurement techniques

6.3.1 Sydney Swallow Questionnaire (SSQ)

17 question self-reported inventory developed and validated by us [17] measuring the severity of oropharyngeal dysphagia. Importantly the SSQ has also been validated in the HNC patient population [18] and demonstrated to be a precise, reliable and valid tool to assess dysphagia severity [17]. SSQ assesses the physiologic aspects of swallow function, and yields a total severity score (range 0-1700; ULN <234 [7]).

6.3.2 Pharyngeal distensibility measurements

Endoluminal Functional Lumen Imaging Probe (EndoFLIP), an impedance planimetry based technique is a TGA Approved (ARTG: 173958) and validated measurement of pharyngeal strictures. Details about the unit and technique are provided in the appendix

6.3.3 Endoscopic dilatation of POJ

Endoscopic dilatation will be performed under conscious sedation. The upper gastrointestinal tract will be examined with a standard adult gastroscope (Ø 9.2 mm) or a pediatric gastroscope (Ø 5.4 mm) if the adult scope could not pass a stricture. Dilatations in all cases will be performed using Savary-Gilliard rigid dilators (Cook Medical, Bloomington, IN, USA) in the standard fashion over an endoscopically placed guide wire [19]. Sequential dilators will be passed with increasing diameters (1-mm increments) until either a mucosal tear is observed or significant resistance is encountered by the endoscopist.

Dilatation will be repeated every fortnight until either a passage of an 18-mm dilator or when the endoscopist feels it unsafe to proceed. Based on existing pilot data, a median of 3 dilatations per patient is required to achieve an outcome [20]. Hence, patients will be re-scheduled for repeat dilatation every 2 weeks until: a) 18mm dilator is passed, or b) further increase in size is deemed unsafe by the endoscopists.

6.4 Study Procedure Risks

6.4.1 Endoscopy and pharyngeal distensibility measurement

Will be performed under sedation at Day Surgery Unit, St George Hospital. A combination of sedative drugs (fentanyl, midazolam, and propofol) will be administered by an anaesthetic team led by an experienced anaesthetic consultant. Such sedation has small potential risk relating cardiac/respiratory function and drug allergic reactions. These risks are managed and minimised by a pre-anaesthetic consultation with anaesthetic consultants, during which any potential issue will be identified and addressed. Participants will only proceed with this procedure if it is deemed safe. During the procedure, participants will be monitored constantly to ensure safety.

Endoscopy involved in this procedure is a diagnostic (non-interventional) procedure utilising standard endoscope (Olympus H190 gastroscope). Thus, no significant risk is anticipated. Pharyngeal distensibility is performed following the endoscopy using a flexible catheter (EndoFLIP) approved for clinical use. Pharyngo-oesophageal distensibility measurement using this technique have been shown to be safe with no known risk to participants [21, 22]. Our laboratory has extensive experience with this technique in over 200 cases confirming its safety [8].

6.4.2 Pentoxifylline (TRENTAL 400) - adverse events

Source TGA Product Information (last amended 25 September 2015)

The following adverse effects have been reported in clinical trials or post-marketing with Trental 400 with dosages of 400 mg two to three times daily, with treatment periods up to 60 weeks

Gastrointestinal

The most frequent (greater than 1% incidence) types of side effects seen with Trental (all formulations) were gastrointestinal upsets, including nausea, dyspepsia, vomiting, belching/flatus/bloating, abdominal pain, epigastric discomfort and diarrhoea. However, the controlled release preparation of Trental 400 resulted in much fewer gastrointestinal side effects, the most common being dyspepsia 2.8% (placebo 4.7%), nausea 2.2% (placebo 0.8%), vomiting 1.2% and belching/flatus/bloating (0.6%). Anorexia, cholecystitis, constipation and a dry mouth/thirst have been reported with a frequency of less than 1%.

Central Nervous System

Side effects related to C.N.S. disturbances with an incidence of greater than 1% included dizziness, headache, insomnia and sleep disturbances and disorders, blurred vision, agitation/nervousness, drowsiness and tremor. Of these, the following were reported for the controlled release preparation Trental 400: dizziness 1.9% (placebo 3.1%), headache 1.2% (placebo 1.6%) and tremor 0.3% (placebo 0.8%). Anxiety and confusion have been reported with a frequency of less than 1%. Isolated cases of aseptic meningitis have been reported.

Cardiovascular

Only angina/chest pain was reported for Trental 400 tablets, with an incidence of 0.3%, while for the capsule formulation flushing and arrhythmia/palpitation/tachycardia were also reported, with an incidence of greater than 1%. Reports of hypotension were rare (<0.1%). Dyspnea and oedema have been reported with a frequency of less than 1%. Haemorrhage has also been reported (frequency unknown).

Hepatic

Isolated cases of intrahepatic cholestasis and jaundice as well as hepatitis and transaminase elevation have been reported.

Haemic and Lymphatic

Decreased fibrinogen, pancytopenia, purpura, aplastic anaemia, neutropenia and leukopenia. Isolated cases of thrombocytopenia have been noted

Respiratory

Epistaxis, flu-like symptoms, laryngitis and nasal congestion have been reported rarely.

Hypersensitivity

Anaphylactic and anaphylactoid reactions have been reported. Pruritus, rashes and urticaria may occur with a frequency of 0.1% to 1% but progression to anaphylactoid shock (angioedema, bronchospasm) occurs only in isolated cases. Erythema (reddening of the skin) has been reported at an unknown frequency.

Miscellaneous

Rarely, the following were reported: brittle fingernails, blurred vision, conjunctivitis, earache, scotoma, bad taste in the mouth, excessive salivation, malaise, sore throat, swollen neck glands, weight change.

6.4.3 Vitamin E (TOCOPHEROL) - Adverse events

Vitamin E is generally considered safe and is available without prescription. The recommended upper limit of Vitamin Supplementation is based on haemorrhagic effects observed in animals given very high doses. Human trials fail to demonstrate consistently an association between excess α-tocopherol intake and haemorrhagic stroke or breathing. However, since both substances exhibit haemorrheological effects patients with history of GI bleeding, impaired clotting and previous haemorrhagic stroke will be excluded from the study.

6.5 Recruitment and Screenings

Potential participants with suspected pharyngeal stricture where endoscopic dilatation is indicated will be identified and screened for eligibility at Swallow Clinic (A/Prof Julia Maclean, Prof Ian Cook, Dr Peter Wu) or during post-cancer-treatment visits at Cancer Care Centre (A/Prof Julia Maclean, A/Prof Peter Graham).

SSQ will be used as a clinical assessment to quantify swallow impairment in post-laryngectomy patients. Score >234 will indicate pharyngeal dysphagia and suitability for this study. Potential participants will then be screened for exclusion criteria (see 5.2).

Screening will be completed after consent as presence of a stricture can only be truly identified during endoscopy while patient is sedated. If participant is eligible they will be enrolled into the study.

6.6 Informed Consent Process

Eligible individuals will be invited to participate in the study at the time of clinic appointment. If the invitees express interest, they will be given a copy of the PIS/CF and continue the discussion on the same day or a later appointment. The initial discussion will be approximately 30 minutes. Invitees who wish to have more time will be encouraged to take the PIS/CF home and contact the investigators at a later date.

Potential participants will typically have 2 or more weeks to consider participation, as they await the date of their Day Surgery Admission for endoscopic dilatation. Consent can be obtained on the day of their endoscopy but before sedation.

6.7 Adverse Event Reporting

Weekly research meeting will be held by investigators to review the study progress and adverse events. Adverse events will be handled according to the guidelines published in: " *Safety monitoring and reporting in clinical trials involving therapeutic goods.(2016) Canberra: National Health and Medical Research Council".*

6.8 Serious Adverse Event Reporting

All serious adverse events as defined in " *Safety monitoring and reporting in clinical trials involving therapeutic goods.(2016) Canberra: National Health and Medical Research Council"* will be reviewed by the DSMB panel as well as reported to ethics committee within 24 hours.

6.9 Data Safety and Monitoring Board

The National Statement on Ethical Conduct in Human Research (2007) permits monitoring arrangements to be commensurate to the risk, size and complexity of the trial. This trial involves TGA approved substances with known risk profiles, is small and single centre, and does not involve interim analysis. Investigators will review and discuss study progress during weekly research meetings and study coordinator will prepare a report monthly to A/Prof Winston Liauw to be reviewed at monthly meeting of the SESLHD Quality use of medicine committee.

7 RANDOMIZATION AND BLINDING

Patients will be randomised during the first endoscopic session following stricture confirmation and endoscopic dilatation (screened and consented prior).

- Ratio 1:1
- blocked randomization with random block sizes

- stratified by 1) treatment naive and 2) previous dilatation(s). Established strictures, which have been dilated previously, may behave differently to those undergoing index dilatation

To ensure double blinding is maintained, blinding of the study medication and dispensing will be managed by Clinical Trials Senior Pharmacist at the hospital pharmacy independent of the study team.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Calculation

The sample size of 40 patients for this pilot is based on the number of patients we estimate to recruit over the course of 12 months and maintain the study within budget.

8.2 Statistical Analysis Plan

This is a pilot study aiming to evaluate the feasibility of a full-scale project as such we will assess the following:

1) Exclusion/enrolment rates
2) Withdrawal rate
3) Tolerance to trial medication
4) Compliance to therapy
5) Data integrity
6) Protocol violations and trial completion rate
7) Dilatations required
8) Adverse Events

Treatment efficacy will be evaluated however the goal is to estimate the trajectory of change of the two continuous outcome variables (SSQ and Pharyngeal Compliance) within subjects from immediately post-dilatation out to 12months. These estimates will help to determine required sample size to show clinically relevant effect and design a full-sized trial competitive for Cat 1 funding.

Outcome measures

Primary: Dysphagia symptom severity - assessed by SSQ (see above) at baseline before dilatation and every 3 months.

Secondary: Pharyngeal compliance assessed by EndoFLIP at 12 months (see above);

9 STORAGE AND ARCHIVING OF STUDY DOCUMENTS

All data will be digitally stored on a secured computer hard drive. Completed questionnaires, endoscopy reports, case report forms will be stored in a locked cabinet inside research office.

The data will be stored for 15 years following publication according to guidelines in case results are challenged or audits are conducted. The data will be securely destroyed according to institutional guidelines using secure document disposal services this will include optical storage media such as CD/DVD. Files on hard drives will be permanently deleted.

10 APPENDICES

10.1 EndoFLIP system and protocol

Strictures of the pharyngo-oesophageal junction (POJ) are conventionally diagnosed fluoroscopically as a narrowed contour. However, we have shown recently that fluoroscopic images frequently fail to detect true stenosis in this population [23]. The likely explanation is that the weakened pharyngeal propulsion is insufficient to distend the hypopharynx (even though it and the POJ may be compliant). This either creates a false appearance of a stricture, or paradoxically, in the absence of adjacent distension, a failure to visualise a real stenosis [23]. For this reason, we now measure directly and objectively both luminal dimensions and tissue distensibility of the POJ using EndoFLIP (Crospon Ltd, Galway, Ireland), an impedance planimetry based technique. We have validated this technique as a highly accurate measures the POJ dimensions and distensibility [8].

In brief, the system comprises a catheter with a series of 17 ringed impedance electrodes (5mm apart) inside a cylindrical bag with infinite distensibility (10cm long) (Figure 1). The catheter is passed trans-orally to position the cylindrical bag within the region of interest in the oesophagus, and the bag infused with solution of known conductivity (0.3% saline) from an external controlled syringe pump integral to the system. During the step-wise distension of the bag, multiple cross-sectional areas along the axial length of the bag are accurately calculated from the measured impedance between paired electrodes at each axial site to create a model of bag area and contour shape. The bag also contains one solid-state manometer continuously measuring intra-bag pressure during inflation. This permits determination of the dynamic pressure-volume-area relationship from which distensibility curves are derived. The infusion is stopped at a predetermined pressure of 60mmHg, to avoid accidental dilatation of the measured organ.

Figure 1 EndoFLIP catheter and system console

10.2 **Follow up phone interview**

At monthly intervals from time of dilatation to 3 months (total 2 phone calls, the first at 4 weeks following enrolment and then at 8 weeks post enrolment.)

The researcher will greet and introduce themselves to participant.

The researcher will explain the purpose of phone call, to assess how the participant is tolerating medication on post dilatation for stricture trial. The researcher will inform the patient that that notes will be taken during the phone call to ensure that there is an accurate record of any issues or concerns raised.

Researcher will ask patient

i. If they have experienced any side effects from medication?

ii. If they have experienced any unexpected or severe bleeding for example prolonged nose bleed, or prolonged bleeding from relatively minor injury.

iii. If they have been able to comply with dosing as prescribed

iv. If they have commenced any new medication or supplement since the last contact

v. If they have any concerns with continuing on the trial

vi. If they have any feedback regarding the medication or trial that they would like us to consider

The researcher will then check that the patient has adequate numbers of medication.

Finally, the researcher will confirm the date and time of the next phone consult. At the 8 week phone call the researcher will confirm the date for the 12 week visit. Which can either be done at the Swallowing Clinic, a Cancer Care Centre follow up appointment or if they are referred from an external centre (or by patient choice) the SSQ can be posted with an addressed return envelope.

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