Original Research

Positive chronotropic effects of theophylline and cilostazol in patients with symptomatic sick sinus syndrome who have declined permanent pacing

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Pacemakers are more commonly recommended than theophylline for sick sinus syndrome (SSS) treatment. The positive effects of cilostazol on bradyarrhythmias also have been reported. However, no comparison of cilostazol and theophylline has been previously reported found. We retrospectively enrolled SSS patients, who refused a pacemaker implantation. Theophylline or cilostazol was administered, and the heart rate (HR) was evaluated in 4-8 weeks using a digital sphygmomanometer and the electrocardiogram (ECG). A 200-400 mg of theophylline or 100-200 mg of cilostazol were administered per day in 50 and 30 patients, respectively. The baseline HR was 54.8 ± 13.5 beats per minute (bpm) on using sphygmomanometry and 51.9 ± 11.8 bpm using the ECG. In the theophylline group, the HR increased by 12.0 ± 16.3 bpm by sphygmomanometry ($P < 0.001$) and 8.4 ± 12.0 bpm by the ECG ($P < 0.001$). In the cilostazol group, the HR increased by 16.8 ± 13.9 bpm by sphygmomanometry ($P < 0.001$) and 12.4 ± 13.4 bpm using the ECG ($P < 0.001$). In 15 of the 50 theophylline patients, the medication was switched to cilostazol. The HR increased from 61.4 ± 13.8 bpm to 64.0 ± 12.6 bpm ($P = 0.338$). Symptoms such as dyspnea, chest discomfort, dizziness, and syncope significantly improved after the administration of the medications. There were no significant differences in the improvement in the symptoms except for dizziness between the two agents. Cilostazol was as effective as theophylline for increasing the HR in SSS patients.

Keywords

Sick sinus syndrome; cilostazol; theophylline

1. Introduction

A decreasing heart rate (HR) in patients with sinus node dysfunction (SND) aggravates the symptoms related to bradycardia such as fatigue, dizziness, dyspnea, and syncope, which are indications for a permanent pacemaker implantation (Alt et al., 1985; Tung et al., 1994). However, some patients are reluctant to undergo permanent pacing due to the fear of having a device implanted in their body. Clinically, some patients may not have severe bradycardia requiring a pacemaker implantation but cannot be observed without some kind of treatment. Some helpful messages have been proposed in several studies (Ling and Crouch, 1998; Moriya et al., 2004; Sonoura et al., 2019; Verza et al., 1996) regarding pharmacological therapy to increase the HR in patients with sick sinus syndrome (SSS).

Theophylline and cilostazol have been shown to have positive chronotropic effects, which may be useful for relieving symptoms related to bradycardia in patients with SND. However, no previous studies or trials have been performed comparing the positive chronotropic effects of these two agents. Therefore, in this study, we compared the effects of theophylline and cilostazol on the HR in patients with SSS.

2. Methods

2.1 Definition

SSS was defined as SND (such as sinus bradycardia, sinus pauses, or tachycardia-bradycardia syndrome) combined with bradycardia-related symptoms such as fatigue, dizziness, dyspnea, or syncope. Sinus bradycardia was defined as an HR of less than 60 beats per minute (bpm) during sinus rhythm (Adán and Crown, 2003). A sinus pause was defined as a temporary absence of P waves and QRS complexes due to dysfunction of the sinus node for more than 2.5 seconds (Shaw and Southall, 1984), and tachycardia-bradycardia syndrome as an alternating presence of atrial origin tachycardias and brady-arrhythmias (Moss and Davis, 1974).

2.2 Study population

From January 2008 to December 2017, we sequentially and retrospectively enrolled patients with SSS, who refused a pacemaker implantation. The study was approved by the ethics committee at Chonnam National University Hospital, Gwangju, Korea (CNUH-2017-033). The patients were administered theophylline or cilostazol and underwent followed-up at our Cardiovascular Center. The patients who concomitantly used negative chronotropic agents such as beta-blockers, calcium channel blockers, and digoxin, discontinued the study drug during the follow-up, or were lost to follow-up, were excluded.

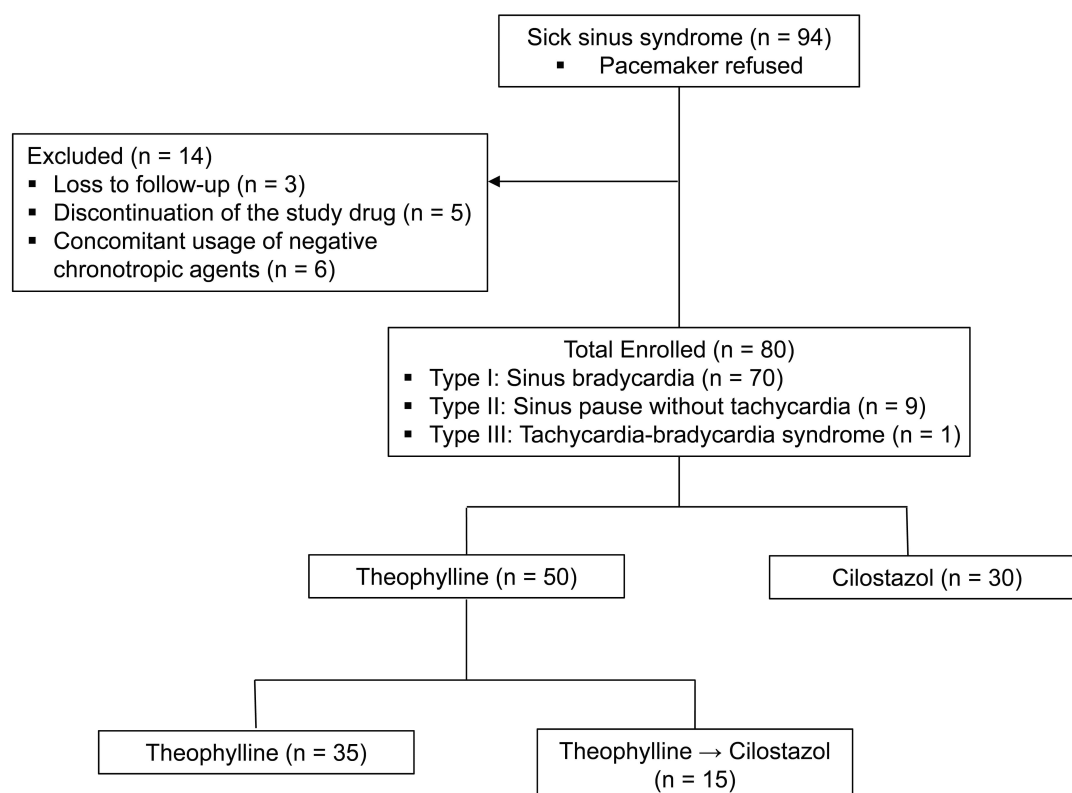After exclusion of those patients, 50 patients were included in

Fig. 1. Study design. After the exclusion of the inelligible patients, 50 patients were included in the theophylline group and 30 in the cilostazol group. Among the theophylline group patients, 15 were switched from theophylline to cilostazol, due to insufficient drug effects or adverse drug reactions to theophylline such as nausea, vomiting, or diarrhea. The HR was evaluated in 4 - 8 weeks when the patients visited the outpatient clinic. The HR was measured by routine vital sign measurements and ECGs. *Abbreviations*: HR, heart rate

the theophylline group and 30 in the cilostazol group. Seventy patients had type I, 9 type II, and one type III SSS according to the Rubenstein classification (Rubenstein et al., 1972). Type III SSS (tachycardia-bradycardia syndrome) and type II SSS (sinus pause without tachycardia) were identified by the index 12-lead electrocardiograms (ECGs), and type I SSS was diagnosed by telemetry when the patients complained of symptoms during the hospitalization. Among the theophylline group, 15 patients were switched from theophylline to cilostazol, due to insufficient drug effects or adverse drug reactions to theophylline such as nausea, vomiting, or diarrhea (Fig. 1).

2.3 Heart rate and symptom evaluation

The HR was evaluated using the ECG (MAC-3500, GE Healthcare Co. Ltd., Chicago, IL, USA) and digital sphygmomanometry (HBP-9020, OMRON Co. Ltd, Kyoto, Japan) in the outpatient clinic. After the administration of theophylline or cilostazol, the HR was re-evaluated in 4-8 weeks at the out-patient clinic. The HR, maximum RR interval, and mean RR interval were compared.

The symptoms such as dyspnea, chest discomfort, syncope, and palpitations were compared between those before and after the administration of theophylline or cilostazol. The severity of the dyspnea was classified into 4 stages according to the New York Heart Association (NYHA) classification. Chest discomfort, syncope, and palpitations were classified as the presence or absence of symptoms.

2.4 Statistical analysis

All analyses were performed using SPSS® Statistics 18.0 for Windows software (SPSS Inc., Chicago, IL, USA). The continuous baseline characteristics were presented as the average values ± standard deviation and categorical baseline characteristics as counts and percentages. The continuous baseline characteristics were compared and evaluated by the use of a Student's *t*-test and the categorical baseline characteristics by a Pearson's chi-square test. We used a paired *t*-test to analyze the difference in the HR between that before and after the administration of theophylline or cilostazol. A *P*-value of < 0.05 was considered as statistically significant.

3. Results

3.1 Baseline characteristics

Overall 80 patients were enrolled in this study (50 patients in the theophylline group and 30 in the cilostazol group). There was no significant difference between the two groups in terms of the age, sex, systolic blood pressure, previous history of hypertension, diabetes, dyslipidemia, and smoking (Table 1).

3.2 Change in the heart rate

Fifty patients were administered 200-400 mg of theophylline per day, and 30 patients, 100-200 mg of cilostazol per day. The baseline HR of the entire 80 patients was 51.9 ± 11.8 bpm on the ECG and 54.8 ± 13.5 bpm on the digital sphygmomanometry.

Table 1. Comparison of the clinical baseline characteristics between the theophylline and cilostazol groups

Characteristics	Theophylline group (n = 50)	Cilostazol group (n = 30)	P value
Age (Years)	67.4 ± 10.1	71.5 ± 8.8	0.084
Sex (Male: Female)	19:31	12:18	0.859
Past history			
HTN (yes/no)	20/30	15/15	0.383
DM (yes/no)	13/37	6/20	0.542
DL (yes/no)	11/39	10/20	0.265
Smoking (yes/no)	4/46	0/30	0.112
Creatinine (mg/dL)	0.8 ± 0.3	0.8 ± 0.3	0.713
NT-proBNP (pg/mL)	389.9 ± 447.3	215.6 ± 175.1	0.296
LV ejection fraction (%)	65.1 ± 9.5	65.1 ± 7.1	0.988
sBP (mmHg)	127.8 ± 13.6	125.4 ± 15.7	0.566
Lowest heart rate (bpm)	43.3 ± 10.8	45.8 ± 12.1	0.334

P-value calculated by a Student's *t*-test for the continuous variables and Pearson's chi-square test for the categorical variables. Abbreviations: bpm, beat per minute; DM, diabetes mellitus; DL, dyslipidemia; HTN, hypertension; LV, left ventricle; sBP systolic blood pressure
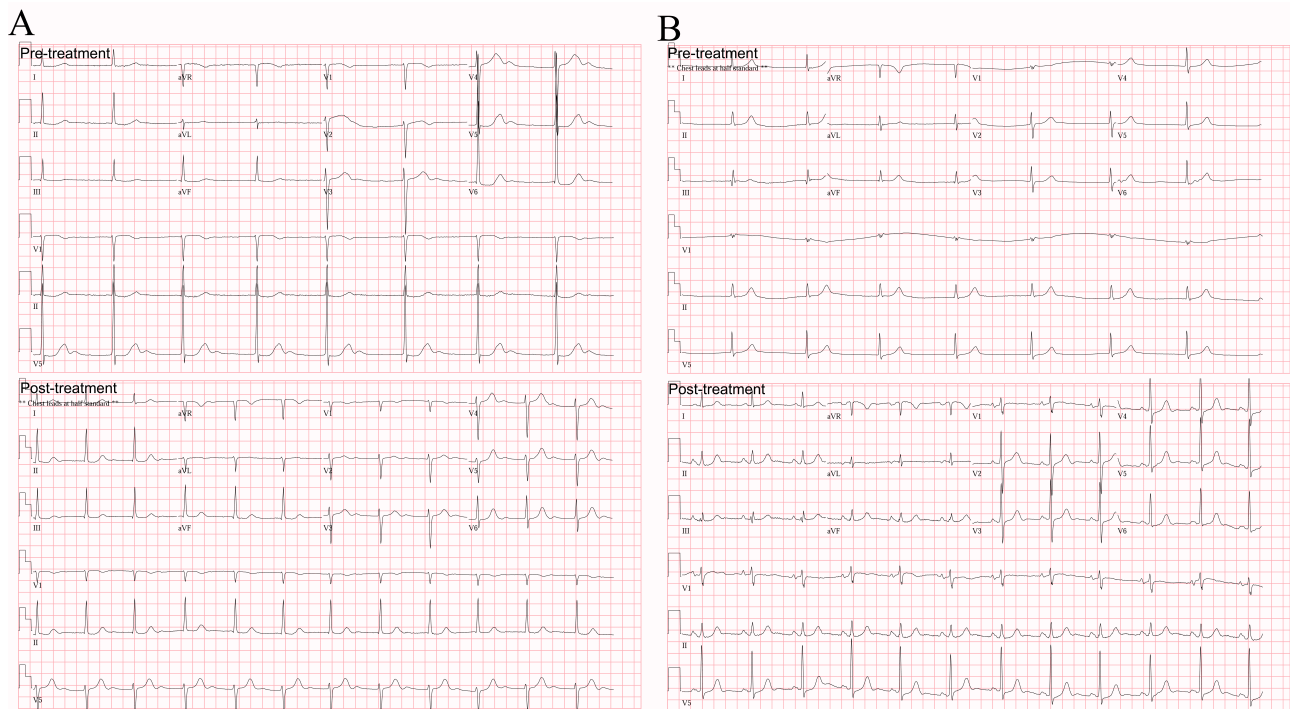

Fig. 2. Representative 12-lead ECGs of pre and post-treatment. A) Pre-treatment ECG showed a junctional rhythm with 47 bpm. Theophylline 400 mg was administered for 14 days. Post-treatment ECG showed a normal sinus rhythm with 71 bpm. B) Pre-treatment ECG showed a junctional rhythm with 46 bpm. Cilostazol 200 mg was administered for 14 days. Post-treatment ECG showed a normal sinus rhythm with 70 bpm. *Abbreviations*: bpm, beat per minute

The mean follow-up period was 31 ± 14.3 days. The representative 12-lead ECGs of pre and post-treatment can be seen in Fig. 2. The HR on the ECG (*P* < 0.001) and digital sphygmomanometry (*P* < 0.001) had a statistically significant increment after the administration of theophylline or cilostazol in the two groups (Table 2 and Fig. 3).

Among the 50 patients in the theophylline group, 15 were switched from theophylline to cilostazol. The drug-naive HR was 48.9 ± 9.4 bpm, and it increased to 61.4 ± 13.8 bpm after the theophylline administration (*P* = 0.002). After switching theo-

phylline to cilostazol, the HR increased to 64.0 ± 12.6 bpm, but there was no statistically significant difference (*P* = 0.338) (Table 3 and Fig. 4).

3.3 Change in the symptoms (*Table 4*)

Overall in the 80 patients, the dyspnea significantly improved after the administration of theophylline or cilostazol (*P* < 0.001). In terms of the dyspnea, classified by the NYHA classification, there were 3 class IV, 15 class III and 19 class II patients before the administration, and they improved to 0 class IV, 4 class III, and 17 class II patients after the administration. The chest discomfort,

Table 2. Analytical results before and after the theophylline and cilostazol administration

Parameter	Before	After	P value
Theophylline			
HR at the clinic (bpm)	53.8 ± 11.9	65.9 ± 15.2	< 0.001
HR on the ECG (bpm)	50.6 ± 10.9	59.0 ± 12.8	< 0.001
Mean RR (ms)	1250.4 ± 291.3	1079.0 ± 23.15	< 0.001
Max.RR (ms)	1385.3 ± 372.8	1163.8 ± 298.3	0.551
PR (ms)	168.8 ± 34.2	165.7 ± 40.8	0.95
sBP (mmHg)	127.9 ± 20.4	127.7 ± 15.9	0.536
dBP (mmHg)	70.9 ± 12.8	72.2 ± 12.6	< 0.001
Cilostazol			
HR at the clinic (bpm)	56.4 ± 13.4	73.3 ± 14.3	< 0.001
HR on the ECG (bpm)	54.0 ± 12.2	66.4 ± 15.1	< 0.001
Mean RR (ms)	1143.7 ± 232.9	970.3 ± 228.7	0.001
Max.RR (ms)	1309.5 ± 388.4	1024.5 ± 233.3	0.001
PR (ms)	161.8 ± 24.6	162.5 ± 35.5	0.929
sBP (mmHg)	125.4 ± 13.2	130.4 ± 16.7	0.096
dBP (mmHg)	73.3 ± 114.4	71.59 ± 12.9	0.513

P-value calculated by a paired *t*-test. Abbreviations: bpm, beat per minute; dBP diastolic blood pressure; ECG, electrocardiogram; HR, heart rate; OPD, out-patient department; PR, PR interval; RR, RR interval; sBP, systolic blood pressure

Table 3. Analytical results after switching from theophylline to cilostazol

Parameter	Baseline	Theophylline	Cilostazol	P value (B → T)	P value (T → C)
HR on the ECG (bpm)	48.9 ± 9.4	61.4 ± 13.8	64.0 ± 12.6	0.002	0.338
Mean RR (ms)	1277.6 ± 266.1	1047.2 ± 258.5	1016.6 ± 189.8	0.003	0.286
Max.RR (ms)	1341.8 ± 319.7	1202.4 ± 376.8	1135.9 ± 223.9	0.146	0.064
PR (ms)	167.2 ± 33.0	162.8 ± 27.1	155.6 ± 23.4	0.433	0.285

P-value calculated by a paired *t*-test. Abbreviations: B, Baseline; bpm, beat per minute; C, Cilostazol; ECG, electrocardiogram; HR, heart rate; PR, PR interval; RR, RR interval; T, Theophylline

dizziness, syncope, and palpitations also significantly improved after the medication administration.

In the 50 patients in the theophylline group, the dyspnea and palpitations improved significantly. There were 2 class IV, 11 class III, and 13 class II patients, and they improved to 0 class IV, 3 class III, and 12 class II patients after the theophylline administration (*P* < 0.001). Four patients had palpitations before the theophylline administration, but none felt any palpitations after the theophylline (*P* = 0.046). However, there was no significant improvement in the chest discomfort, syncope, or dizziness.

In the 30 patients in the cilostazol group, the dyspnea and dizziness significantly improved. There was 1 class IV, 4 class III, and 6 class II patients, and they improved to 0 class IV, 1 class III, and 5 class II patients after the cilostazol administration (*P* = 0.002). Eleven patients experienced dizziness before the cilostazol administration, but only 2 after the cilostazol (*P* = 0.003). However, there was no significant improvement in the chest discomfort, syncope, or palpitations.

When comparing the two drugs in terms of the symptom improvement, cilostazol had a significantly better results for the dizziness than theophylline (Table 5). In terms of the side effects of the drugs, there were 5 patients with nausea, 0 with diarrhea, 3 with headaches, 3 with new arrhythmias (e.g.: atrial fibrillation,

flutter, or premature atrial complexes), and 1 with numbness of the extremities in the theophylline group. There were 4 patients with headaches and 1 with diarrhea in the cilostazol group (Table 6).

After a median follow-up of 2 years and 9 months, there was no significant difference in the clinical course between the two groups (Table 6).

4. Discussion

SND is often related to age-dependent, progressive, and degenerative fibrosis of the sinus nodal tissue and surrounding atrial myocardium. SSS is a clinical syndrome characterized by SND. However, historically, SND used to be referred to as SSS. In the present study, when we emphasized the histopathologic characteristics, we used "SND". When the symptoms were emphasized, we used "SSS".

The increment in the HR is helpful for improving symptoms such as general weakness, fatigue, dizziness, and syncope in patients with SSS (Alt et al., 1985; Tung et al., 1994). Permanent pacemaker implantations are the most frequently used and most effective treatment option and are almost always considered as a first-line treatment. Therefore, only a few studies have investigated the effectiveness of the pharmacological therapy for SSS, and thus far, the diversity of the various pharmacological therapies for these

Table 4. Change in the symptoms after the theophylline or cilostazol administration

	Overall			Theophylline			Cilostazol		
	Before	After	*P* value	Before	After	*P* value	Before	After	*P* value
Dyspnea (NYHA Fc)									
I	43	59	< 0.001	24	35	< 0.001	19	24	0.002
II	19	17		13	12		6	5	
III	15	4		11	3		4	1	
IV	3	0		2	0		1	0	
Chest discomfort									
Yes	11	5	0.034	6	3	0.083	5	2	0.18
No	69	75		44	47		25	28	
Dizziness									
Yes	30	16	0.014	19	14	0.439	11	2	0.003
No	50	64		31	36		19	28	
Syncope									
Yes	4	0	0.046	3	0	0.083	1	0	0.317
No	76	80		47	50		29	30	
Palpitations									
Yes	8	1	0.008	4	0	0.046	4	1	0.083
No	72	79		46	50		26	29	

P-value calculated by a Wilcoxon signed-rank test. Abbreviations: NYHA Fc, New York heart association function class

Table 5. Comparison of the rate of symptom improvement between theophylline and cilostazol

	Theophylline		Cilostazol		*P* value
	Improved	Not-Improved	Improved	Not-Improved	
Dyspnea	20 (40%)	30 (60%)	10 (33%)	20 (67%)	0.551
Chest discomfort	3 (50%)	3 (50%)	3 (60%)	2 (40%)	0.74
Dizziness	5 (26%)	14 (74%)	9 (82%)	2 (18%)	0.003
Syncope	3 (100%)	0 (0%)	1 (100%)	0 (0%)	NA
Palpitations	4 (100%)	0 (0%)	3 (75%)	1 (25%)	0.285

P-value calculated by a Chi-square test. Abbreviations: NA, not available

patients is still low.

There have been many reports on the positive chronotropic effects of theophylline, which acts to block adenosine and leads to an increase in sinus node automaticity and atrioventricular (AV) conduction (Gambhir et al., 1995; Szentmiklosi et al., 1980). Several studies have shown that theophylline improves the severity of bradycardia-related symptoms in newborn babies, and that theophylline increases the HR in patients with late advanced AV block complicated with acute myocardial infarction and who undergo heart transplantations (Altun et al., 1998; Ellenbogen et al., 1988; Myers et al., 1980; Shannon et al., 1975). Thus, this agent could be used to increase the HR in patients with SND. However, a prospectively assessed randomized controlled trial (THEOPACE) has revealed that permanent pacemakers are more effective than theophylline in reducing the occurrence of syncope (Alboni et al., 1997). Cilostazol, a phosphodiesterase-III (PDE-III) inhibitor, was first developed in Japan for the treatment of symptoms of intermittent claudication in patients with peripheral arterial occlusive disease. Cilostazol has anti-platelet effects and positive hemodynamic effects on peripheral circulatory defects by the selective inhibition of cyclic nucleotide PDE-III in platelets and vascular smooth muscle. Therefore, this agent is first treatment option for vascular inflammatory diseases, such as coronary artery disease or peripheral arterial occlusive disease (Kambayashi et al., 2003; Kawamura et al., 1985; Liu et al., 2001; Shintani et al., 1985).

Cilostazol is considered to have positive chronotropic effects via several speculated mechanisms (MacDonald et al., 2020; Mangoni and Nargeot, 2008). Firstly, Fischmeister et al. (2006) revealed that cyclic adenosine monophosphate (cAMP) plays an important role in the beta-adrenergic receptors that stimulate the HR. Gs-protein (stimulatory G-protein) activation (e.g., via β-adrenoceptors) induces adenylyl cyclase. The adenylyl cyclase dephosphorylates adenosine triphosphate (ATP) to form cAMP. The cAMP then activates protein kinase-A (PK-A) and causes an increased cellular influx of Ca^{++} by phosphorylation and activation of L-type calcium channels, and an enhanced release of Ca^{++} by the sarcoplasmic reticulum in the heart. These events increase the inotropy and chronotropy (Klabunde, 2012; Mangoni and Nargeot, 2008). cAMP is degradated by PDE-III. Eventually, cilostazol (PDE-III inhibitor) would increase the chronotropy (Liu

Table 6. Adverse effects after the drug administration and long-term clinical course in the theophylline and cilostazol groups

	Theophylline group (n = 50)	Cilostazol group (n = 30)
Adverse effect		
Headache	3	4
Diarrhea	0	1
Nausea	5	0
New arrhythmia	3	0
Extremity numbness	1	0
Long-term course		
Syncope	0	0
CV hospitalization	1 HF, 1 AMI	2 UAP
CV death	0	0

Abbreviations: AMI, acute myocardial infarction; CV, cardiovascular; HF, heart failure; UAP, unstable angina

A

B
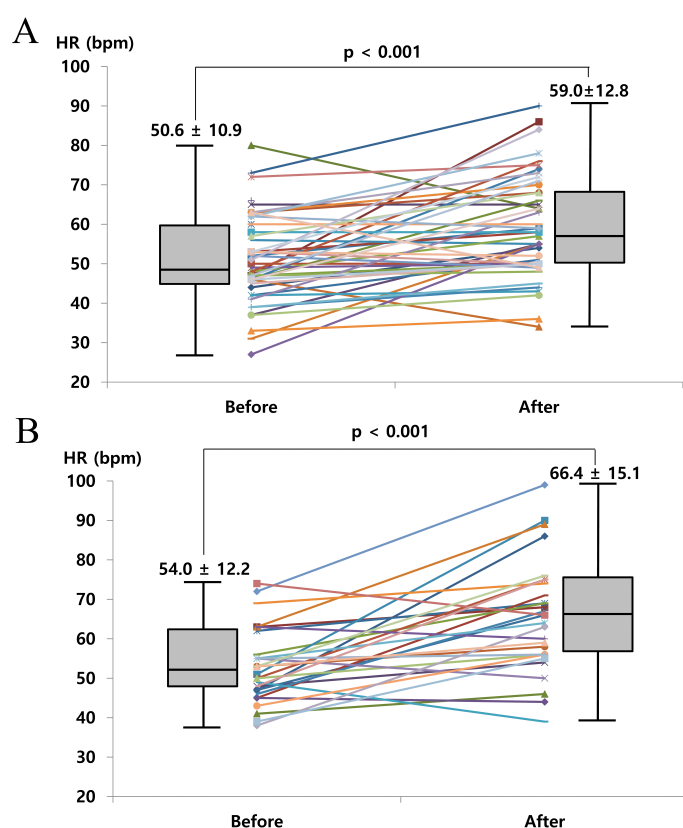
Fig. 3. Comparison of the HR before and after the theophylline and cilostazol administration. A) The HR evaluated by the ECG increased from 50.6 ± 10.9 bpm (before) to 59.0 ± 12.8 bpm (after) in the theophylline group. B) The HR evaluated by the ECG increased from 54.0 ± 12.2 bpm (before) to 66.4 ± 15.1 bpm (right) in the cilostazol group. Data are represented as the mean ± standard deviation. *P*-value calculated by paired *t*-test, Abbreviations: HR, heart rate

Fig. 4. Changes in the HR after switching from theophylline to cilostazol. The baseline HR evaluated by the ECG was 48.9 ± 9.4 bpm (baseline), and the HR increased to 61.4 ± 13.8 bpm (theophylline) after the theophylline administration. The *P*-value calculated by a paired *t*-test was 0.002, which was statistically significant. After switching from theophylline to cilostazol, the HR increased to 64.0 ± 12.6 bpm (cilostazol). The data are represented as the mean ± standard deviation. *P*-value calculated by paired *t*-test, Abbreviations: HR, heart rate

I_f current but also to the voltage-gated calcium currents and intracellular Ca^{++} dynamics described above (Lakatta et al., 2010). Thirdly, cilostazol induces systemic vasodilation, and thus it produces reflex adrenergic stimulation (in other words, a baroreceptor reflex) that contributes to positive chronotropy (Klabunde, 2012). Fourthly, cilostazol may have inhibitory effects on the adenosine uptake or may have an antagonizing effect on adenosine triphosphate (Liu et al., 2001). Finally, cilostazol can improve the coronary blood supply to the sinus node (SA) or AV node. If the patient has ischemia of the SA or AV node, it may improve the automaticity or conductivity.

Therefore, it was considered that cilostazol would be a reasonable pharmacological treatment for SSS by increasing the HR, and several studies on that have been performed. Ueda et al. (2001) evaluated 24-hour ambulatory ECG monitoring after cilostazol administration and revealed that the HR increases and the frequency of sinus pauses decreases after cilostazol administration.

The present study compared the positive chronotropic effects

et al., 2001; Moriya et al., 2004). Secondly, the increased cAMP level also can lead to the activation of the I_f currents and an increase in the HR (DiFrancesco, 2010; Irisawa et al., 1993). However, the increment in the HR due to cAMP is not only due to the
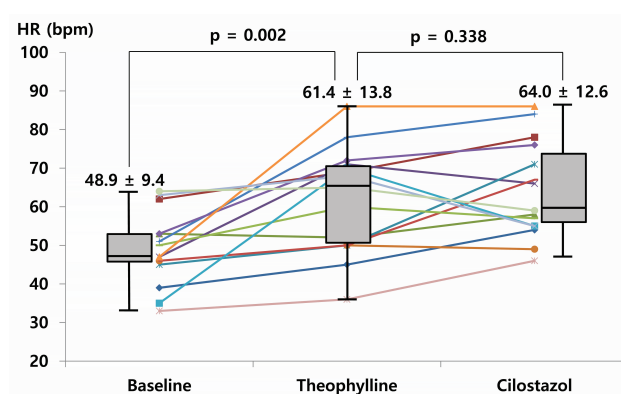
between theophylline and cilostazol, and although the HR significantly increased after the administration of theophylline and cilostazol, there was no difference between the two groups. Moreover, the symptoms such as dyspnea, chest discomfort, and dizziness improved after the administration of theophylline and cilostazol. Interestingly, in terms of the dizziness, cilostazol resulted in a significant improvement when compared to theophylline. We believed that the max RR interval increment, which is shown in Table 2, could explain the significant improvement in the dizziness in the cilostazol group. Also, as we described above, it might be a result of the positive chronotropic and vasodilation effects.

Theophylline has a narrow therapeutic index, and theophylline toxicity may occur at toxic levels. That includes symptoms from mild gastrointestinal symptoms such as nausea, vomiting, and diarrhea to severe and fatal cardiac arrhythmias or a central nervous system manifestation such as seizures. In this study, nausea was the most frequent adverse effect. Therefore, regular evaluation of the serum theophylline level may be required and helpful to minimize the adverse drug reactions (Gaudreault and Guay, 1986). However, the optimum dose of cilostazol has been determined (100 mg twice daily) and there is no need to monitor the serum levels. The vasodilation effect of cilostazol causes some side effects such as headaches and diarrhea, but they are almost always mild symptoms and improve after conservative treatment and the discontinuation of the cilostazol (Liu et al., 2001). In this study, there were 4 patients with headaches and 1 with diarrhea in the cilostazol group. The headaches disappeared by their next clinic visit.

This study had some limitations. First, the study was a retrospective and single center-based study, so selection bias and recall bias may have occurred and the baseline patient characteristics could have influenced the outcome. Second, we did not control the dosage of theophylline and cilostazol, so it may have been difficult to accurately investigate the effects of both agents. Further, since we used the ECG to evaluate the patient's HR, the HR only reflected that at the time of the ECG. Twenty-four hour ambulatory ECG monitoring may be required to evaluate the continuous HR, including the circadian rhythms, in the patients. In the overall patients, the symptoms improved significantly and also tended to improve when the patients were divided into the theophylline and cilostazol groups, however, some improvements in the overall patients were not statistically significant. This may have been due to the lack of an adequate number of patients or because the symptoms were subjective, and we did not classify the severity of the symptoms.

In conclusion, this study suggested that cilostazol, like theophylline, might be used for supportive management in patients with SSS, especially when the patients do not want a pacemaker or their symptoms are not very severe. Moreover, there are some advantages to using cilostazol. Since SSS frequently occurs in elderly patients and they tend to have comorbid peripheral arterial occlusive disease, there may be an advantage of using cilostazol in elderly patients. However, further studies are needed due to several limitations of this study.

Authors' contribution

ITJ was a major contributor to the writing of the manuscript. NY contributed to the design, literature search, experimental studies, data acquisition, data analysis, manuscript preparation, manuscript editing, manuscript review, approval of the final version of the manuscript, and agreement of all aspects of the work. HKJ contributed to the literature search, experimental studies, data analysis, statistical analysis, manuscript editing, manuscript review, approval of the final version of the manuscript, and agreement of all aspects of the work. KHL contributed to the manuscript review, approval of the final version of the manuscript, and agreement of all aspects of the work. HWP contributed to the conception of the work, manuscript review, approval of the final version of the manuscript, and agreement of all aspects of the work. JGC contributed to the conception of the work, definition of the intellectual content, manuscript editing, manuscript review, approval of the final version of the manuscript, and agreement of all aspects of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the ethics committee at Chonnam National University Hospital, Gwangju, Korea (CNUH-2017-033), where exempted informed consent from enrolled patients because of retrospective study protocol.

Acknowledgments

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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