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RAPID COMMUNICATION

Impact of Cilostazol Administration on Prevention of Aspiration Pneumonia in Patients With Chronic Limb-Threatening Ischemia

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Background: Cilostazol has reported effectiveness for preventing aspiration pneumonia in patients with ischemic stroke, but whether it is similarly beneficial for patients with chronic limb-threatening ischemia (CLTI) is unclear.

Methods and Results: This retrospective single-center study enrolled 1,368 CLTI patients treated with endovascular therapy (EVT). In the multivariate analysis, predictors for aspiration pneumonia were age (hazard ratio [HR] 1.06 [95% confidence interval (CI) 1.03–1.10]), non-ambulatory status (HR 2.54 [95% CI 1.38–4.65]), the Geriatric Nutritional Risk Index (HR 0.97 [95% CI 0.95–0.99]), and cilostazol (HR 0.37 [95% CI 0.16–0.87]).

Conclusions: Cilostazol administration reduced the risk of aspiration pneumonia in patients with CLTI undergoing EVT.

Key Words: Aspiration pneumonia; Chronic limb-threatening ischemia; Cilostazol

Cilostazol is an antiplatelet agent widely prescribed to improve walking distance in patients with lower extremity artery disease (LEAD).[1] In addition, cilostazol increases the level of substance P, which affects the coughing reflex and thus potentially reduces the risk of aspiration pneumonia in patients with acute ischemic stroke.[2,3] Chronic limb-threatening ischemia (CLTI) is a most advanced manifestation of LEAD, characterized by ischemic foot pain at rest, ischemic ulcerations, or gangrene. Patients with CLTI have poor life expectancy, and the common cause of death is infectious disease, especially pneumonia.[4] However, whether cilostazol reduces aspiration pneumonia in patients with CLTI has not been well studied.

Methods

This retrospective single-center study evaluated 1,368 consecutive patients with CLTI who were primarily treated with endovascular therapy (EVT) between April 2010 and December 2019. The study was performed in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. Aspiration pneumonia was defined by 3 criteria: (1) swallowing disturbance, including choking, repeatedly recognized clinically, (2) consolidation detected on chest X-ray or computed tomography scan, and (3) ≥2 of the following features: fever ≥37.5°C, abnormally high C-reactive protein level >0.30 mg/dL, increase of 9,000/mL in white blood cell count, and respiratory tract symptoms including sputum production.[2] The primary outcome measure was the incidence of aspiration pneumonia after EVT, and the effect of cilostazol administration on the incidence of aspiration pneumonia was also evaluated.

Data are presented as mean±standard deviation for continuous variables and as percentages for discrete variables. The cumulative incidence of the primary outcome was estimated using the Kaplan-Meier method. Independent associations were explored using a multivariate Cox proportional hazard model. Variables that showed a significant association with aspiration pneumonia in the univariate analysis and follow-up index[5] to avoid attrition bias were included in the multivariate analysis using forced entry models. Statistical significance was set at $P<0.05$.

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Table 1. Baseline Characteristics of CLTI Patients

	All	Cilostazol (+)	Cilostazol (–)	P value
No. of patients	1,368	331	1,037	
Patient characteristics				
Male sex	825 (60.3)	202 (61.0)	623 (60.1)	0.80
Age, years	74±10	75±10	74±10	0.43
Body mass index, kg/m^2	21.5±3.8	21.1±3.5	21.6±4.0	0.033
Non-ambulatory status	594 (43.4)	151 (45.6)	443 (42.7)	0.37
Hypertension	881 (66.1)	205 (63.1)	676 (67.1)	0.20
Dyslipidemia	486 (36.5)	114 (35.1)	372 (36.9)	0.55
Diabetes mellitus	812 (61.0)	195 (60.0)	617 (61.3)	0.70
Hemodialysis	700 (51.2)	163 (49.2)	537 (51.8)	0.41
Coronary artery disease	653 (49.2)	141 (43.4)	512 (51.1)	0.037
Congestive heart failure	102 (7.5)	12 (3.6)	90 (8.7)	0.002
Previous stroke	216 (16.3)	50 (15.4)	166 (16.6)	0.34
LVEF, %	61±13	63±13	60±13	0.002
Serum albumin, g/dL	3.3±0.6	3.3±0.6	3.3±0.6	0.17
Medications				
Aspirin	916 (67.0)	210 (63.4)	706 (68.1)	0.12
Clopidogrel	613 (44.8)	132 (39.9)	481 (46.4)	0.042
Prasugrel	69 (5.0)	11 (3.3)	58 (5.6)	0.11
Warfarin	251 (18.3)	60 (18.1)	191 (18.4)	0.94
DOAC	43 (3.1)	5 (1.5)	38 (3.7)	0.068
Limb characteristics				
Ankle-brachial index	0.63±0.21	0.63±0.23	0.63±0.21	0.42
Skin perfusion pressure, mmHg	27±16	28±19	27±15	0.003
Rutherford classification				0.57
4 (rest pain only)	218 (15.9)	57 (17.2)	161 (15.5)	
5 (minor tissue loss)	818 (59.8)	190 (57.4)	628 (60.6)	
6 (major tissue loss)	332 (24.3)	84 (25.4)	248 (23.9)	

Data are presented as n (%) or mean±standard deviation (SD). CLTI, chronic limb-threatening ischemia; DOAC, direct oral anticoagulant; LVEF, left ventricular ejection fraction.

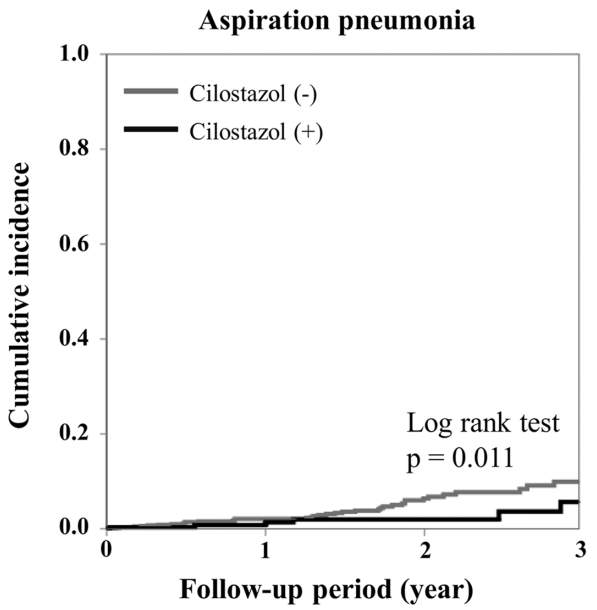
Statistical analyses were performed using SPSS Version 24.0 J (IBM Corp., Armonk, NY, USA).

Results

The baseline characteristics are summarized in **Table 1**. The mean patient age was 74 years, and 60.3% were male. Notable comorbidities included diabetes mellitus (61.0%, n=812), hemodialysis (51.2%, n=700), and coronary artery disease (49.2%, n=653). In this study, 16% of patients had a history of stroke, and that history was more frequent in patients with aspiration pneumonia than in those without. Regarding the dose of cilostazol, 200 mg/day and 100 mg/day were prescribed in 36.9% and 63.1% of the patients, respectively, and after a mean follow-up of 17.1 months, aspiration pneumonia had occurred in 61 patients (4.4%). In the Kaplan-Meier analysis, the rate of aspiration pneumonia at 3 years were 5.7% and 9.9% in patients with and without cilostazol, respectively (log-rank P=0.011, **Figure**). Regarding other clinical outcomes, the 3-year all-cause death, cardiovascular death, and major amputation rates were 39.1%, 15.4%, 10.8%, respectively. Multivariate Cox regression analysis revealed that age (hazard ratio [HR] 1.06 [95% confidence interval 1.03–1.10], P<0.001) and non-ambulatory status (HR 2.54 [1.38–4.65], P=0.003) were positively associated with aspiration pneumonia, whereas the Geriatric Nutritional Risk Index (GNRI)[6] (HR 0.97 [95% CI 0.95–0.99]; P=0.047) and cilostazol administration (HR 0.37 [95% CI 0.16–0.87], P=0.022) were negatively associated (**Table 2**).

Discussion

The protective effect of cilostazol on the incidence of pneumonia was reported in the subanalysis of the Cilostazol Stroke Prevention Study, which was a randomized controlled trial comparing cilostazol with placebo in the secondary prevention of cerebral infarction and a meta-analysis.[7,8] During a 3.3-year follow-up, the rate of pneumonia was 0.57% in the cilostazol group and 2.86% in the placebo group, with statistical significance. Several studies have revealed that the common causes of death in CLTI patients are cardiovascular and infectious diseases, mainly pneumonia.[4,9] Although guideline-directed medical therapy reduces the risk of cardiovascular death,[10,11] there are few reports of the efficacy of medical therapy on long-term risk reduction of infectious disease in the CLTI population. The true mechanism for the reduction of aspiration pneumonia by cilostazol in patients with CLTI remains unclear. CLTI is generally characterized by older age, impaired performance of activities of daily life, and severe frailty, which potentially leads to impaired swallowing function



	year	0	1	2	3
Cilostazol (-)	at risk	1037	535	245	97
	%±SE	0	2.9±0.5	6.4±1.2	9.9±1.9
Cilostazol (+)	at risk	331	172	90	45
	%±SE	0	1.4±0.8	2.0±1.0	5.7±2.7

Figure. The 3-year incidence of aspiration pneumonia after endovascular therapy was 5.7% and 9.9% in patients treated with and without cilostazol, respectively (log-rank P=0.011). SE, standard error.

Table 2. Association Between Baseline Clinical Characteristics and Aspiration Pneumonia

	Univariate analysis		Multivariate analysis	
	HR [95% CI]	P value	HR [95% CI]	P value
Male	1.30 [0.76–2.23]	0.34		
Age, per 1-year increase	1.05 [1.02–1.08]	<0.001	1.06 [1.03–1.10]	<0.001
Body mass index, per 1.0 kg/m^2 increase	0.90 [0.84–0.97]	0.006	0.98 [0.88–1.10]	0.082
Non-ambulatory status	2.29 [1.36–3.89]	0.002	2.54 [1.38–4.65]	0.003
Diabetes mellitus	0.92 [0.55–1.55]	0.75		
Hemodialysis	1.09 [0.65–1.81]	0.75		
Previous stroke	2.28 [1.27–4.10]	0.006	1.73 [0.91–3.30]	0.095
Ejection fraction, per 1% increase	1.00 [0.98–1.02]	0.85		
Serum albumin, per 1 g/dL increase	0.86 [0.56–1.30]	0.47		
WIfI stage, per 1 stage increase	0.95 [0.74–1.22]	0.69		
GNRI, per 1 point increase	0.96 [0.95–0.98]	<0.001	0.97 [0.95–0.99]	0.047
Cilostazol administration	0.46 [0.22–0.98]	0.044	0.37 [0.16–0.87]	0.022
Follow-up index	0.48 [0.21–1.09]	0.081	0.61 [0.27–1.38]	0.23

Hazard ratios (HRs) are presented together with their 95% confidence intervals (CI). GNRI, Geriatric Nutritional Risk Index; WIfI, wound, ischemia, and foot infection.

and cough reflex. Therefore, cilostazol admiration may improve the cough reflex, resulting in a decrease in the incidence of aspiration pneumonia. Based on the results of this study, additional cilostazol therapy could be an option for CLTI patients in terms of reducing the incidence of pneumonia if the side effects are acceptable.

This study had several limitations. First, it was retrospective using medical records, which may have underestimated the outcome evaluation such as hospitalization elsewhere. In addition, we could not completely distinguish complication with other types of pneumonia from aspiration pneumonia alone. Second, cilostazol administration was confirmed at discharge and adherence was unknown. Third, we conducted a multivariate analysis to adjust for patient characteristics such as age, wound severity, and ambulatory status. However, potential unmeasured con-

founding variables may exist. Fourth, the background data on non-ambulatory status, such as cerebral infarction or orthopedic reasons, were not collected. Fifth, standard treatment or patient managements for CLTI and aspiration pneumonia could have changed during the study period. Finally, we did not collect data on the side effects of cilostazol.

Conclusions

Cilostazol administration reduced the risk of aspiration pneumonia in patients with CLTI undergoing EVT.

Funding / Conflicts of Interest

None.

IRB Information

The present study was approved by the Ethics committee of Kansai Rosai Hospital (reference no. 22D054g).

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