The Effect of Percutaneous Endoscopic Gastrostomy on Prognosis of Patients at Risk of Malnutrition

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ABSTRACT **Background:** Despite its wide use, evidence is inconclusive regarding the effect of percutaneous endoscopic gastrostomy (PEG) in patients with chronic diseases and dementia among hospitalized patients with malnutrition.

Objectives: To examine the effect of PEG insertion on prognosis after the procedure.

Methods: This retrospective analysis of medical records included all adult patients who underwent PEG insertion between 1 January 2009 and 31 December 2013 during their hospitalization. For each PEG patient, two controls similar in age, sex, referring department, and underlying condition were randomly selected from the entire dataset of patients admitted. The effect of PEG on mortality and repeated admissions was examined.

Results: The study comprised 154 patients, 49 referred for PEG insertion and 105 controls (mean age 74.8 ± 19.8 years; 72.7% females; 78.6% admitted to internal medicine units). Compared to controls, the PEG group had a higher 2-year mortality rate (59.2% vs. 17.1%, $P < 0.001$) but the 2-year readmission rate did not differ significantly (44.9% vs. 56.2% respectively, $P = 0.191$). Regression analysis showed PEG was associated with increased risk of the composite endpoint of death or readmission (hazard ratio 1.514, 95% confidence interval 1.016–2.255, $P = 0.041$). No specific characteristic of admission was associated with increased likelihood of death or readmission. Among readmitted patients, reasons for admission and baseline laboratory data, including albumin and cholesterol, did not differ between the PEG patients and controls.

Conclusions: In-hospital PEG insertion was associated with increased mortality at 2 years but had no effect on readmissions.

IMAJ 2023; 25: 215–220

KEY WORDS: malnutrition, mechanical feeding, mortality, percutaneous endoscopic gastrostomy (PEG), readmission

Malnutrition is a state in which there is an imbalance between protein and energy consumption and energy expenditure and is associated with adverse outcomes [1]. Malnutrition is steadily increasing among elderly individuals, likely due to increased survival with chronic diseases [2].

Among hospitalized individuals, the rate of malnutrition may be as high as 50% [3], depending on the population screened and the measurement tool used [2,3]. Malnutrition is associated with repeated hospital admissions and increased mortality [4]. Among reasons for admission are chronic disease exacerbations [4] and trauma due to falls and fractures [5]. Treatment of malnutrition is based on supporting nutrition intake. Nutrition supplements have been shown to reduce surgical complications when given during the hospitalization period [6]. In addition, they have been shown to prevent readmissions when prescribed for longer periods of time [7]. Among chronic obstructive pulmonary disease and congestive heart failure patients, for example, nutrition support has been shown also to reduce mortality, but with no effect on the hospital readmission rate [8].

Patients with swallowing difficulties have an increased risk of malnutrition [9]. One method for providing nutrition care in patients with difficulty swallowing is mechanical nutrition support, specifically percutaneous endoscopic gastrostomy (PEG). This method bypasses the swallowing mechanism and supplies food directly into the stomach. Insertion of PEG is done in cases when oral nutrition care is impossible, either due to a problem with the mechanics of swallowing or due to damage to the esophagus.

Nutrition support with PEG has become the leading choice for long-term nutrition intervention [10-12]. Although this method is probably more effective in preventing aspirations (but not pneumonia) compared to nasogastric (NG) tubes, this method is associated with higher mortality rates [13]. Despite this, PEG has been shown to reduce mortality in specific populations, most notably patients with malignancy of the head and neck. Despite its wide use, the effect of PEG in patients with chronic diseases [14] and dementia [15] is still not clear, and evidence is lacking regarding the effect of PEG among hospitalized patients with malnutrition.

We aimed to investigate the effect of PEG insertion on hospital readmission and survival among inpatients.

PATIENTS AND METHODS

ETHICS

The study was approved by the institutional review board as an observational study. The need for signed informed consent was waived.

STUDY DESIGN

We conducted a retrospective analysis of medical records.

STUDY POPULATION

For the past several years, the MEasuring NUtrition Risk in Hospitalized Patients (MENU) has been ongoing. The project protocol, and later Ministry of Health guidelines, calls for screening of all newly admitted adult patients to the hospital. Originally, this task was performed using the NRS2002 screening tool, Later the Malnutrition Universal Screening Tool (MUST) was used per Ministry of Health guidelines. In accordance with the study protocol and Ministry of Health guidelines, patients identified as being at increased risk for malnutrition risk patients received a complete nutrition assessment and treatment plan by a registered clinical dietitian [9].

For this study, we included all adult (≥ 18 years) patients admitted to the Wolfson Medical Center for whom a PEG was inserted between 1 January 2009 and 31 December 2013. Patients were excluded if PEG was performed on an outpatient basis, if they were younger than 18 years old when PEG was inserted, or if the admission was for replacing an old PEG. We also excluded patients with active malignancy (patients receiving chemotherapy, immunotherapy, or radiation) but included patients with malignancies in remission or past malignancy (cured). For each patient in the PEG group, two controls were randomly selected from the general patient population admitted to the hospital after matching for age (within 1 year), sex, by year of admission, and department of referral/admission. Departments included internal medicine units (including neurology and hematology), surgery (i.e., general surgery, obstetrics and gynecology, and orthopedics), and intensive care unit.

An index admission was defined as the hospitalization in which the PEG was inserted (for PEG patients). For the control group, it was the first admission in the corresponding year. The following information was extracted from the electronic medical record: number and duration of admissions in the 12 months prior and in the 12 and 24 months following the index admission, co-morbidities, date of death (when applicable), and laboratory data at the time of hospital admission. For patients who had a readmission during the follow-up period, date of first readmission, the reason, and laboratory data were also extracted. A composite endpoint of death or readmission for 1- and 2-year follow-up time points was calculated for each patient.

STATISTICAL ANALYSIS

All information was recorded using Microsoft Excel™ 2010 Version (Microsoft® Corporation, Redmond, WA, USA). Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA). Continuous variables, described as mean ± standard deviation, were tested for normality using the Kolmogorov-Smirnov test. Normally distributed parameters were compared between cases and controls using the *t*-test for independent samples. Variables with distributions significantly deviating from normal were compared between cases and controls using the Mann-Whitney U test. Nominal variables were summarized in frequency tables and presented as n (%). These variables were compared using the chi-square test or Fischer's exact test as appropriate. The paired *t*-test was used to compare changes in laboratory data across admissions. Cox regression models were used to examine the effects of PEG insertion on 2-year mortality and separately readmissions or the composite endpoints of mortality or readmission at a 2-year time point. For mortality, the model included 2-year mortality as the dependent variable and age, sex, the Charlson Comorbidity Index [16], and the patient group as covariates. For readmissions or the composite endpoint of death or readmission, the model included only age, sex, and the patient group as covariates.

RESULTS

During the data acquisition period, 49 patients who underwent PEG insertions during their hospitalization fulfilled the inclusion criteria. They were matched to 105 patients similar in terms of age, sex, and hospitalization within the same period. The study population is presented by at the index admission in Table 1. Co-morbidity prevalence was more frequently observed in the PEG group, and the Charlson Comorbidity Index was significantly higher. Despite this, index admission serum albumin, glucose, and creatinine levels were similar between PEG patients and controls. Most of the patients in both the PEG and control groups were discharged home following the index admission.

EFFECT OF PEG ON READMISSIONS AND MORTALITY

The rate of admissions in the 12 months preceding the index admission was similar between the PEG and control groups (70.4% vs. 69.8%, respectively, $P = 0.959$). In the 12 months (38.8% in PEG vs. 42.9% in controls, $P = 0.632$) and 24 months (44.9% in PEG vs. 56.2% in controls, $P = 0.191$) following the index admission, readmission did not differ by group. The rate of 30-day mortality was slightly higher among PEG-inserted patients compared to the control group (14.3% vs. 5.7%, respectively, $P = 0.075$). PEG insertion was associated with a signif-

Table 1: Demographic parameters, reason for admission, co-morbidities, and baseline laboratory data of the index admission

Parameter	PEG, n=49	Control, n=105	*P*-value
Age (years)	75.3 ± 19.4	74.5 ± 20.0	0.813
Female sex (%)	73.5	72.4	0.888
Department of admission			
Internal medicine (%)	79.6	78.1	0.105
Surgery, all types (%)	12.2	20.0	
Intensive care unit, all types (%)	8.2	1.9	
Index admission laboratory data			
Albumin (g/dl)	3.4 ± 0.7	3.5 ± 0.6	0.553
Hypoalbuminemia (%)	47.8	47.9	0.993
Creatinine (mg/dl)	1.1 ± 0.6	1.1 ± 0.7	0.572
Hemoglobin (g/dl)	12.8 ± 1.8	12.2 ± 2.2	0.097
Average glucose (mg/dl)	137 ± 49	120 ± 74	0.091
First glucose (mg/dl)	155 ± 79	146 ± 141	0.678
Reason for admission/acute conditions			
Infection (%)	25	38	0.096
Cerebrovascular accident (%)	16	3	0.002
Aspiration (%)	2	3	0.923
Pressure ulcer (%)	17	3	0.002
Decompensated congestive heart failure (%)	0	9	0.153
Decompensated chronic obstructive pulmonary disease (%)	0	6	0.432
Fluid and electrolyte imbalance (%)	25	3	< 0.001
Acute renal failure (all causes) (%)	4	6	0.670
Acute coronary syndrome (%)	6	8	0.429
Co-morbidities			
Charlson Comorbidity Index	1.3 ± 1.7	0.7 ± 1.1	0.029
Malignancy all types all stages (%)	10.2	3.2	0.021
Congestive heart failure (%)	8.2	5.8	0.563
Hyperlipidemia (%)	24.5	16.2	0.220
Ischemic heart disease (%)	8.2	13.3	0.352
Diabetes mellitus (%)	34.7	14.3	0.009
Renal failure (%)	4.1	8.6	0.314
Peripheral vascular disease (%)	0	3.8	0.166

icant increase of 1-year (44.9% in PEG vs. 15.2% in controls, $P < 0.001$) and 2-year mortality (59.2% in PEG vs. 17.1% in controls, $P < 0.001$).

Cox regression models were used to examine the effect of PEG on mortality, readmissions, and the composite endpoints of mortality or readmission at 2-year time point [Figure 1]. PEG was associated with increased 2-year mortality (hazard ratio [HR] 3.749, 95% confidence interval [95%CI] 2.039–6.894, $P < 0.001$). In addition, age and the Charlson Comorbidity Index significantly increased mortality risk, while sex did not.

No variable was significantly associated with readmission at any time point. This finding was robust when patients who died during the follow-up period were omitted from the analysis. PEG insertion was associated with increased likelihood of the composite endpoint of death or readmission (HR 1.514, 95%CI 1.016–2.255, $P = 0.041$). Age and sex were not associated with this endpoint. Figure 1 shows the survival curves for death, readmission, and the composite endpoint at the 2-year time point. Similar results were obtained after excluding patients with malignancies.

EFFECT OF PEG ON REASON FOR READMISSION AND CHANGES IN LABORATORY DATA

Patients were compared by the presence of the composite endpoint of death or readmission layered by group (PEG vs. control) [Table 2]. Patients with the composite endpoint had more infections at the index admission but fewer aspirations. In addition, patients with the composite endpoint had more co-morbidities, a higher Charlson Comorbidity Index, and a tendency toward older age. Within the PEG group, no characteristic of the index admission was associated with the composite endpoint.

Characteristics of the first post-index admission are presented by group in Table 3. Patients in the PEG group who were readmitted in the follow-up period did not differ significantly from the control group by any characteristic measured.

DISCUSSION

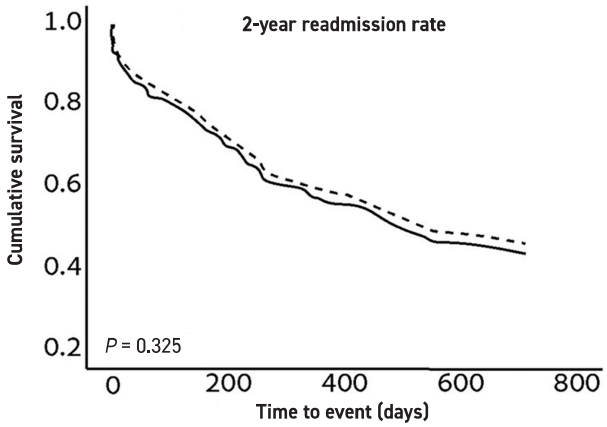
Insertion of PEG in hospitalized individuals is associated with increased composite endpoint, driven by the increase in mortality, but no obvious effect on readmission rate during 2 years of follow-up. This finding persists after matching patients for age (within 1 year), year of admission, department of referral/admission, and Charlson Comorbidity Index.

Overall, mortality rates in the total study population are similar to what is reported in the literature [17], especially for elderly populations [18]. Our results suggest that the increased 2-year mortality among PEG patients may not be attributed to higher rates of severe co-morbidities since the Charlson Comorbidity Index was controlled for in models. Additional possibilities could include higher rates of frailty, sarcopenia, and muscle wasting. It is also possible that PEG

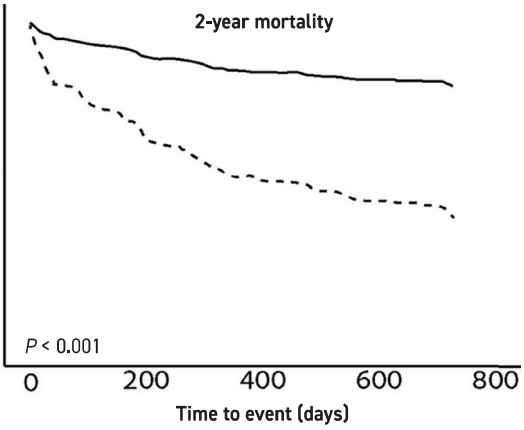
Figure 1. Cox analysis results across study groups

*Excluded patients who died during the follow-up period
PEG = percutaneous endoscopic gastrostomy

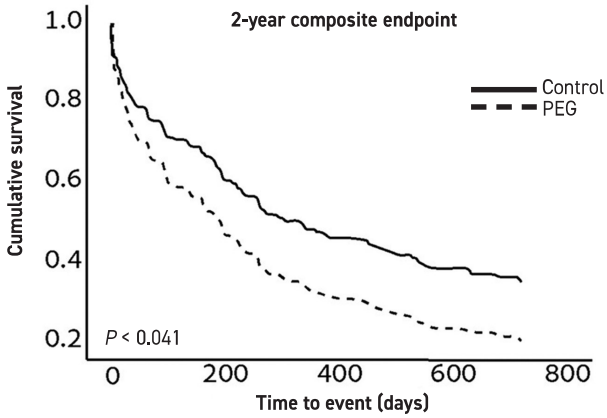
[A] 2-year readmission rates



[B] 2-year mortality



[C] composite endpoint of death or readmission



patients succumbed to complications such as increased rates of pneumonias [19]. Our findings suggest that PEG insertion was not associated with reduced, but rather increased long-term mortality rates.

Compared to controls, PEG patients had similar hospital admission rates prior to the index admission as well as in the 2 years following the index hospitalization. Moreover, the distribution of reasons for hospital readmission was similar among PEG patients and controls. Furthermore, laboratory measures, including serum albumin and cholesterol, both of which are associated with nutrition status [20,21], were similar between PEG patients and controls. This finding suggests that the nutritional effects of PEG should be evaluated in specific populations and that the actual access of feeding does not necessarily indicate improved nutritional status.

Despite the study's limitations, findings of the present study cast doubt on the efficacy of PEG for preventing readmission and/or mortality among all hospitalized patient sub-populations. Most of the PEG patients were admitted to internal medicine departments at the index hospitalization, and a greater proportion of these patients had a history of stroke, infections, and pressure sores. Nevertheless, differences in outcomes persisted after controlling for Charlson Comorbidity Index, indicating that differences in 2-year mortality and the composite endpoint cannot be attributed solely to increased morbidity among PEG patients. However, given the design of the study, and despite the attempts to control for the differences in co-morbidities between the groups, we cannot attribute the increased mortality observed to the actual PEG insertion.

This finding underlines the uncertainty surrounding PEG efficacy for treating increased malnutrition risk in all patient populations, although this aspect was not directly tested. PEG is naturally considered beneficial in patients with feeding difficulties because of the ease of access to nutritional care. However, information regarding the long-term effects of PEG are not clear and add to the confusion surrounding this topic [22,23]. Based on the findings, a clinical trial directly testing the efficacy of PEG vs. other intervention (control) on clinical outcomes in various patient populations is needed. It is possible that PEG may confer benefit only in specific patient groups, such as patients with esophageal and/or motor neuron diseases [24].

LIMITATIONS

In this study, the exposure analyzed (PEG) could not be isolated from the reason for PEG insertion. Specifically, we could not rule out that the reason for PEG insertion rather than PEG insertion per se was associated with between-group differences in outcomes. Therefore, we cannot conclude that PEG insertion was the cause for the increased mortality observed. Another limitation is the lack of data regarding complications of PEG insertion. We can only assume that serious complications were associated with increased rates of readmission and mortality.

Table 2: Comparison of patients across study and composite endpoint groups

Parameter	PEG		Control	
	Composite endpoint		Composite endpoint	
	yes n=39	no n=10	yes n=68	no n=37
Age (years)	76.5 ± 20.2	70.6 ± 15.8	76.9 ± 18.9	70.1 ± 21.4
Female sex (%)	76.9	60.0	64.9	76.5
Albumin (g/dl)	3.3 ± 0.6	3.7 ± 0.9	3.5 ± 0.6	3.5 ± 0.6
Creatinine (mg/dl)	1.2 ± 0.6	0.8 ± 0.2*	1.1 ± 0.5	1.3 ± 0.9
C-reactive protein (mg/dl)	7.6 ± 9.3	2.2 ± 4.4*	1.6 ± 5.4	3.3 ± 7.7
Hemoglobin (g/dl)	12.6 ± 1.9	13.5 ± 1.0	12.0 ± 2.3	12.6 ± 2.0
White blood cells (mm × 10^3)	14.9 ± 8.1	12.7 ± 4.3	8.2 ± 6.2	9.3 ± 8.5
First glucose (mg/dl)	163 ± 84	122 ± 44	161 ± 152	116 ± 114
Charlson Comorbidity Index	1.3 ± 1.8	1.3 ± 1.3	0.8 ± 1.3	0.4 ± 0.7*
Chief complaint and acute illness				
Cerebrovascular (%)	12.8	30	0	1.5
Aspiration (%)	0	10*	0	2.7
Pressure ulcer (%)	5.1	10	1.5	0
Co-morbidity				
Congestive heart failure (%)	7.7	10	7.4	0
Hypertension (%)	56.4	10*	36.8	8.1*
Hyperlipidemia (%)	30.8	0*	20.6	8.1
Ischemic heart disease (%)	10.3	0	17.6	5.4
Diabetes mellitus (%)	30.8	50	20.6	2.7*
Renal failure (%)	10.3	0	2.9	2.7

*Significant compared to composite endpoint sub-group, same study group

Table 3: Comparison of demographics, admission laboratory information and chief complaint at the first post-index admission across study groups

Parameter	PEG, n=22	Control, n=59	*P*-value
Age (years)	71.9 ± 19.7	76.1 ± 19.4	0.395
Female sex (%)	72.7	74.6	0.866
Admission laboratory data			
Albumin	1.8 ± 1.7	2.0 ± 1.4	0.665
Delta albumin from index	1.7 ± 1.9	1.4 ± 1.4	0.435
Urea (mg/dl)	44 ± 58	40 ± 28	0.760
Hemoglobin (g/dl)	8.2 ± 5.9	9.7 ± 4.3	0.214
Cholesterol (mg/dl)	85 ± 89	99 ± 74	0.502
Chief complaints at admission			
Fever/Infection (%)	31.8	18.6	0.205
Respiratory failure (%)	4.5	16.9	0.147
Trauma (%)	4.5	11.9	0.326
Volume overload (%)	4.5	5.1	0.921
Arrythmia	0	3.4	0.382
Electrolyte imbalance (%)	9.1	3.4	0.292
Pain (%)	9.1	10.2	0.885
Renal failure (%)	0	6.8	0.210

Another major limitation is the lack of information regarding the amount of forced feeding (using nasogastric tubes) and the rate of adequate nutrition in either group. We cannot conclude that the ease of access was associated with higher rates of adequate nutrition. In addition, nutrition intake information was not collected in this study, precluding attribution of causality to between-group differences in nutrition intake. We do not have information about the means with which nutrition was provided to the control group. We assume that patients with PEG receive nutrition at a given amount that is higher in caloric intake compared to patients without mechanical feeding. Other limitation of the study is that matching for co-morbidities was not performed in cases of multiple co-morbidities.

CONCLUSIONS

Among hospitalized individuals, PEG insertion during the hospitalization period was associated with worst prognosis compared to other hospitalized individuals. PEG insertion was associated with increased 1- and 2-year mortality rates and with no effect on readmissions. However, our study was underpowered to reach final conclusions regarding the effects of PEG on increased mortality or reduced readmissions. Additional studies should address this issue.

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Capsule

FXR inhibition may protect from SARS-CoV-2 infection by reducing *ACE2*

Preventing SARS-CoV-2 infection by modulating viral host receptors, such as angiotensin-converting enzyme 2 (ACE2), could represent a new chemoprophylactic approach for COVID-19 that complements vaccination. However, the mechanisms that control the expression of ACE2 remain unclear. **Brevini** and colleagues showed that the farnesoid X receptor (FXR) is a direct regulator of *ACE2* transcription in several tissues affected by COVID-19, including the gastrointestinal and respiratory systems. The authors then used the over-the-counter compound z-guggulsterone and the off-patent drug ursodeoxycholic acid (UDCA) to reduce FXR signaling and downregulate *ACE2* in human lung, cholangiocyte, and intestinal organoids and in the corresponding tissues in mice and hamsters. They showed that the UDCA-mediated downregulation of *ACE2* reduces susceptibility to SARS-CoV-2 infection in vitro, in vivo, and in human lungs and livers perfused ex situ. Furthermore, they revealed that UDCA reduces the expression of ACE2 in the nasal epithelium in humans. Finally, they identified a correlation between UDCA treatment and positive clinical outcomes after SARS-CoV-2 infection using retrospective registry data, and confirm these findings in an independent validation cohort of recipients of liver transplants.

Nature 2023; 615: 134

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