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Rationale and Design of a Trial for Prophylactic Nutritional Support (Pronus) During Treatment for Head and Neck Cancer: A Single-Center, Randomized, Controlled Trial Comparing Effects of Percutaneous Endoscopic Gastrostomy Tube and Nasogastric Tube Placement on Nutritional Status of Patients

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Abstract

Background: Prophylactic nutritional support of head and neck cancer patients being treated with chemoradiation through placement of either a percutaneous endoscopic gastrostomy (PEG) tube or a nasogastric (NG) tube is well-established in clinical care. There is, however, little scientific evidence to support one over the other.

Methods: We planned to conduct a randomized controlled trial to compare the effects of PEG tube or NG tube on nutritional status and quality of life of patients; the rates of clinical complications; and the cost of care. The trial was conducted at a tertiary care cancer specialist center in Lahore, Pakistan.

Results: The study was closed early because of refusal of eligible patients to be randomly assigned to the NG arm of the study. 7 patients were assessed for eligibility of whom 2 withdrew from the study after one week in the NG arm and 5 refused to be randomized to the NG arm.

Conclusion: We concluded that NG tube placement is not an appropriate first-line option for prophylactic nutritional support among head and neck cancer patients at our center and should not be offered.

Keywords: Chemoradiotherapy; Enteral nutrition; Head and neck neoplasms; Nutritional support; Quality of Life

Introduction

Malnutrition and serious weight loss of more than 10% of body weight as a result of mucositis and dysphagia are common among patients with head and neck cancers (HNC) undergoing chemoradiotherapy [1,2]. This exacerbates the poor nutritional status already seen in an estimated 25-50% of patients with HNC even before the start of treatment due to the location of the tumor [3]. Mucositis and dysphagia, with concomitant weight loss, compromise patients' quality of life, increase the risk of clinical complications and premature cessation of treatment, impact post-treatment recovery, and are prognostic of morbidity and mortality from HNC [4-7].

Recent guidelines have recommended prophylactic nutritional support in patients with HNC undergoing chemoradiation [8-14]. This can be offered either by placement of a percutaneous endoscopic gastrostomy (PEG) tube, or a nasogastric (NG) tube. Use of either PEG tube or NG tube is well-established in clinical care. There is, however, little evidence to support one over the other in prophylactic nutritional support in patients of HNC. A recent systematic review highlighted the paucity of evidence supporting the use of either modality [15].

Data from population-based cancer registries as well as hospital-based data indicate that head and neck cancers (cancer of the lip, oral cavity, pharynx, and larynx) are common in South Asian populations, including Pakistan [16]. One estimate from Karachi, Pakistan showed that HNC accounted for approximately 21% of the cancers in males and about 11% in females [17,18]. The age standardized incidence rate was 37.1/100,000 in males and 21.7/100,000 in females. In males, oral cavity and larynx were the commonly affected sites, followed by pharynx. In females, oral cavity was the predominant site [18]. Data from institution-based registries has similarly shown a high burden of HNC with late presentation and sub-optimal treatment [18,19].

The relatively high incidence of HNC in Pakistani population makes it even more important to assess the optimum method of nutritional support in patients undergoing treatment for HNC. We designed a randomized controlled trial to compare the effect of either PEG tube or NG tube placement on the nutritional status of HNC patients undergoing chemoradiation at the end of 24 weeks after treatment initiation. Our secondary objectives were to assess the rates of complication and quality of life of patients during the study period.

Methods

Study setting

Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCH&RC), the study site, is a 189-bed non-profit tertiary-care specialist cancer hospital with a referral base from all over the country and adjoining regions. In 2011, the hospital saw over 142,000 outpatient visits, 7600 admissions, 7800 surgical operations, 54,600 chemotherapy visits, and 44,500 radiation treatments [20]. Head and neck out-patient clinics are held twice a week where a consultant radiation oncologist and a consultant oral/maxillofacial surgeon are on service. In 2012, a total of 462 new HNC patients were registered at our center out of which 121 patients (26.2%) had prophylactic PEG tube placement.

Eligibility

All adult, treatment-naïve HNC patients presenting to the head and neck clinic and referred to the gastroenterology service for enteral feeding tube placement prior to initiation of chemoradiation were eligible. We excluded patients who had previously received cancer treatment, had presented with a relapse, had a contraindication to enteral feeding tube placement, and patients with moderate to severe mental or physical disabilities because such disabilities might preclude assessment of functional status deterioration related to the disease or its treatment.

Interventions

Radiation therapy: HNC patients received radiation therapy using large opposing lateral portals at 2.0 Gy per fraction, once a day, 5 days a week to a total dose of 70 Gy in 35 fractions in 7 weeks using 6 MV Siemens Primus linear accelerator. Dose to spinal cord was limited to 45 Gy from the lateral portals through shrinking field technique. The anterior neck field was treated at 2 Gy per fraction, 5 fractions per week to a dose of 45-50 Gy in 25 fractions over 5 weeks. Acute treatment toxicity was scored using the European Organisation for Research and Treatment of Cancer Radiation Therapy Oncology Group (EORTC/RTOG) toxicity criteria [21]. Severe acute toxicity in particular dysphagia is a common, debilitating and potentially life-threatening sequel of concurrent chemoradiation for head and neck malignancy. Grade 3-4 therapy-induced mucositis and/or dysphagia were expected to develop in about two thirds of patients.

Chemotherapy: Concurrent chemotherapy with Cisplatin was administered as a three weekly schedule (75 mg/m^2 day 1, 22 and 43) with prophylactic hydration and antiemetics.

PEG tube placement: 20 Fr PEG tubes (Wilson-Cook, Boston Scientific) were placed endoscopically using Ponsky's pull technique, under conscious sedation, as a day-case procedure. A single dose of a prophylactic intravenous antibiotic (1.2 g co-amoxiclav, 30 minutes prior to the procedure, unless evidence of penicillin allergy) was given to all patients undergoing PEG tube insertion. Patients were monitored for one hour prior to discharge following PEG tube insertion.

NG tube placement: All nasogastric tubes, mostly fine-bore 14 Fr tubes, were inserted in a standard manner by a gastroenterology fellow following which a post-procedure abdominal X-ray was performed to confirm correct placement.

Outcomes

Nutritional status: In addition to patients' demographic information and baseline clinical status, nutritional status was assessed using Patient-Generated Subjective Global Assessment (PG-SGA) tool – specifically developed for use in the cancer population; anthropometric data; and biochemical data [22-24].

Quality of life: Health related quality of life was assessed using the Urdu translation of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) version 3.0 [25]. The core questionnaire (EORTC QLQ-C30) consists of six function scales (physical, emotional, cognitive, social, role, and global health), three symptom scales (fatigue, pain, nausea or vomiting), and six single items assessing symptoms and the financial impact of the disease. In addition, we used a head and neck cancer specific quality of life instrument Functional Assessment of Cancer Therapy Head and Neck (FACT H&N) version 4 [26,27]. In addition, patients' mental and emotional health was assessed using Hospital Anxiety and Depression Scale (HADS). This brief, self-reported, 14-item scale was developed to screen for symptoms of depression and anxiety among patients being treated for medical problems in a hospital [28]. HADS has been widely used and validated in a variety of settings and has been specifically used in patients with head and neck cancers [29-32]. Studies have suggested that a combination of EORTC QLQ C-30, EORTC H&N-35, and HADS is a sensitive combination to assess QOL among HNC patients [31,32].

To calculate the required sample size, we assumed that the weight loss in both arms would be equal and would be 5 kg (Standard deviation SD: 2.3 kg) at 24 weeks follow up compared to the baseline. Fixing the probability of alpha error at 0.05 with two-tailed tests of hypotheses, our calculated sample size of 82 patients (41 in each arm of the study) gave us a 95% power to detect a difference of 2 kg or more between the two study arms. We planned to enroll 50 patients in each arm (n=100). Based on the data from our center that suggested that on average 10 HNC patients had prophylactic PEG tube placed every month during 2012, we expected that the enrollment would be complete in one year after the initiation of the study. This study was approved by the Institutional Review Board of SKMCH&RC.

Results

The study was opened for enrollment in February 2014. We identified 9 eligible patients for participation in the study. Their demographic and baseline clinical information is provided in Table 1. Two patients who were randomized to the NG tube arm dropped out of the study before the first follow up at 4 weeks. 5 eligible patients refused to be randomized to the NG tube arm. By the end of our planned enrollment period of one year from the start date, we had been unable to randomize any patients to the NG tube arm and therefore closed the trial. We discuss our patients' reasons for refusal in greater detail below.

Sex	Age	Primary site of tumor	Tumor histology	cT	cN	cM	stage	Weight (kg)	ECOG	BMI	SGA rating	Participation status
F	49	Nasopharynx	Undifferentiated carcinoma	T4	N2	M0	IV	60	0	27.4	3	Refused randomization
M	46	Nasopharynx	Undifferentiated carcinoma	T3	N3	M0	IV	74.5	0	24.6	1	Withdrew from study
M	64	Glottis	Squamous cell carcinoma	T3	N0	M0	III	101.4	0	34.7	1	Refused randomization
M	34	Nasopharynx	Undifferentiated carcinoma	T4	N0	M0	IV	82.6	0	26.6	2	Refused randomization
F	18	Nasopharynx	Undifferentiated carcinoma	T4	N1	M0	IV	43.9	0	19.3	3	Refused randomization
F	20	Postcricoid region	Squamous cell carcinoma	T4	N2	M0	IV	38.8	1	17.02	3	Withdrew from study
F	62	Nasopharynx	Undifferentiated carcinoma	T4	N2	M0	IV	42.7	0	17	0	Refused randomization

Table 1: Demographic and baseline clinical characteristics of patients found eligible for participation in the study.

Discussion

We designed a randomized controlled trial to compare the effect of prophylactic placement of PEG tube versus NG tube on nutritional status and quality of life of HNC patients undergoing chemoradiation. The impetus for this trial was a recent Cochrane Collaboration review that found inconclusive evidence comparing PEG tubes with NG tubes and called for more trials in this area [15]. A second reason to conduct this study was a lack of data from Pakistan that might help clinicians makes appropriate decisions within the local context. We were unable to meet our targets for enrollment because of patients' reluctance to be randomized to the NG arm.

In this study, while the patients were assessed for participation at the head and neck clinic, the steps of explaining randomization, the study processes, and follow up were undertaken by the officials of the research office who were not otherwise involved in the study. These officials surveyed the eligible participants regarding their unwillingness to be randomized to the NG arm. Patients were reluctant to have NG tubes inserted because they thought that NG tubes were uncomfortable, inconvenient, messy and cosmetically unacceptable. One possible explanation for patients' reluctance is that the current practice at our center is to place a PEG tube in all HNC patients who are planned to undergo chemoradiation treatment. Although, based on available evidence, a clinical equipoise exists regarding the choice between PEG or NG tube placement for nutritional support in HNC patients, our patients' probable knowledge of our center's practices contributed to their unwillingness to try a different, albeit shorter and less invasive, intervention.

Failure to enroll patients in a trial comparing PEG tubes and NG tubes among cancer patients has been reported previously. An Australian trial had to be stopped because of poor patient accrual (33 patients in 3 years), but this trial reported that while nutritional support with both tubes was good, there were no significant differences in overall complication rates and patient quality of life [33]. The trial's conversion into a prospective study and subsequent data analysis with 105 patients also failed to detect any differences between the two groups [34]. Other studies have also presented mixed findings. One prospective study comparing PEG tube with NG tube placement in HNC patients undergoing treatment found significantly less weight loss and fewer complications in patients with PEG tube compared to NG tube [35]. A retrospective 2-year audit of 32 HNC patients found that patients receiving enteral feeding using NG tubes had lower complication rates and higher rates of full oral intake at 6 months compared to patients with PEG tubes [36]. Similarly, a retrospective review of 90 stage-IV HNC patients at a single institution who were treated with PEG tube or NG tube placement on clinical indications suggested that while the nutritional outcomes were similar in the two groups, patient with PEG tube placement had fewer mechanical failures and infections, and better quality of life [37]. A retrospective review of 91 clinically-indicated enteral feeding tube placements over 8 years at a single institution found that PEG tube placements were associated with longer duration of tube placement, more persistent dysphagia, and an increased need for pharyngoesophageal dilatation in HNC patients who underwent radiotherapy or chemoradiotherapy [38]. Finally, a recent review of randomized controlled trials found mixed evidence as well [39].

While the available evidence that we have surveyed is mixed with a few studies favoring prophylactic placement of NG tubes as a lower cost and less-invasive intervention with lower patient-dependence, our experience reported here, suggests that patients may view PEG tubes as a superior intervention. The reasons for this preference, as we discuss above, are likely related to the discomfort associated with NG tube along with the higher risk of its accidental dislodgement. The greater visibility of NG tube compared to PEG tube is also likely to be a deciding factor. Our findings suggest that the trials comparing PEG tubes and NG tubes may no longer be feasible. Patients' reluctance to be randomized in this trial, as in one other recent trial, suggests that it may be appropriate to view PEG tubes as a first-line intervention for prophylactic nutritional support in patients with head and neck cancer with NG tubes reserved for those patients who are ineligible for PEG tube placement.

Conflict of Interest Statement

Compliance with ethical standards: This study received no grant from any organization. It was funded through internal hospital resources for clinical research.

Conflict of interest: The authors declare that they have no conflict of interest.

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