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ORIGINAL ARTICLE

Cilostazol is Effective to Prevent Stroke-Associated Pneumonia in Patients Receiving Tube Feeding

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Abstract

Stroke-associated pneumonia (SAP) is a frequent complication in acute ischemic stroke (IS) patients, especially those receiving tube feeding (TF). In this retrospective study, we investigated whether or not cilostazol, a pluripotent phosphodiesterase III-specific inhibitor with anti-platelet and vasculogenic effects, can prevent SAP in these patients and reduce their duration of stay in intensive care unit/hospitalization. We recruited 158 IS patients receiving TF. Patients' characteristics (including age, gender, past history), National Institute of Health Stroke Scale and serum albumin level on admission, concomitant medications associated with SAP prevention (including cilostazol), and stroke characteristics (bilateral subcortical white matter lesion, brainstem involvement, large infarction, and asymptomatic hemorrhagic infarction) were compared between the SAP(−) and SAP(+) groups. Cilostazol was more frequently used in the SAP(−) group (20.8% vs. 6.1%, $p < 0.05$). Duration of intensive care unit was longer in patients with SAP (9 ± 8 vs. 6 ± 6 days, $p < 0.05$). However, the length of stay in an intensive care unit and duration of hospitalization were not reduced due to the prevention of SAP by cilostazol treatment. Cilostazol administration was associated with reduced SAP incidence in acute IS patients receiving TF.

Keywords Cilostazol · Stroke-associated pneumonia · Ischemic stroke · Aspiration pneumonia · Tube feeding · Nutrition

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Introduction

Stroke-associated pneumonia (SAP) develops as a complication in about 20% of acute ischemic stroke (IS) patients [1], and development of SAP is associated with increased mortality [2, 3]. Dysphagia is considered to be an important risk factor for SAP, which is frequently detected (64%) by swallowing endoscopy within 10 days after onset in acute IS patients [4]. Clinically, about half of patients with dysphagia develop SAP [5], and hence early detection and treatment of dysphagia are important. There have been several clinical studies on SAP prevention and on examinations for SAP prediction [3, 6–8]. In particular, the incidence of ventilator-associated SAP in acute IS patients is correlated with advanced age, consciousness level, immune suppression, and bedridden status [3]. On the other hand, little is known about the relationship between SAP and duration of stay in intensive care unit (ICU)/hospitalization.

Tube feeding (TF) via nasogastric tube/percutaneous endoscopic gastrostomy (NG/PEG) is often performed in patients with disturbance of consciousness and/or dysphagia [9]. In patients in intensive care, early enteral nutrition by TF within 48 h after admission is considered to be important for prevention of infection, reducing mortality, and reducing the duration of stay in the ICU [10]. The effectiveness of early enteral nutrition (started within 3 days or 7 days) in acute IS patients has been examined, but no clear benefits in terms of mortality and neurological outcomes were found [7]. Also, although early enteral nutrition is recommended in terms of improvement in immune function [10], about 37% of tube-fed acute IS patients develop SAP and nasogastric tube can be a predictor for SAP [11].

Administration of atorvastatin before IS onset is associated with a better outcome of SAP [12]. Cilostazol, angiotensin-converting-enzyme inhibitor [ACEI], and amantadine are also effective to prevent SAP in the chronic phase of IS [13–15]. However, the relationship between SAP prevention therapy and outcomes in acute IS patients receiving TF has not been sufficiently assessed.

Since early administration of drugs in acute IS appears to contribute to prevention of SAP, we hypothesized that it might also reduce the duration of hospitalization/stay in ICU of IS patients receiving TF. In particular, cilostazol is frequently used for secondary prevention of chronic IS, as well as for acute IS, although its efficacy is not fully established. Therefore, the aims of this work were to examine retrospectively the incidence of SAP in acute IS patients receiving TF who were treated with cilostazol, compared with other concomitant medications, and also to investigate whether cilostazol administration influences the duration of hospitalization/stay in ICU of these patients.

Materials and Methods

Study Design and Ethics Considerations

This study was a retrospective study and the subjects were selected from 1511 consecutive acute IS patients admitted to the Department of Neurology, Tokai University Hospital between April 2009 and March 2014. This study was approved by the Tokai University Ethics Committee (No. 14R-238). Informed consent was obtained from all recruited patients. The information about this study was informed to patients by poster posting in our hospital.

Patient Population

We recruited 158 patients (72 females [45.6%]; mean age ± SD, 77 ± 13 years) who had suffered IS and met the following criteria: required ICU management in the acute phase; admitted within a week after onset; an ischemic lesion was detected by magnetic resonance imaging; received TF via nasogastric tube within a week after onset. Diagnosis and classification of ischemic stroke were based on the criteria of The Trial of Org 10172 in the Acute Stroke Treatment classification [16]. In these patients, TF was started at the discretion of the attending clinician, based on the consciousness state and presence of dysphagia. We also adopted the following exclusion criteria: comorbidity of aspiration pneumonia on admission; discharge within 2 weeks; managed by mechanical ventilation from admission; received craniotomy; received antibiotics for infections other than pneumonia.

Data Collection

The following patient data were collected from medical records at our hospital: age, gender, past history (hypertension, diabetes mellitus, dyslipidemia), National Institute of Health Stroke Scale (NIHSS) on admission, serum albumin level on admission, concomitant medications associated with SAP prevention and improvement of gastrointestinal motility (cilostazol, ACEI, amantadine, laxative [sennoside, picosulfate, and magnesium oxide], intestinal prokinetic agent [mosapride and domperidone]), and stroke characteristics based on magnetic resonance imaging or computed tomography (bilateral subcortical white matter lesion [WML], brainstem involvement [17], large infarction [larger than one-third of the territory of each vessel governing region] [18], and asymptomatic hemorrhagic infarction [19]). Further, we also checked the

strongly recommended reasons for ICU management except for severe stroke symptoms (SAP [NIHSS > 17, large infarction in middle cerebral artery territory, and evidence of brainstem dysfunction], complications after pharmacological/mechanical thrombectomy, postoperatively following decompressive craniectomy, the other infections, and cardiac dysfunction) [20, 21].

Definition of Aspiration Pneumonia

We defined aspiration pneumonia as previously described [22]: (1) temperature of at least 37.5 °C or higher on two consecutive measurements or one measurement of 38.0 °C; (2) a white blood cell count higher than 11,000/μl, and chest infiltrates on radiography; (3) exclusion of other diagnoses.

Primary and Secondary Outcomes

Primary endpoints were the incidence of SAP within 3 or 14 days from admission and the number of cilostazol treatments up to the appearance of SAP (or up to 14 days after admission, if SAP did not develop), according to previous studies. Secondary endpoints were duration of stay in ICU/hospitalization. Concomitant medications started after the primary endpoints were not considered.

Statistical Analysis

The Chi-square test and *t* test were used for categorical data. Some data were non-parametric, and these were expressed as median [interquartile range (IQR)] and analyzed with the Mann–Whitney *U* test. Statistical analyses were performed using SPSS 23.0 (SPSS, Inc., Chicago, IL, USA). The significance level was set at $p < 0.05$.

Results

IS subtypes of recruited patients were classified as follows: large-artery atherosclerosis (AT), $n = 28$ (17.7%); cardioembolism (CE), $n = 89$ (56.3%); small-vessel occlusion, $n = 4$ (2.6%); and other determined etiology, $n = 37$ (23.4%). CE was most frequently seen. Of the 158 patients, 33 (20.9%) developed SAP within 14 days after admission. Fourteen of these (42.4%) developed SAP within 72 h after admission.

Patients' Characteristics

Tables 1 and 2 compare the characteristics of patients in the SAP(−) group and SAP(+) group. There was no significant difference of age, gender, NIHSS at admission (an indicator of the severity of IS), or serum level of albumin at admission (reflecting nutritional condition) between the two groups. There was also no significant difference of past history of IS risk factors (hypertension, diabetes mellitus, and dyslipidemia). There was no bias in lesion localization, lesion size, stroke etiology, or co-existence of symptomatic hemorrhage during hospitalization. The results were similar in all IS patients and in non-CE patients.

Relationship Between SAP Incidence and Cilostazol Treatment

We examined the relationship between SAP incidence and drug administration (Tables 1, 2). Administrations of ACEI, amantadine, laxative, and intestinal prokinetic agent were unrelated to SAP incidence. On the other hand, cilostazol (200 mg/day) was more frequently used in the SAP(−) group than in the SAP(+) group (20.8% vs. 6.1%, $p < 0.05$). A significant difference was also seen in non-CE patients (49.0% vs. 10.0%, $p < 0.05$). We found no other significant difference between the characteristics of patients in the SAP(−) and SAP(+) groups. Although bilateral subcortical WML is one of the risk factors for SAP, it was more frequently seen in SAP(−) group (69.9% vs. 35.0%).

Treatment Course with Cilostazol

Cilostazol was administered as an initial treatment in 28 (17.7%) patients after admission. Patients' characteristics between SAP(−) group and SAP(+) group were not significantly difference (Suppl. Table 1). Twenty-three patients continued to receive cilostazol, while cilostazol was stopped in 5 patients within 10–14 days after admission. Although these 5 patients were initially considered as AT, 3 were subsequently diagnosed as CE due to paroxysmal atrial fibrillation (Paf [$n = 2$]) or intracardiac thrombus ($n = 1$) and cilostazol was switched to warfarin, while 2 were switched to monotherapy with aspirin or clopidogrel. Side effects were also seen in 8 cilostazol-treated patients as follows: gastrointestinal bleeding ($n = 2$ [7.1%]), sinus tachycardia ($n = 5$ [17.9%]), and liver dysfunction ($n = 1$ [7.1%]). However, these adverse events did not affect to stop the cilostazol treatment because of minor symptoms.

Length of Stay in ICU and Hospitalization

We next considered the length of stay in ICU and duration of hospitalization (Figs. 1, 2). On this study, the length of stay in ICU and duration of hospitalization in all patients were 7 ± 6 and 46 ± 21 days, respectively. Twelve of SAP(+) patients (36.4%) and 39 of SAP(−) patients

Table 1 Patients' characteristics

	SAP(−) (n = 125)	SAP(+) (n = 33)	p value
Age (years)[a]	74 ± 11	80 ± 10	NS
Female gender[b]	58 (46.4)	13 (39.4)	NS
NIHSS at baseline[a]	13 ± 25	16 ± 10	NS
Albumin at baseline (g/dl)[a]	3.5 ± 0.2	3.2 ± 0.2	NS
Past history			
Hypertension[b]	76 (60.8)	21 (63.6)	NS
Diabetes mellitus[b]	32 (25.6)	12 (36.4)	NS
Dyslipidemia[b]	51 (40.8)	11 (33.3)	NS
Drug			
Cilostazol[b]	26 (20.8)	2 (6.1)	< 0.05
ACEI[b]	8 (6.4)	3 (9.1)	NS
Amantadine[b]	14 (11.2)	1 (3.0)	NS
Laxative[b]	44 (35.2)	8 (24.2)	NS
Intestinal prokinetic agent[b]	25 (20.0)	4 (12.1)	NS
Stroke characteristics			
Bilateral subcortical WML[b]	85 (68.0)	23 (69.7)	NS
Brainstem involvement[b]	24 (19.2)	4 (12.1)	NS
Cardiac embolism[b]	74 (59.2)	16 (48.5)	NS
Large infarction[b]	52 (41.6)	13 (39.4)	NS
Symptomatic hemorrhage[b]	9 (7.2)	5 (15.2)	NS

Data are presented as mean ± SD or numbers (%)

SAP stroke-associated pneumonia, *NIHSS* National Institute of Health Stroke Scale, *ACEI* angiotensin-converting-enzyme inhibitor, *WML* white matter lesion, *Large infarction* the infarct size is larger than one-third of the territory

[a] t test

[b] χ^2 test

(31.2%) stayed in ICU for over 7 days. And also, the length of stay in ICU was longer in patients with SAP than in patients without SAP (9 ± 8 vs. 6 ± 6 days, $p < 0.05$) among all patients, although there was no significant difference in the length of stay in hospitalization. However, the length of stay in ICU and duration of hospitalization were not reduced due to the prevention of SAP by cilostazol treatment.

Aside from SAP, several factors were also related with the continuous ICU management (Table 3). "Severe stroke symptoms" was the most frequently seen as the strongly recommended reason for ICU management (n = 81, 51.3%). As the other infections, 4 urinary-tract infection and 2 thoracic empyema, were seen in SAP(−) group. There was no significant difference between the two groups. Only standard stroke management in ICU was performed to 39 (31.2%) IS patients in SAP(-) group, which was decided by attending physicians.

Discussion

IS is often complicated by aspiration pneumonia, especially in association with dysphagia, brainstem lesion and higher stroke severity (including high NIHSS score), and in patients under nutrition by TF [3, 5–7, 17]. In this study, we examined the incidence of SAP in acute IS patients receiving TF who were treated with cilostazol, compared with other concomitant medications. We also evaluated the effect of cilostazol on the length of stay in ICU/hospitalization in these patients. The frequency of SAP among these patients (20.9%) was similar to that in a previous report (22.0%) [1, 23]. Notably, we found that SAP incidence was significantly reduced by cilostazol, but not by any other medication, among IS patients receiving TF management. However, this did not lead to any significant difference in the length of stay in ICU/hospitalization. The other strongly recommended reasons for ICU management could be considered to affect it. Actually, only 24.2–31.2% IS patients were received standard stroke management in ICU, except for SAP treatment. The length of stay in ICU/hospitalization could be also affected by the severity of

Table 2 Subgroup analysis of patients with non-cardiogenic embolic stroke

	SAP(−) (n = 49)	SAP(+) (n = 20)	p value
Age (years)[a]	84 ± 6	67 ± 2	NS
Female gender[b]	24 (49.0)	11 (55.0)	NS
NIHSS at baseline[a]	18 ± 9	7 ± 8	NS
Albumin at baseline (g/dl)[a]	3.2 ± 0.8	3.3 ± 0.4	NS
Past history			
Hypertension[b]	28 (57.1)	12 (60.0)	NS
Diabetes mellitus[b]	15 (30.6)	8 (40.0)	NS
Dyslipidemia[b]	22 (44.9)	8 (40.0)	NS
Drug			
Cilostazol[b]	24 (49.0)	2 (10.0)	< 0.05
ACEI[b]	0 (0.0)	3 (15.0)	NS
Amantadine[b]	6 (12.2)	2 (10.0)	NS
Laxative[b]	21 (42.9)	5 (25.0)	NS
Intestinal prokinetic agent[b]	9 (18.4)	5 (25.0)	NS
Stroke characteristics			
Bilateral subcortical WML[b]	34 (69.9)	7 (35.0)	< 0.01
Brainstem involvement[b]	12 (24.5)	1 (5.0)	NS
Large infarction[b]	12 (24.5)	5 (25.0)	NS
Symptomatic hemorrhage[b]	4 (8.2)	4 (20.0)	NS

Data are presented as mean ± SD or numbers (%)

SAP stroke-associated pneumonia, *NIHSS* National Institute of Health Stroke Scale, *ACEI* angiotensin-converting-enzyme inhibitor, *WML* white matter lesion, *Large infarction* the infarct size is larger than one-third of the territory

[a] t test

[b] χ^2 test

complications. On the other hand, all patients who developed SAP had a longer duration of ICU than those who did not among all patients. Hence, we believed that the prevention of SAP using cilostazol was important in IS patients.

Cilostazol was previously reported to be effective for SAP prevention in both acute IS patients and chronic IS patients [8, 12]. The major mechanism of SAP to develop in IS patients is the reduction of substance P. Once IS is occurred, dopamine production in the corpus nigrostriatal can be decreased. The reduction of dopamine production also induces the reduction of substance P at the glossopharyngeal nerve and at the cervical parasympathetic ganglion of the sensory branch of that nerve [12]. Actually, blockade of dopamine D1 receptors has been reported to induce the reduction of substance P in experimental model [25]. On the other hand, cilostazol induces to upregulation of substance P, and can maintain the swallow reflex and cough reflex [12]. From this mechanism, cilostazol treatment has been considered to be effective for SAP prevention. Our present study shows for the first time that cilostazol is also effective for SAP prevention in IS patients being managed with TF. Nevertheless, although cilostazol can contribute to SAP prevention in acute IS patients regardless of severity and subtype, undetected Paf should be considered in acute IS patients, because there is no evidence of secondary prevention of CE [26]. Actually, many CE patients, who did not receive cilostazol therapy, were recruited in our study. One of the reasons was considered that our study was focused on the IS patients with TF management in acute phase. In stroke patients, TF management is recommended to the patients who have not only dysphagia but also severe symptoms such as disturbance of consciousness. CE is the most severe stroke subtype [27], hence CE patients were the most frequency seen in our study. Further, dual anti-platelet therapy with aspirin and clopidogrel is currently mainly used in the acute phase of IS [28], whereas combined therapy with cilostazol and aspirin is not proven to have efficacy in acute IS [29]. That was the reason why cilostazol was less frequently used in acute IS. However, the pleiotropic effects of cilostazol were not sufficiently assessed on these previous studies. SAP risk predictors, such as advanced age, long-term bed rest, higher stroke severity, pontine infarction, and some risk scores (A2DS2 score and ISAN score), should be considered before administration of cilostazol in acute IS [3, 17, 30].

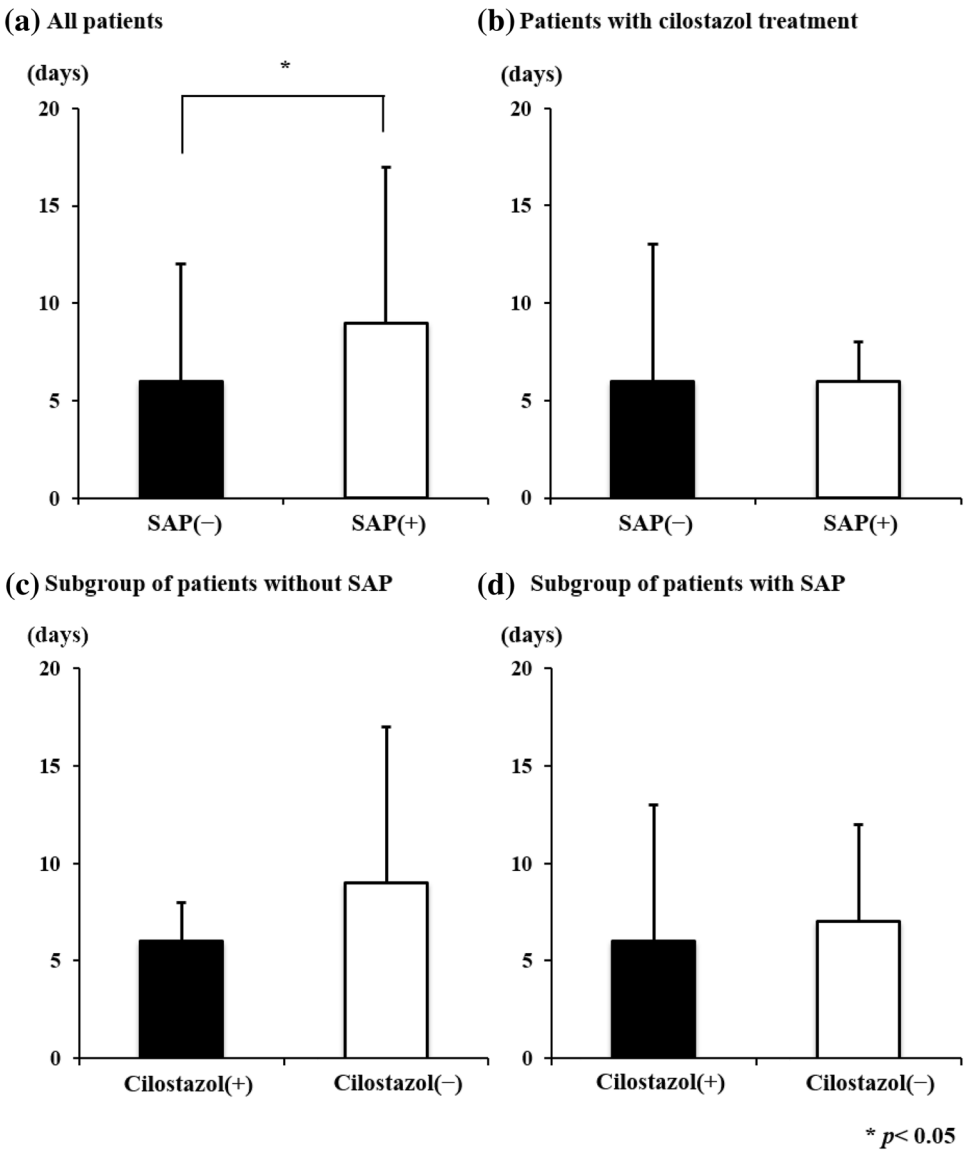

Fig. 1 Length of stay in ICU. **a** The length of stay in ICU was longer in the SAP(+) group than in the SAP(−) group in all IS patients (9 ± 8 vs. 6 ± 6 days, $p < 0.05$). **b** In cilostazol-treated patients, the length of stay in ICU was not significantly dependent on the development of SAP as a complication (6 ± 7 [SAP(−)] vs. 6 ± 2 [SAP(+)] days). **c** In the SAP(−) group, the length of stay in ICU was not significantly dependent on cilostazol treatment (6 ± 7 [cilostazol(+)] vs. 7 ± 5 [cilostazol(−)] days). **d** In the SAP(+) group, the length of stay in ICU was not significantly dependent on cilostazol treatment, although it tended to be reduced (6 ± 2 [cilostazol(+)] vs. 9 ± 13 [cilostazol(−)] days). *SAP* stroke-associated pneumonia

Our inclusion criteria was also limited the number of patients, because IS patients with only intravenous nutrition in acute phase were excluded, considering of SAP risk factors. While early enteral nutrition within 48 h was reported to reduce the incidence of infection and the length of stay in ICU/hospitalization [10], early onset pneumonia (within 72 h of admission) accounted for 70% of SAP in IS patients, because of dysphasia and consciousness disorder [23]. Further, early initiation of TF does not improve outcomes or reduce mortality in patients with IS and traumatic brain injury [7, 24]. Hence, a part of severe IS patients was excluded from our criteria.

Finally, it is important to note that patients' background characteristics showed no significant inter-group differences that might have affected the evaluation of cilostazol efficacy. But, on the other hand, our study has some limitations. In particular, the number of patients was small, and we were unable to recruit sufficient number of IS patients with cilostazol treatment, as described above. Aside from it, selection bias arising from the judgment of the attending physician and non-randomization could have influenced the outcome. Further, we could not evaluate the classification of aspiration risk, because this study was retrospective. Hence, a prospective study would be desirable to confirm our findings.

In conclusion, our results indicate that cilostazol can reduce SAP incidence in acute IS patients receiving TF, but does not significantly reduce the duration of stay in ICU/hospitalization. We are planning a prospective study to examine the efficacy of cilostazol both in IS patients receiving TF and in those receiving oral nutrition, taking account of the classification of aspiration risk.

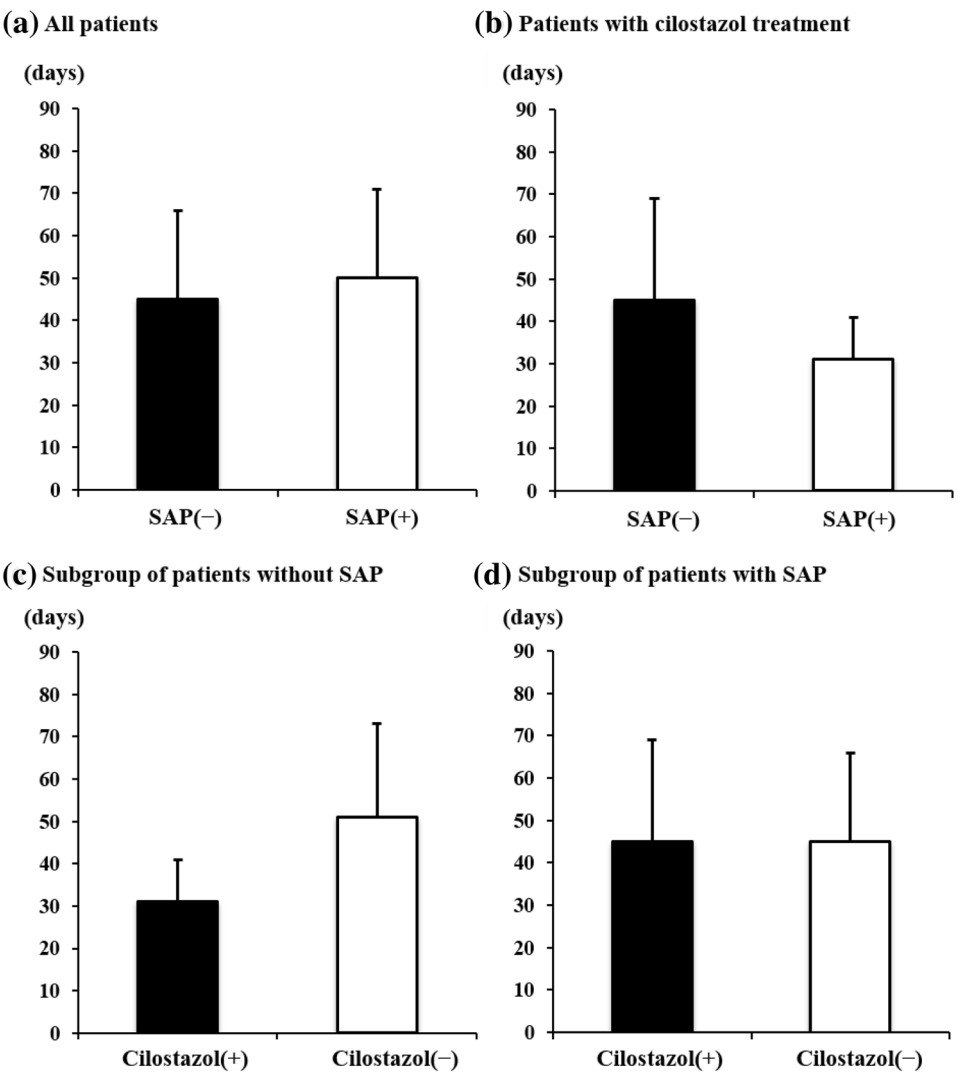

Fig. 2 Length of hospitalization. **a** The length of hospitalization was not significantly dependent on the development of SAP as a complication (45 ± 21 [SAP(−)] vs. 50 ± 21 [SAP(+)] days). **b** In cilostazol-treated patients, the length of hospitalization was not significantly dependent on the development of SAP as a complication (45 ± 24 [SAP(−)] vs. 31 ± 10 [SAP(+)] days). **c** In the SAP(−) group, the length of hospitalization was not significantly dependent on cilostazol treatment (45 ± 24 [cilostazol(+)] vs. 45 ± 21 [cilostazol(−)] days). **d** In the SAP(+) group, the length of hospitalization was not significantly dependent on cilostazol treatment, although it tended to be reduced (51 ± 13 [cilostazol(+)] vs. 31 ± 10 days[cilostazol(−)]). *SAP* stroke-associated pneumonia

Table 3 Strongly recommended reasons for ICU management except for SAP

	SAP(−)			SAP(+)		
	Cilostazol(+) (n = 26)	Cilostazol(−) (n = 99)	Total (n = 125)	Cilostazol(+) (n = 2)	Cilostazol(−) (n = 31)	Total (n = 33)
Severe stroke symptoms[a]	16 (61.6)	49 (49.5)	61 (48.8)	1 (50.0)	19 (61.3)	20 (60.6)
Complications after pharmacological/ mechanical thrombectomy	1 (3.8)	10 (10.1)	11 (8.8)	0 (0.0)	2 (6.5)	2 (6.1)
Postoperatively following decompressive craniectomy	0 (0.0)	2 (2.0)	2 (1.6)	0 (0.0)	1 (3.2)	1 (3.0)
Other infections[b]	1 (3.8)	5 (5.1)	6 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac dysfunction	0 (0.0)	2 (2.0)	2 (1.6)	1 (50.0)	1 (3.2)	2 (6.1)
No other reasons[c]	8 (30.8)	31 (31.3)	39 (31.2)	0 (0.0)	8 (25.8)	8 (24.2)

Data are presented as numbers (%)

ICU intensive care unit, *SAP* stroke-associated pneumonia

[a]Severe stroke symptoms; NIHSS > 17, large infarction in middle cerebral artery territory, and evidence of brainstem dysfunction

[b]Other infections include 4 urinary-tract infection and 2 thoracic empyema (only in cilostazol(−) group)

[c]"No other reasons" includes "standard stroke management"

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Author contributions SN and AM wrote the article and prepared the figures and tables. Data collection was performed by SN, AM, MS, and SY. Data analysis was performed by AM. EN and ST developed the study design, and revised the manuscript. All authors approved the final version.

Compliance with Ethical Standards

Conflict of interest The authors state that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Langhorne P, Stott DJ, Robertson L, et al. Medical complications after stroke: a multicenter study. Stroke. 2000;31:1223–9.
2. Chang CY, Cheng TJ, Lin CY, et al. Reporting of aspiration pneumonia or choking as a cause of death in patients who died with stroke. Stroke. 2013;44:1182–5. https://doi.org/10.1161/STROKEAHA.111.000663.
3. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med. 1999;27(5):887–92.
4. Mann G, Hankey GJ, Cameron D. Swallowing function after stroke: prognosis and prognostic factors at 6 months. Stroke. 1999;30(4):744–8.
5. Smithard DG, O'Neill PA, England RE, Park CL, Wyatt R, Martin DF, et al. The natural history of dysphagia following a stroke. Dysphagia. 1997;12:188–93. https://doi.org/10.1007/PL00009535.
6. Ribeiro PW, Cola PC, Gatto AR, da Silva RG, Luvizutto GJ, Braga GP, et al. Relationship between dysphagia, National Institutes of Health Stroke Scale Score, and predictors of pneumonia after ischemic stroke. J Stroke Cerebrovasc Dis. 2015;24(9):2088–94. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.05.009.
7. Dennis MS, Lewis SC, Warlow C, FOOD Trial Collaboration. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. Lancet. 2005;365(9461):764–72. https://doi.org/10.1016/S0140-6736(05)17983-5.
8. Osawa A, Maeshima S, Tanahashi N. Efficacy of cilostazol in preventing aspiration pneumonia in acute cerebral infarction. J Stroke Cerebrovasc Dis. 2013;22(6):857–61. https://doi.org/10.1016/j.jstrokecerebrovasdis.2012.06.008.
9. Rowat A. Enteral tube feeding for dysphagic stroke patients. Br J Nurs. 2015;24(3):138, 140, 142–145. https://doi.org/10.12968/bjon.2015.24.3.138.
10. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN. 2003;27:355–73. https://doi.org/10.1177/0148607103027005355.
11. Brogan E, Langdon C, Brookes K, Budgeon C, Blacker D. Respiratory infections in acute stroke: nasogastric tubes and immobility are stronger predictors than dysphagia. Dysphagia. 2014;29(3):340–5. https://doi.org/10.1007/s00455-013-9514-5.
12. Yu Y, Zhu C, Liu C, Gao Y. Effect of prior atorvastatin treatment on the frequency of hospital acquired pneumonia and evolution of biomarkers in patients with acute ischemic stroke: a multicenter prospective study. Biomed Res Int. 2017;2017:5642704. https://doi.org/10.1155/2017/5642704.
13. Shinohara Y. Antiplatelet cilostazol is effective in the prevention of pneumonia in ischemic stroke patients in the chronic stage. Cerebrovasc Dis. 2006;22:57–60. https://doi.org/10.1159/000092922.
14. Shinohara Y, Origasa H. Post-stroke pneumonia prevention by Angiotensin-converting enzyme inhibitors: results of a meta analysis of five studies in Asians. Adv Ther. 2012;29:900–12. https://doi.org/10.1007/s12325-012-0049-1.
15. Nakagawa T, Wada H, Sekizawa K, et al. Amantadine and pneumonia. Lancet. 1999;353:1157. https://doi.org/10.1016/S0140-6736(98)05805-X.
16. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41.
17. Fandler S, Gattringer T, Eppinger S, Doppelhofer K, Pinter D, Niederkorn K, et al. Frequency and predictors of dysphagia in patients with recent small subcortical infarcts. Stroke. 2017;48:213–5. https://doi.org/10.1161/STROKEAHA.116.015625.
18. Toyoda K, Arihiro S, Toda K, Yamagami H, Kimura K, Furui E, et al. Trends in oral anticoagulant choice for acute stroke patients with nonvalvular atrial fibrillation in Japan: the SAMURAI-NVAF study. Int J Stroke. 2015;10(6):836–42. https://doi.org/10.1111/ijs.12452.
19. Nezu T, Koga M, Nakagawa J, Shiokawa Y, Yamagami H, Furui E, et al. Early ischemic change on CT versus diffusion-weighted imaging for patients with stroke receiving intravenous recombinant tissue-type plasminogen activator therapy: stroke acute management with urgent risk-factor assessment and improvement (SAMURAI) rt-PA registry. Stroke. 2011;42(8):2196–200. https://doi.org/10.1161/STROKEAHA.111.614404.
20. Kirkman MA, Citerio G, Smith M. The intensive care management of acute ischemic stroke: an overview. Intensive Care Med. 2014;40(5):640–53.
21. Faigle R, Sharrief A, Marsh EB, Llinas RH, Urrutia VC. Predictors of critical care needs after IV thrombolysis for acute ischemic stroke. PLoS ONE. 2014;9(2):e88652. https://doi.org/10.1371/journal.pone.0088652.
22. Kalra L, Irshad S, Hodsoll J, Simpson M, Gulliford M, Smithard D, Patel A, Rebollo-Mesa I, STROKE-INF Investigators. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. Lancet. 2015. https://doi.org/10.1016/s0140-6736(15)00126-9.
23. Walter U, Knoblich R, Steinhagen V, Donat M, Benecke R, Kloth A. Predictors of pneumonia in acute stroke patients admitted to a neurological intensive care unit. J Neurol. 2007;254(10):1323–9. https://doi.org/10.1007/s00415-007-0520-0.
24. Azim A, Haider AA, Rhee P, Verma K, Windell E, Jokar TO, et al. Early feeds not force feeds: enteral nutrition in traumatic brain injury. J Trauma Acute Care Surg. 2016;81(3):520–4. https://doi.org/10.1097/TA.0000000000001089.
25. Jia YX, Sekizawa K, Ohrui T, Nakayama K, Sasaki H. Dopamine D1 receptor antagonist inhibits swallowing reflex in guinea pigs. Am J Physiol. 1998;274:R76–80.
26. Shinohara Y, Katayama Y, Uchiyama S, Yamaguchi T, Handa S, Matsuoka K, et al. Cilostazol for prevention of secondary stroke

(CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. Lancet Neurol. 2010;9(10):959–68. https://doi.org/10.1016/S1474-4422(10)70198-8.
27. Arihiro S, Todo K, Koga M, Furui E, Kinoshita N, Kimura K, et al. Three-month risk-benefit profile of anticoagulation after stroke with atrial fibrillation: the SAMURAI-Nonvalvular Atrial Fibrillation (NVAF) study. Int J Stroke. 2016;11(5):565–74. https://doi.org/10.1177/1747493016632239.
28. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369(1):11–9. https://doi.org/10.1056/NEJMoa1215340.
29. Uchiyama S, Sakai N, Toi S, Ezura M, Okada Y, Takagi M, et al. Final results of cilostazol-aspirin therapy against recurrent stroke with intracranial artery stenosis (CATHARSIS). Cerebrovasc Dis Extra. 2015;5(1):1–13. https://doi.org/10.1159/000369610.
30. Smith CJ, Bray BD, Hoffman A, Meisel A, Heuschmann PU, Wolfe CD, et al. Can a novel clinical risk score improve pneumonia prediction in acute stroke care? A UK multicenter cohort study. J Am Heart Assoc. 2015;4(1):e001307. https://doi.org/10.1161/JAHA.114.001307.

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