Timing of Direct Enteral Tube Placement and Outcomes after Acute Stroke

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Background: Direct enteral feeding tube (DET) placement for dysphagia after stroke is associated with poor outcomes. However, the relationship between timing of DET placement and poststroke mortality and disability is unknown. We sought to determine the risk of mortality and severe disability in patients who receive DET at different times after stroke. *Methods:* We used the Ontario Stroke Registry and linked administrative databases to identify patients with acute ischemic stroke or intracerebral hemorrhage between 2003 and 2013 who received DET (gastrostomy or jejunostomy) during their hospital admission. We grouped patients by week of DET placement and evaluated mortality at 30 days and 6 months after DET insertion, and disability at discharge. We used Cox proportional hazard models and multiple logistic regression to determine the association between time from admission to DET placement and outcomes, adjusting for patient and hospital factors. *Results:* In the study sample of 1367 patients, the median time from admission to DET placement was 17 days. After adjustment, each week of delay to DET placement was associated with lower mortality at 30 days (adjusted hazard ratio [aHR] .88, 95% confidence interval [CI] .79-.98), but not at 6 months (aHR .98, 95% CI .91-1.05), and a higher likelihood of severe disability at discharge (adjusted odds ratio 1.35, 95% CI 1.13- 1.60). *Conclusions:* Later DET placement after stroke was associated with lower 30-day mortality but higher severe disability at discharge. Further research is needed to understand the reasons for these observations and to optimize patient selection and timing of DET.

Key Words: Dysphagia—PEG—DET—stroke outcomes—feeding tubes—timing

Introduction

Dysphagia occurs in a high proportion of patients after stroke, and is commonly managed with nasogastric tubes when oral intake is unsafe.[1] In severe or persistent cases, direct enteral tube (DET) insertion through gastrostomy or jejunostomy can be considered when compatible with patients' goals of care.[2] Despite guideline recommendations to delay placement for 2-4 weeks,[2-4] in practice there is wide variability in timing and over half of patients undergo placement within 7 days of stroke in the United States.[5] Patients with DET

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have poor functional outcomes and a high mortality of approximately 50% at 6 months,[6] but whether outcomes differ by timing of insertion is unknown.

We used linked population-based clinical and administrative data to determine the risk of mortality and severe disability in patients who receive DET at different times after stroke.

Methods

Data Sources and Study Sample

The Ontario Stroke Registry collected detailed clinical information on all consecutive patients with acute stroke seen at regional stroke centers in Ontario, Canada and on a population-based sample of patients from every acute care hospital in the province between 2003 and 2013, to include the entire span of the registry. We used the registry to provide information on baseline patient characteristics, comorbid conditions, stroke severity, stroke type, place of admission, palliative care (defined as a decision to provide a palliative approach to care), hospital type, and length of stay. Stroke severity was assessed on admission with the Canadian Neurological Scale (CNS), and categorized as mild (CNS $\geq$ 8), moderate (CNS 5- 7), or severe (CNS 0- 4). We used the Ontario Registered Persons Database to identify all-cause mortality. We obtained the primary cause of death from the Office of the Registrar General—Deaths. These datasets were linked using unique encoded identifiers and analyzed at ICES.

We included consecutive patients with ischemic stroke or intracerebral hemorrhage (ICH) who were hospitalized between July 1, 2003 and March 31, 2013 and received DET insertion during admission. We identified DET placement and date of procedure from Canadian Institute for Health Information databases using Canadian Classification of Health Interventions (CCI) procedure codes, excluding those with open surgical placement of tubes. Use of endotracheal intubation and tracheostomy was also obtained using CCI codes (See Supplementary Table 1). Patients were excluded if they were younger than 18 years of age, had an in-hospital stroke, were admitted to the hospital more than 72 hours from stroke symptom onset, were not admitted, had a transient ischemic attack, subarachnoid hemorrhage, or isolated intraventricular hemorrhage, or had DET placement prior to the index stroke, on day of arrival, or very late ($\geq$50 days).

Outcomes

The primary outcome was all-cause mortality at 30 days after DET placement. Mortality was measured from DET placement rather than from time of stroke onset to avoid immortal time bias. The secondary outcomes were severe disability at discharge, defined as a modified Rankin Scale (mRS) score 4-5 among those discharged alive, and all-cause mortality at 6 months after DET placement.

Analysis

We used SAS 9.4 (Cary, NC) to conduct all analyses. We compared baseline characteristics and outcomes of patients who received DET in weeks 1, 2, 3, 4, and 5-7 using Cochrane-Armitage test of trends for variables with less than or equal to 2 levels, and Jonckheere-Terpstra test for variables with greater than 2 levels.

We constructed Kaplan-Meier curves for mortality from DET placement until 6 months, stratified by week of insertion. We used Cox proportional hazard models to evaluate the association between the timing of DET placement (in 1-week intervals) and 30-day mortality after DET, adjusting for age, sex, Charlson co-morbidity index, pre-admission independence (fully independent for all activities and instrumental activities of daily living), arrival from long-term care facility, prior stroke, dementia, atrial fibrillation, diabetes, hypertension, hyperlipidemia, smoking, stroke type (ischemic versus ICH), stroke severity, stroke unit admission, intensive care unit admission, palliative care, index year (2003-2008 versus 2009-2013), and center type (regional stroke center versus other, where regional stroke centers are large institutions with advanced stroke care resources and expertise comparable to comprehensive stroke centers in the United States). To account for differences in life-sustaining care, we also adjusted for endotracheal intubation and tracheostomy, counted only if the procedure date was prior to or the same day as DET placement. We performed the same analysis for 6-month mortality. We determined the proportion of deaths at 30 days after DET placement which were attributed to vascular (stroke and cardiovascular) causes (see Supplementary Table 2 for codes).

Lastly, among those who survived to discharge, we used multiple logistic regression to evaluate the association between the timing of DET placement in 1-week intervals and severe disability at discharge, adjusting for the baseline factors described above.

Data collection for the registry is done without patient consent, since ICES is named as a prescribed entity under provincial privacy legislation. This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

Results

Among 37,870 patients with ischemic stroke and ICH who met inclusion criteria, 1384 patients underwent DET placement during hospitalization. Seventeen patients were excluded due to lack of mRS score, leaving 1367 patients (3.6%). The median time to DET placement was 17 days (interquartile range 11-24; see Fig 1). The baseline characteristics and outcomes of study participants are shown in Tables 1 and 2.

Compared to those with early placement, patients with later DET placement had a lower rate of mortality at 30 days after placement (25.2% among those with

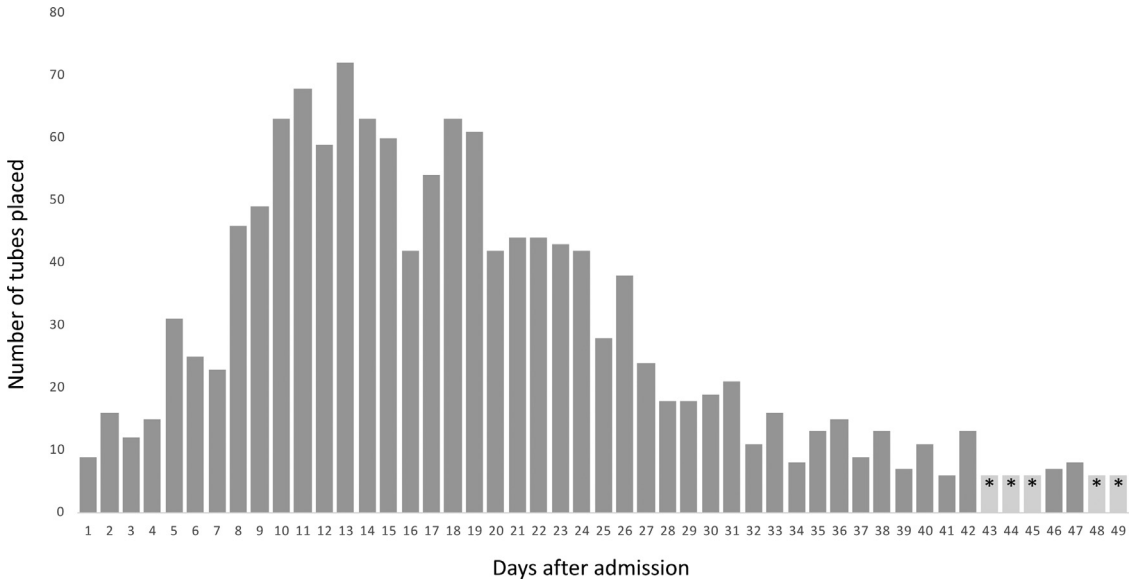

Figure 1. *Distribution of timing of direct enteral tube placement among all included patients. *Bars with less than 6 patients suppressed to maintain confidentiality as per ICES policy.*

placement in week 1, 14.6% among those with placement in weeks 5-7; *P*value for trend = .005; see Fig 2 and Table 2). Those who died after early insertion were more likely than those who died after later insertion to be aged over 80 years, to have severe strokes, dementia, and a vascular cause of death (Table 3). The proportion of patients discharged with severe disability was high in all groups, and increased with later DET placement (84.0% among

Table 1. *Baseline characteristics of patients with direct enteral tube placement, stratified by timing of insertion*

Baseline variables	Week 1	Week 2	Week 3	Week 4	Weeks 5-7	*P* value (trend)
N	131	420	366	237	213	
Length of stay, median days (IQR)	21 (12-40)	28 (19-49)	36 (24-60)	43 (32-64)	61 (46-85)	<.001
Age 80+, n (%)	55 (42%)	180 (42.9%)	166 (45.4%)	100 (42.2%)	72 (33.8%)	.09
Female	70 (53.4%)	198 (47.1%)	187 (51.1%)	114 (48.1%)	94 (44.1%)	.25
Charlson score 2+	100 (76.3%)	303 (72.1%)	297 (81.1%)	190 (80.2%)	166 (77.9%)	.04
Preadmission independence	86 (65.6%)	269 (64%)	223 (60.9%)	159 (67.1%)	145 (68.1%)	.35
Long-term care residence	13 (9.9%)	40 (9.5%)	32 (8.7%)	11 (4.6%)	<6*	<.001
Past stroke	37 (28.2%)	97 (23.1%)	79 (21.6%)	50 (21.1%)	54 (25.4%)	.65
Dementia	18 (13.7%)	53 (12.6%)	48 (13.1%)	19 (8%)	15 (7%)	.008
Atrial fibrillation	29 (22.1%)	94 (22.4%)	105 (28.7%)	56 (23.6%)	43 (20.2%)	.78
Diabetes	29 (22.1%)	108 (25.7%)	104 (28.4%)	69 (29.1%)	64 (30%)	.07
Hypertension	94 (71.8%)	307 (73.1%)	280 (76.5%)	177 (74.7%)	152 (71.4%)	1.0
Hyperlipidemia	47 (35.9%)	168 (40%)	143 (39.1%)	87 (36.7%)	68 (31.9%)	.14
Current smoking	24 (18.3%)	62 (14.8%)	53 (14.5%)	37 (15.6%)	44 (20.7%)	.28
ICH	33 (25.2%)	95 (22.6%)	74 (20.2%)	64 (27%)	66 (31%)	.04
Stroke severity						.85
Severe stroke (CNS 0-4)	59 (45%)	156 (37.1%)	142 (38.8%)	94 (39.7%)	81 (38%)	
Moderate stroke (CNS 5-7)	26 (19.8%)	106 (25.2%)	105 (28.7%)	65 (27.4%)	55 (25.8%)	
Mild stroke (CNS 8+)	35 (26.7%)	128 (30.5%)	87 (23.8%)	50 (21.1%)	57 (26.8%)	
Stroke unit admission	77 (58.8%)	287 (68.3%)	270 (73.8%)	147 (62%)	140 (65.7%)	.96
ICU admission	46 (35.1%)	124 (29.5%)	117 (32%)	100 (42.2%)	97 (45.5%)	<.001
Endotracheal intubation	28 (21.4%)	64 (15.2%)	72 (19.7%)	70 (29.5%)	75 (35.2%)	<.001
Tracheostomy	15 (11.5%)	47 (11.2%)	33 (9%)	34 (14.3%)	56 (26.3%)	<.001
Palliative care order	26 (19.8%)	83 (19.8%)	76 (20.8%)	41 (17.3%)	41 (19.2%)	.64
Regional stroke centre	104 (79.4%)	322 (76.7%)	309 (84.4%)	204 (86.1%)	180 (84.5%)	.004

Abbreviations: CNS, Canadian Neurological Scale; ICH, intracerebral hemorrhage; ICU, intensive care unit; IQR, interquartile range.
*Cells with less than 6 patients suppressed to maintain confidentiality as per ICES policy.

Table 2. *Mortality and disability among patients with direct enteral tube placement, stratified by timing of insertion*

Outcomes	Week 1	Week 2	Week 3	Week 4	Weeks 5-7	*P* value (trend)
N	131	420	366	237	213	
Alive at discharge, n (%)	100 (76.3%)	341 (81.2%)	303 (82.8%)	199 (84%)	173 (81.2%)	.26
Severe disability at discharge	84 (84%)	291 (85.3%)	278 (91.7%)	190 (95.5%)	161 (93.1%)	<.001
Mortality at 30 days after DET	33 (25.2%)	82 (19.5%)	58 (15.8%)	35 (14.8%)	31 (14.6%)	.005
Mortality at 6 months after DET	51 (38.9%)	151 (36%)	131 (35.8%)	81 (34.2%)	74 (34.7%)	.43

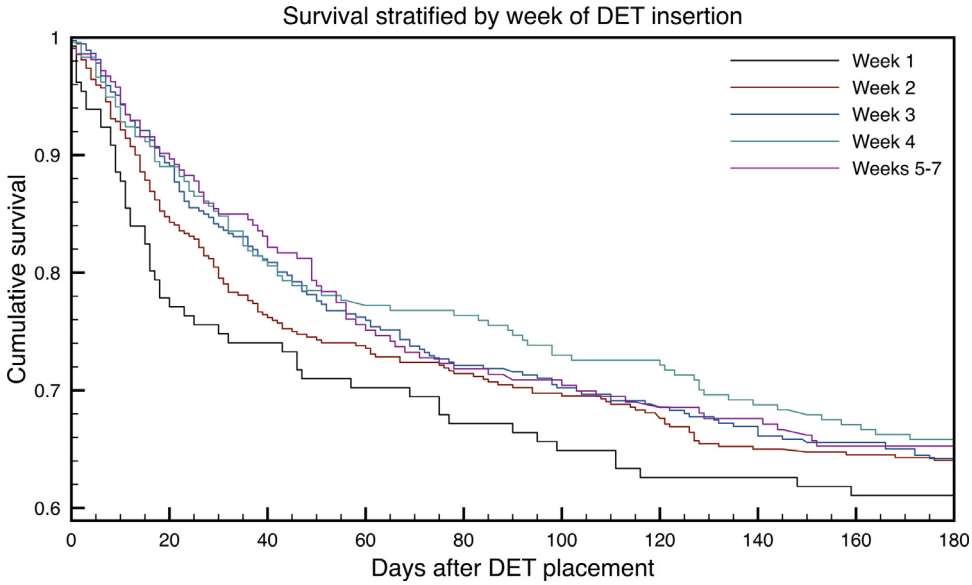

Figure 2. *Mortality stratified by timing of DET placement. Unadjusted Kaplan-Meier curves for 6 month mortality from date of DET insertion in patients who received DET in each time interval.*

Table 3. *Characteristics of patients who died within 30 days of receiving direct enteral tube, stratified by timing of insertion*

Baseline variables	Week 1	Week 2	Week 3	Week 4	Weeks 5-7	*P* value (trend)
N	33	82	58	35	31	
Length of stay, median days (IQR)	14 (11-20)	22 (16-28)	29 (24-36)	33 (29-46)	49 (42-58)	<.0001
Age 80+, n (%)	21 (63.6%)	50 (61%)	36 (62.1%)	18 (51.4%)	13 (41.9%)	.048
Female	19 (57.6%)	42 (51.2%)	30 (51.7%)	18 (51.4%)	18 (58.1%)	.91
Charlson score 2+	28 (84.8%)	63 (76.8%)	53 (91.4%)	28 (80%)	25 (80.6%)	.73
Preadmission independence	16 (48.5%)	38 (46.3%)	32 (55.2%)	21 (60%)	16 (51.6%)	.33
Dementia	8 (24.2%)	13 (15.9%)	12 (20.7%)	<6	<6	.046
ICH	6 (18.2%)	17 (20.7%)	9 (15.5%)	<6	10 (32.3%)	.52
Stroke severity						.01
Severe stroke (CNS 0-4)	23 (69.7%)	35 (42.7%)	19 (32.8%)	11 (31.4%)	12 (38.7%)	
Moderate stroke (CNS 5-7)	<6*	15 (18.3%)	12 (20.7%)	8 (22.9%)	7 (22.6%)	
Mild Stroke (CNS 8+)	<6	22 (26.8%)	20 (34.5%)	11 (31.4%)	8 (25.8%)	
ICU admission	21 (63.6%)	63 (76.8%)	41 (70.7%)	26 (74.3%)	19 (61.3%)	.58
Vascular cause of death	29 (87.9%)	69 (84.1%)	45 (77.6%)	26 (74.3%)	21 (67.7%)	.013
Cardiovascular	7 (21.2%)	25 (30.5%)	15 (25.9%)	<6	<6	
Stroke	22 (66.7%)	44 (53.7%)	30 (51.7%)	21 (60%)	20 (64.5%)	

Abbreviations: CNS, Canadian Neurological Scale; ICH, intracerebral hemorrhage; ICU, intensive care unit; IQR, interquartile range.
*Cells with less than 6 patients suppressed to maintain confidentiality as per ICES policy.

those with placement in week 1, 93.1% among those with placement in weeks 5-7; *P*value for trend < .001).

After adjustment for baseline characteristics, for each week in delay to DET placement there was a lower hazard of 30-day mortality (adjusted hazard ratio [aHR] .88, 95% confidence interval [CI] .79-.98), a higher odds of severe disability at discharge (adjusted odds ratio 1.35, 95% CI 1.13- 1.60), and no association with 6-month mortality (aHR .98, 95% CI .91- 1.05).

Discussion

In this large cohort of patients with direct enteral feeding tube placement after stroke, those with later placement were less likely than those with earlier placement to die within 30 days of DET insertion, but were more likely to be severely disabled at discharge.

Stroke guidelines recommend time-limited trials of nasogastric tube feeding prior to insertion of DET, typically for 2-4 weeks.[2-4] Delayed placement of DET is supported by the potential for dysphagia to improve early after stroke[7] and the low transition rate (28%) to gastrostomy feeding in those with nasogastric feeding.[6] Furthermore, the high disability in those with DET placement necessitates appropriate goals of care discussions prior to insertion.[6,8] However, current practice patterns are generally not in line with recommendations, with 2 US studies showing short median time to placement of 7 days.[5,9]

We found that 30-day mortality after DET was lower in patients with later compared to earlier DET placement, and that this was driven by lower mortality from cardiovascular causes. This presumably reflects survival of the early period after stroke, when the risks of death to acute stroke and its complications are highest, and when decisions to withdraw life-sustaining measures are often made.[10,11] Factors known to be associated with stroke case fatality, including older age, dementia, and severe stroke were all more common among those who died after early placement. All groups had a very high rate of severe disability at discharge (>85%), emphasizing the degree of dependence in this patient population, and with an increase in the rate of severe disability with later placement.

Our study has limitations. We did not have information on patient functional status at the time of DET placement, on patient/family preferences or on discussions preceding DET insertion or withdrawal of care, and could not identify patients who were considered for but ultimately did not receive DET. Given the varying times of DET insertion, there was no adequate control group with which to compare outcomes. Compared to prior US studies, our population had longer time to intervention (median 17 days versus 7 days), and a much smaller proportion of patients with early placement (10% versus 54%),[5,9] likely reflecting differences in patient selection and affecting the generalizability of our results to other regions. Most importantly, our results should not be interpreted to suggest that early DET placement causes worse outcomes, or that delaying insertion would improve outcomes. The observed association between the timing of DET placement and outcomes is almost certainly explained by confounding and selection bias, with higher mortality in the early groups related to factors such as stroke severity, comorbidity, and withdrawal of care, and higher disability in the later groups possibly due to in-hospital complications and prolonged intensive care unit stay. Rather, our findings should be seen as a source of real-world information on the likely outcomes after DET placement at different points in time, and highlight the potential for futile DET insertion during the early time period.

In conclusion, patients with later DET placement after stroke have higher short-term survival but greater disability compared to those with earlier placement. This information may be useful to clinicians and families in decision-making about feeding tube placement. Further studies are needed to understand the reasons for large variability in DET placement after stroke, and how timing of insertion and patient factors promote survival and functional outcomes. A better understanding of individual prognosis after acute dysphagic stroke can help to optimize shared decision-making surrounding the timing of DET placement.

Conflict of Interest

There are no potential conflicts of interest.

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In 2018, the institute formerly known as the Institute for Clinical Evaluative Sciences formally adopted the initialism ICES as its official name. This change acknowledges the growth and evolution of the organization's research since its inception in 1992, while retaining the familiarity of the former acronym within the scientific community and beyond.

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Data Access

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.104401.

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