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Original article

Efficacy of cilostazol for sick sinus syndrome to avoid permanent pacemaker implantation: A retrospective case–control study

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ABSTRACT

Background: Currently, bradycardia treatment is limited to permanent pacemaker (PM) implantation. No consensus exists as to its optimal medication regimen. However, as cilostazol accelerates heart rate (HR) in bradycardia, we investigated its efficacy for sick sinus syndrome (SSS) to avoid permanent PM implantation.

Methods: This was a retrospective, case-control study. We included 192 consecutive patients diagnosed with SSS (after applying some exclusion criteria), of whom 54 received cilostazol (cilostazol group) and 138 did not receive cilostazol (control group). The primary endpoint was the PM implantation rate after 6 months; secondary endpoints were 1- and 3-month PM implantation rates, HR after 1 week, 1 and 6 months, and cilostazol side effects.

Results: The 6-month PM implantation rate was lower in the cilostazol than the control group (20.4% vs. 55.8%, respectively; $p < 0.001$). In multivariate analysis, cilostazol decreased the 6-month PM implantation rate (OR: 0.22; 95% CI: 0.08–0.55; $p = 0.001$). Although baseline HR was significantly lower in the cilostazol group, HR in this group increased and did not significantly differ between the two groups after 1 week, 1 and 6 months. In subgroup analyses of symptomatic patients, the PM implantation rates after 6 months were significantly lower in the cilostazol group than in the control group.

Conclusions: Cilostazol was effective for symptomatic SSS to avoid PM implantation by increasing HR.

Introduction

The number of patients with sick sinus syndrome (SSS) is increasing with the aging of the global population [1]. Despite the high prevalence of bradycardia, its treatment is currently limited to permanent pacemaker (PM) implantation; no consensus on its optimal medication regimen exists. Intravenous atropine and β-stimulators are effective in the short term but are harmful over the long term because of their side effects, which include cardiotoxicity and ventricular arrhythmia [2]. Implantation of a permanent PM is the first-line treatment for patients with symptomatic bradyarrhythmia [3]. Although the efficacy and safety of permanent PM have been established, implantation and generator replacement are sometimes accompanied by complications, such as infection or bleeding [4,5].

Several recent case reports and case series studies have indicated that cilostazol increases the heart rate (HR) and improves subjective symptoms caused by SSS [6,7]. Cilostazol was initially developed as an antiplatelet agent that acts as a selective inhibitor of type III phosphodiesterase (PDEIII) [8]. Inhibition of PDEIII increases cyclic adenosine monophosphate, which results in increased myocardial contractility and faster HR [9,10]. Ishii et al. reported that cilostazol was effective in preventing bradycardia during carotid artery stenting [11]. Therefore, we hypothesized that cilostazol could be used to treat bradycardia. In Japan, cilostazol is widely accepted and is used clinically for bradycardia [12]. Some Japanese cardiologists prescribe daily cilostazol for bradycardia and have thus avoided implanting PMs. However, studies on the efficacy of cilostazol in abating the need for PM implantation in patients with bradycardia are lacking. The present study was performed to determine the effects of cilostazol

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on SSS and whether it could be used to avoid the need for PM implantation.

Methods

Study population

The initial study population comprised 233 consecutive patients who were clinically diagnosed with SSS by a cardiologist at Asahi General Hospital between March 2007 and September 2016. Each case was checked by two cardiologists upon inclusion in this study to determine whether the clinical diagnosis of SSS was reasonable. Exclusion criteria included prior PM implantation, hyperkalemia, hypercalcemia, and loss to follow-up. Cardiologists followed up on individual cases. The criteria for PM implantation were based on the published guidelines [3]. Prior PM implantation was determined from the patients' medical records. We excluded 41 patients from the study based on the criteria outlined below (Fig. 1): 26 with prior PM implantation, 5 with bradycardia due to hyperkalemia, 1 with bradycardia due to hypercalcemia, and 9 who were lost to follow-up (visited only once). Among the 192 patients finally included in the study, 54 were treated with cilostazol (cilostazol group), and the other 138 did not receive this drug (control group).

Procedure

This was a retrospective, single-center, case–control study. We examined the background characteristics of individual patients in both groups. The primary endpoint of this study was PM implantation rate after 6 months. Secondary endpoints were PM implantation rates after 1 and 3 months, HR after 1 week, 1 and 6 months, the longest sinus arrest interval, and side effects of cilostazol. Patients' respective observation periods started on the day SSS was diagnosed for those in the control group, and on the day when cilostazol began to be administered in the cilostazol group. The HR data were collected by electrocardiogram (ECG) or from medical records of vital signs. In cases for which there were several HR data, we used the lowest rate as the representative value. The data of the longest sinus arrest intervals were collected by Holter ECG and medical records. Data on side effects of cilostazol, such as tachycardia, headache, bleeding, and arrhythmia, were obtained from medical records.

Statistical analysis

We retrospectively analyzed the effects of cilostazol on SSS patients to determine whether it could reduce their need for PM implantation. The chi-square test was used to compare the PM implantation rates between the cilostazol and control groups. We compared HR between groups using Student's *t*-test or Wilcoxon's rank-sum test. Categorical variables were compared using Fisher's exact test. Multivariate analyses used logistic regression analyses to adjust for confounding factors. In all analyses, $p < 0.05$ was considered significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [13].

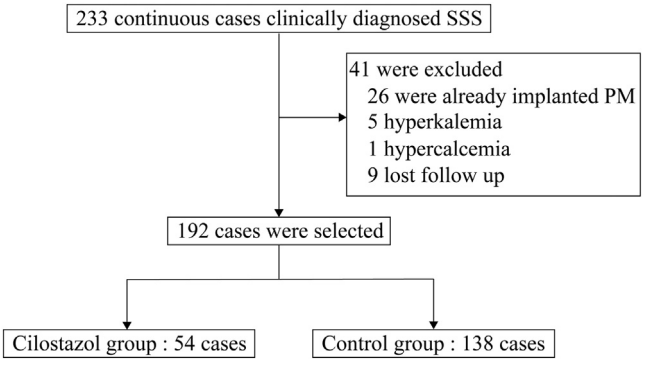

Fig. 1. Flow chart of patient selection. SSS, sick sinus syndrome; PM, pacemaker.

Results

Table 1 shows patients' baseline characteristics. The percentage of patients with SSS type 1 was greater in the cilostazol group, whereas the percentage with SSS type 3 was greater in the control group. The two groups did not significantly differ in percentages of patients with SSS type 2. Baseline mean HR was significantly lower in the cilostazol group than in the control group (44.6 ± 10.3 bpm vs. 54.1 ± 19.1 bpm, respectively; $p = 0.001$). The groups did not significantly differ in the use of medications that may influence HR, such as calcium channel blockers (CCBs), β-blockers, levothyroxine, theophylline, antiarrhythmic, digitalis, and antipsychotic agents.

The PM implantation rate after 6 months was significantly lower in the cilostazol group (20.4%) than in the control group (55.8%; $p < 0.001$; Fig. 2). Analysis by SSS type showed that the PM implantation rate after 6 months for SSS type 2 was significantly lower in the cilostazol group than in the control group (33.3% vs. 73.7%, respectively; $p = 0.011$), but the two groups did not significantly differ in implantation rates for SSS types 1 (7.4% vs. 18.8%, respectively; $p = 0.31$) and 3 (50.0% vs. 84.2%, respectively; $p = 0.089$). The PM implantation rates after 1 and 3 months were also significantly lower in the cilostazol group than in the control group (Fig. 2). In the control group, 39 patients were considered to have had no chance to receive cilostazol because they required emergent or relatively early PM implantation. When these patients were excluded from our analysis, the 6-month PM implantation rate still tended to be lower in the cilostazol group, but not significantly so (20.4% vs. 35.3%, respectively; $p = 0.080$).

The two groups did not significantly differ in mean HR after 1 week (cilostazol: 67.8 ± 16.4 bpm, control: 65.5 ± 17.5 bpm; $p = 0.48$), 1 month (cilostazol: 69.4 ± 19.2 bpm, control: 63.8 ± 16.3 bpm; $p = 0.12$), or 6 months (cilostazol: 67.8 ± 18.9 bpm, control: 65.6 ± 14.1 bpm; $p = 0.49$; Fig. 3). However, the increase in mean HR compared with baseline was greater in the cilostazol group than the controls after 1 week (23.0 ± 15.3 bpm vs. 9.3 ± 23.3 bpm, respectively; $p = 0.002$), 1 month (26.6 ± 17.1 bpm vs. 10.8 ± 20.9 bpm, respectively; $p < 0.001$), and 6 months (25.2 ± 20.6 bpm vs. 11.1 ± 21.7 bpm, respectively; $p = 0.010$). The two groups did not significantly differ in mean longest sinus arrest interval at baseline (cilostazol group, 4685.4 ± 2811.7 ms, $n = 22$; control group, 3769.8 ± 2172.7 ms, $n = 91$; $p = 0.098$). However, the mean longest sinus arrest interval at follow up was less in the control group than the cilostazol group (cilostazol group, 1917.2 ± 1292.2 ms, $n = 21$; control group, 1105.0 ± 669.7 ms, $n = 77$; $p < 0.001$).

Age, sex, the presence of symptoms, use of CCB, and coexistence of hypertension, dyslipidemia, atrial fibrillation, and renal dysfunction significantly influenced PM implantation rates after 6 months. Additionally, PM implantation tended to be performed more in elderly, female, and symptomatic patients, who were more likely to use CCBs, and to have hypertension, dyslipidemia, atrial fibrillation, and renal dysfunction. We performed multivariate analysis for these factors (Table 2). Multivariate analyses also showed that cilostazol use significantly decreased the PM implantation rate after 6 months (OR: 0.22; 95% CI: 0.08–0.55;

Table 1
Baseline characteristics of patients in this study.

Characteristic	Cilostazol group	Control group	*p*
Total	54 (100)	138 (100)	
Age in years	71.8 ± 11.9	70.7 ± 15.6	0.65
Male sex	24 (44.4)	56 (40.6)	0.63
Type of SSS			
Type 1	21 (60.4)	82 (40.6)	0.016*
Type 2	15 (28.3)	42 (30.4)	0.86
Type 3	6 (11.3)	40 (29.0)	0.013*
Hypertension	18 (33.3)	62 (44.9)	0.19
Diabetes mellitus	10 (18.5)	24 (17.4)	0.84
Dyslipidemia	6 (11.1)	41 (29.7)	0.008*
Cardiac surgery	15 (27.8)	14 (10.1)	0.003*
Ischemic heart disease	12 (22.2)	13 (9.4)	0.030*
Valvular disease	16 (29.6)	12 (8.7)	<0.001*
Hyper- or hypothyroidism	4 (7.4)	6 (4.3)	0.47
Atrial fibrillation (AF)	2 (3.7)	14 (10.1)	0.24
Paroxysmal atrial fibrillation (PAF)	6 (11.1)	9 (6.5)	0.37
Arrhythmias except AF and PAF	10 (18.5)	11 (8.0)	0.042*
Cerebrovascular disease	7 (13.0)	9 (6.5)	0.16
Renal dysfunction (eGFR < 50 ml/min/1.73 m^2)	7 (13.0)	36 (26.1)	0.056
Episodes of heart failure	20 (37.0)	25 (18.1)	0.008*
Symptomatic	27 (50.9)	87 (64.0)	0.14
Medication use			
Calcium channel blocker	17 (31.5)	45 (32.6)	1.00
β-blocker	6 (11.1)	18 (13.0)	0.81
Levothyroxine	3 (5.6)	5 (3.6)	0.69
Theophylline	2 (3.7)	4 (2.9)	0.67
Antiarrhythmic	3 (5.6)	7 (5.1)	1.00
Digitalis	1 (1.9)	6 (4.3)	0.68
Antipsychotic	2 (3.7)	4 (2.9)	0.67
Heart rate-bpm	44.6 ± 10.3	54.1 ± 19.1	0.001*
Systolic blood pressure-mmHg	128.3 ± 29.2	136.2 ± 22.8	0.09
Diastolic blood pressure-mmHg	65.0 ± 14.4	71.6 ± 14.1	0.019*

Data are shown as *n* (%) or as mean ± standard deviation
SSS, sick sinus syndrome; eGFR, estimated glomerular filtration rate.
* Statistically significant.

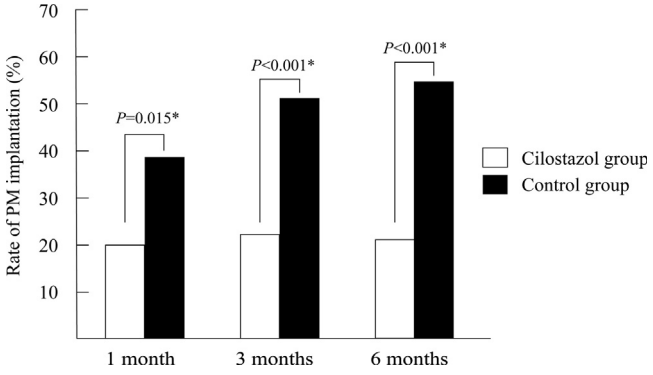

Fig. 2. Permanent pacemaker (PM) implantation rates. The cilostazol group and control group significantly differed after 1 month (20.0% vs. 39.1%, respectively, $p = 0.015$), 3 months (20.8% vs. 50.4%, respectively, $p < 0.001$), and 6 months (20.4% vs. 54.8%, respectively, $p < 0.001$).

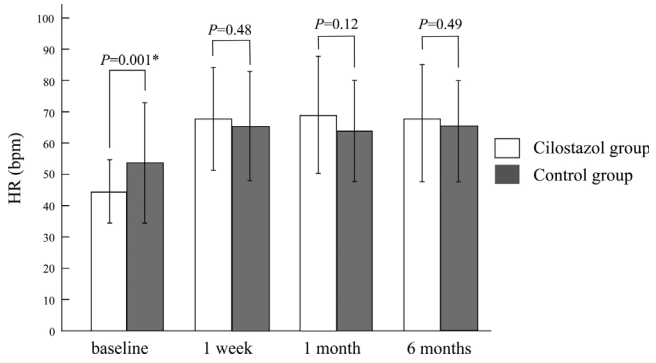

Fig. 3. Heart rate (HR) at baseline, after 1 week, 1 month, and 6 months. At baseline, mean HR was significantly lower in the cilostazol group (44.6 ± 10.3 bpm vs. 54.1 ± 19.1 bpm, respectively; $p = 0.001$), but did not significantly differ after 1 week (67.8 ± 16.4 bpm vs. 65.5 ± 17.5 bpm, respectively; $p = 0.48$), 1 month (69.4 ± 19.2 bpm vs. 63.8 ± 16.3 bpm, respectively; $p = 0.12$), or 6 months (67.8 ± 18.9 bpm vs. 65.6 ± 14.1 bpm, respectively; $p = 0.49$).

$p = 0.001$). Presence of symptoms and use of CCB were also independent risk factors for PM implantation after 6 months. Initially, the cilostazol group had 27 (50.9%) symptomatic patients and the control group had 87 (64.0%; Table 1), but after 6 months they had decreased to one (1.9%) and one (0.7%), respectively.

Subgroup analysis of symptomatic patients showed PM implantation rates were significantly lower in the cilostazol group than the control group at all time points examined (Fig. 4).

Table 3 shows the breakdown of symptoms. Rates for each symptom did not significantly differ between the two groups. Several asymptomatic patients underwent PM implantation because of risk of syncope or sudden death (cilostazol group, $n = 4$; control group, $n = 2$), to control heart failure (cilostazol group, $n = 0$; control group, $n = 1$), or because the patient wished to drive (cilostazol group, $n = 0$; control group, $n = 2$). In the cilostazol group, PM implantation after 6 months tended to be performed for patients with dizziness or who were taking CCB. In the cilostazol group, side effects of cilostazol prompted cessation of administration in four cases (headache, $n = 1$; tachycardia, $n = 3$). Cilostazol showed no fatal side effects and did not induce ventricular arrhythmia in the present study.

Table 2
Results of multivariate analyses.

	OR	95% CI	p
Age	1.02	0.99–1.05	0.30
Male sex	0.54	0.22–1.28	0.16
Hypertension	0.9	0.36–2.29	0.83
Dyslipidemia	1.07	0.43–2.69	0.88
Renal dysfunction (eGFR < 50 ml/min/1.73 m^2)	2.32	0.80–6.72	0.12
Atrial fibrillation	2.59	0.51–13.20	0.25
Use of calcium channel blocker	3.2	1.15–8.90	0.026*
Symptomatic	8.14	3.27–20.20	<0.001*
Administration of cilostazol	0.22	0.08–0.55	0.001*

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.
* Statistically significant.

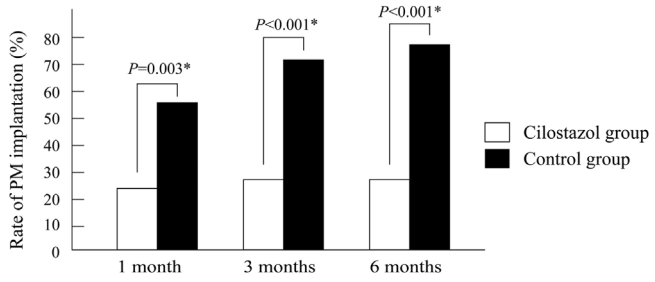

Fig. 4. Subgroup analyses. In symptomatic patients, pacemaker (PM) implantation rates were significantly lower in the cilostazol group than the control group after 1 month (23.1% vs. 57.5%, respectively; $p = 0.003$), 3 months (24.0% vs. 71.1%, respectively; $p < 0.001$) and 6 months (24.0% vs. 76.5%, respectively; $p < 0.001$).

Table 3
Breakdown of symptoms.

	Cilostazol group ($N = 54$)	Control group ($N = 138$)	p
None	27 (50.0)	51 (37.0)	0.11
Syncope	8 (14.8)	31 (22.5)	0.32
Dizziness	15 (27.8)	33 (23.9)	0.58
Chest discomfort	1 (1.9)	8 (5.8)	0.45
Dyspnea	6 (11.1)	7 (5.1)	0.20
Malaise	1 (1.9)	1 (0.7)	0.48
Palpitation	3 (5.6)	7 (5.1)	1.00
Vomiting	0 (0.0)	2 (1.5)	1.00

Discussion

The results of the present study showed that cilostazol administration for patients with SSS significantly decreased PM implantation after 6 months and increased HR after 1 week, 1 and 6 months. Thus, cilostazol decreased PM implantation incidence by increasing HR. Interestingly, the percentages of symptomatic patients after 6 months were not significantly different in the two groups. From these results, we conclude that cilostazol could increase HR without PM implantation and improve symptoms related to bradycardia. PM implantation is not only a clinically important endpoint but also an unequivocal outcome that is not subject to measurement error. Although baseline HR was significantly lower in the cilostazol group (indicating more severe clinical conditions), it had a lower PM implantation rate. This circumstance both indicates the efficacy of cilostazol in this setting and shows that the baseline HR differences did not bias the study. Subgroup analysis showed that cilostazol was particularly effective in symptomatic patients. We observed no serious side effects or deaths related to cilostazol use in this study.

Although the two groups did not significantly differ in mean HR at 1 week, 1 and 6 months later (Fig. 3), the percentage of patients who received PMs was higher in the control group (Fig. 2). This is because the analysis of HR included patients who had already received PMs; our HR data therefore included their pacing rates. In the control group, the higher PM implantation rates resulted in higher HR, whereas in cilostazol group, HR was increased by use of cilostazol. Consequently, HR increased in both groups; coincidentally, the two groups did not significantly differ in HR.

Although mean longest sinus arrest intervals improved in both groups compared with baseline, the control group had a shorter mean pause than did the cilostazol group. This circumstance probably also resulted from the control group's higher PM implantation rates. This result implies that PM implantation can more reliably prevent long pauses than cilostazol can. However, cilostazol can also shorten the sinus arrest interval, although not as much as PM implantation did.

The results reported here are comparable with previous studies. A previous case report suggested that cilostazol is useful in SSS patients with syncope [14]. Our subgroup analyses indicate that cilostazol is particularly effective in symptomatic patients. Although a previous case report showed that cilostazol could cause ventricular arrhythmia [15], we saw no critical side effects of cilostazol, including ventricular arrhythmia, in the present study. Whereas a previous case series study showed that cilostazol was effective for SSS to increase minimal HR and total heartbeat count, and cilostazol increased mean HR by an average of 22 bpm [6], we found cilostazol increased HR on average by 23 bpm after 1 week, 27 bpm after 1 month, and 26 bpm after 6 months. We also found that symptoms associated with bradycardia were reduced by use of cilostazol, leading to avoidance of PM implantation.

Our results suggest that cilostazol's efficacy would be clearest in patients with SSS type 2 who are not using CCB. Cilostazol seemed to be ineffective for SSS type 3, bradycardia-tachycardia syndrome, because it accelerates HR. In other words, cilostazol was effective for bradycardia, but it was harmful for patients with tachycardia. We consider that cilostazol is likely effective for SSS type 1, although the result of present study showed no significant difference, probably because the number of patients was insufficient. The negative chronotropic effect of CCB canceled the positive chronotropic effect of cilostazol, which resulted in resistance for cilostazol and finally led to PM implantation. Therefore, cilostazol is more effective for patients who do not take CCB.

We propose the use of cilostazol particularly for symptomatic SSS patients, because SSS rarely leads to sudden death by itself, although it does lead to syncope. Therefore, patients with SSS have sufficient time to try cilostazol treatment with relative safety if we can manage syncope. Furthermore, the effects of cilostazol are seen very early after initial use. In this study, HR increased by an average of 23 bpm after only 1 week of using cilostazol. Therefore, SSS patients might be administered cilostazol for a week before deciding on PM implantation.

This study had several limitations, the greatest of which was its retrospective nature, which is associated with several types of bias. The control group was about twice as large as the cilostazol group, and the backgrounds of the two groups were dissimilar in some respects. Although multivariate analysis demonstrated the efficacy of cilostazol as an independent factor in preventing the need for PM implantation after 6 months, this finding may reflect some sampling bias. Despite these limitations, and the fact that this study is not a randomized controlled study, the results seem generally applicable to patients with SSS, as our patients were selected as continuous cases without unreasonable exclusion criteria. The difference in observation start dates between the two groups may be advantageous for the cilostazol group. However, the analysis that excluded patients who received emergent or early

PMs showed that at 6 months, the PM implantation rate tended to be lower in the cilostazol group, but not significantly so—probably because of the relatively low number of patients. We consider a randomized controlled trial necessary to establish accurate results.

Conclusion

The results of the present study show that cilostazol was effective for symptomatic SSS to avoid PM implantation, by increasing HR.

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Conflict of interest

The authors declare that there is no conflict of interest.

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