Comparison of the Transdermal Bisoprolol Patch with Oral Bisoprolol Fumarate Administration as a Therapeutic Agent for Idiopathic Frequent Premature Ventricular Contractions

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Summary
The transdermal bisoprolol patch (TB) was designed to maintain a sustained concentration of bisoprolol in plasma by a higher trough concentration than oral bisoprolol (OB). We compared the efficacy between TB and OB in patients with idiopathic premature ventricular contractions (PVCs) while considering their duration of action.

A total of 78 patients with a PVC count of ≥3,000 beats/24 hours were divided into groups treated with TB 4 mg (n = 43) or OB 2.5 mg (n = 35). PVCs were divided into positive heart rate (HR)-dependent PVCs (P-PVCs) and non-positive HR-dependent PVCs (NP-PVCs) based on the relationship between the hourly PVC density and hourly mean HR. Twenty-four-hour Holter electrocardiograms were performed before and 1 to 3 months after the initiation of therapy.

There were no significant between-group differences in the baseline characteristics. Both the TB (from 14.6 [9.9-19.2] to 7.6 [1.7-15.8]%, P < 0.001) and OB (from 13.2 [7.6-21.9] to 4.6 [0.5-17.0]%, P = 0.0041) significantly decreased the PVC density, and there was no significant difference between the two groups (P = 0.73). Compared to OB, the TB had similar effects in reducing the PVC density for P-PVCs (P = 0.96), and NP-PVCs (P = 0.71). The TB significantly decreased the P-PVC density from baseline not only during daytime (P < 0.001) but also night-time (P = 0.0017), while the OB did not significantly decrease the P-PVC density from baseline during night-time (P = 0.17).

Compared to OB, the TB could be used with the same efficacy of reducing idiopathic PVCs. The TB may be a more useful therapeutic agent than OB for P-PVCs during a 24-hour period.

Key words: Selective β1-blocker, Transdermal drug, Holter electrocardiogram

Premature ventricular contractions (PVCs) are common problems in daily practice. In general, idiopathic PVCs have been considered to be relatively benign. However, symptoms such as palpitations may result in a quality of life decline. Also, a high PVC density can result in an impaired left ventricular ejection fraction (LVEF). Among the β-blockers, bisoprolol is recommended as the first-line therapy to suppress PVCs because of its highly selective β1-blocking action and sympatholytic effect. The transdermal bisoprolol patch (TB) is a new β-blocker formulation with a transdermal delivery system containing bisoprolol, which is a free base of bisoprolol fumarate available as an oral formulation. The TB is designed to maintain a sustained plasma concentration of bisoprolol by having a lower peak plasma bisoprolol concentration and higher trough concentration than oral bisoprolol (OB). Recently, we reported the efficacy and safety of TB in treating idiopathic PVCs. However, it is unclear whether the TB is as effective and safe in treating idiopathic PVCs as OB. In the present study, we compared the efficacy and safety between the TB and OB in treating idiopathic PVCs while considering their duration of action.

Methods

Study population: Among patients with frequent PVCs without structural heart disease (SHD) who visited Toho University Omori Hospital between October 2015 and April 2019, 78 consecutive patients prescribed 4 mg TB or 2.5 mg OB were retrospectively investigated. A total of 103 eligible patients were analyzed after excluding 8 pa-
tients using other antiarrhythmic agents, 7 treated with the TB and 8 treated with OB lost to follow up, and 2 treated with the TB that withdrew due to the occurrence of adverse events (AEs). A comparison was performed between the patients treated with the TB (n = 43) and OB (n = 35). The patients needed to have frequent PVC counts, defined as more than 3,000 beats as measured by 24-hour Holter electrocardiograms (ECGs), regardless of any clinical symptoms. SHD was excluded based on a history, physical examination, and transthoracic echocardiography. The LVEF was calculated using Simpson’s formula by 2 readers. The LVEF had to be ≥ 50% without any evidence of wall motion abnormalities or left ventricle dilatation.

**Study design:** The TB was administered once daily at a dose of 4 mg. The patients were instructed to attach the TB to their chest, back, or upper arms in the morning. The OB was administered once daily at a dose of 2.5 mg in the morning. In clinical practice, a mid-range β-blocker dose is often administered to treat PVCs. The TB at 4 mg was an equivalent value to the OB at 2.5 mg. Therefore, we assessed to what extent the TB at 4 mg or the OB at 2.5 mg was effective in treating idiopathic frequent PVCs. To evaluate the efficacy, 24-hour Holter ECGs were performed at baseline and at 1 to 3 months after the initiation of the therapy, and the clinical symptoms such as palpitations related to the PVCs were evaluated. For a safety assessment, we measured the systolic blood pressure, diastolic blood pressure, HR, and clinical laboratory tests, and the AEs were investigated.

**Holter ECGs:** A 12-lead Holter ECG recording was used in each patient for a 24-hour period during their normal daily activities (SCM-8000, Fukuda Denshi, Tokyo). Ventricular arrhythmias were analyzed for the PVC count, PVC density, and ventricular tachycardia (VT). The PVC density was defined as the total number of PVCs divided by the total HR. Nonsustained VT was defined as 3 or more consecutive PVCs. The origins of the PVCs were determined by the most frequent PVC morphology. They were characterized as the site of origin: (1) right ventricular outflow tract (RVOT): left bundle branch block pattern with an inferior axis, tall R waves in inferior leads, and a transition zone in lead V3 or V4; (2) left ventricular outflow tract (LVOT): right bundle branch block pattern with an inferior axis, tall R waves in inferior leads; or left bundle branch block pattern with an inferior axis and a transition zone in lead V1 or V2; (3) RV non-OT: left bundle branch block pattern without RVOT features; and (4) LV non-OT: right bundle branch block pattern without LVOT features.

**Relationship between PVC density and HR:** The PVCs were classified into two types based on their HR dependency, which was evaluated by the relationship between the hourly PVC density and hourly mean HR measured by 24-hour Holter ECGs. This classification was fundamentally the same as that reported by He, et al. They demonstrated that there are different relationships between the PVC density and HR for idiopathic PVCs, and that PVCs with their density positively related to the HR might be induced by sympathetic activation, PVCs with their density negatively related to the HR might be induced by the parasympathetic activation, and when no evident relationship between the PVC density and HR exists, those PVCs might have an independent autonomic nervous system relationship. In the present study, PVCs with their density positively related to the HR were defined as positive HR-dependent PVCs (P-PVCs). When no evident positive relationship between the PVC density and HR was shown, the PVCs were defined as non-positive HR-dependent PVCs (NP-PVCs). NP-PVCs consisted of PVCs with their density negatively or not related to the HR. Figure 1 shows the representative cases classified by the HR dependency of the PVCs. Cases (1) positive HR-dependent PVCs and (2) negative HR-dependent PVCs were regarded as cases with the strongest positive and negative correlations between the hourly PVC density and hourly mean HR, respectively.

**Study outcomes:**

**Efficacy outcome** We evaluated the change in the PVC density from baseline. When analyzing the mean 24-hours by Holter ECGs, the PVC density was measured during the entire 24 hours, day-time (6 AM to 8 PM), and nighttime (8 PM to 6 AM). According to the day-to-day variability in the PVCs, the response to treatment with a PVC number reduction of 70% within a 24-hour period was defined as a “responder”. In addition, we conducted a separate comparison of the positive HR-dependent PVC (P-PVC) and non-positive HR-dependent PVC (NP-PVC) groups. To evaluate the clinical symptom improvement, we checked the symptom logbook recorded by the patient after the initiation of the therapy. The frequency of symptoms was monitored, and when the frequency decreased, the condition was considered an “improvement.”

**Safety outcome** The safety was assessed based on the incidence of AEs that were considered treatment-related and adverse drug reactions. AEs that required hospitalization, resulted in a significant disability, and crucial medical events were classified as serious AEs.

**Ethical consideration:** The study protocol was approved by the Toho University Omori Medical Center Ethical Committee on September 12, 2017 (approval no.: 24-123).

**Statistical analysis:** Statistical analyses were performed with EZR on R-commander version 1.24 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). All continuous variables were tested for the normality of the distribution using the Kolmogorov-Smirnov test. Continuous variables with a normal distribution were described as the mean ± standard deviation (SD), continuous variables with a skewed distribution were described as the median (quartile: 25%–75%), and categorical variables were described as the frequency (percentage). A Pearson’s correlation coefficient was computed to determine the relationship between the hourly PVC density and hourly mean HR measured by 24-hour Holter ECGs. If the P value was less than 0.05, this correlation was considered significant. A paired t-test and Wilcoxon signed-rank test were used for the comparison of the baseline data and data after the medical therapy when the efficacy of the treatment was considered. Comparisons between groups were analyzed using Fisher’s exact test, Unpaired t-test, or Mann-Whitney test. In all tests, a P value of less than 0.05 was considered statistically significant.
Results

Patient characteristics: A total of 78 patients (TB, \( n = 43 \); OB, \( n = 35 \)) were enrolled in the present study. Forty-two patients (53.8%) were male. The mean age was 61.4 ± 14.2 years. The average LVEF was 66.7 ± 9.6%. Presenting clinical symptoms were palpitations (85.0%), chest pain (13.8%), dyspnea (5.0%), and presyncope (1.3%). Table I shows the baseline clinical characteristics in both groups. There were no significant between-group differences in the origin of the PVCs, mean HR, PVC density, or type of PVCs.

Comparison of therapy outcome:

All patients The PVC reduction effect of the TB and OB is shown in Table II. Both the TB and OB significantly decreased the PVC density after the initiation of the therapy (\( P < 0.001, P = 0.0041 \), respectively), and a comparison between the groups showed no significant difference (\( P = 0.73 \)). Considering the therapy effect on the PVCs during the day-time and night-time, both the TB and OB also significantly decreased the PVC density during the day-time (\( P = 0.041, P = 0.0027 \), respectively). The TB significantly decreased the P-PVC density during the night-time (\( P < 0.001 \), while OB did not (\( P = 0.081 \)). The responder rate for the treatment was 37.2% (16/43 patients) in the TB group and 42.9% (15/35 patients) in the OB group. The improvement rate in the subjective symptoms was 68.4% (13/19 patients) in the TB group and 61.9% (13/21 patients) in the OB group. These differences did not reach a statistically significant level (\( P = 0.65, P = 0.75 \), respectively).

AEs that were considered treatment-related were observed in 4 patients (2 patients with application site pruritus and 2 patients with application site dermatitis) in group TB and in 2 patients (bradycardia with lightheadedness) in group OB, which was not statistically significant (\( P = 1.0 \)). Neither the TB nor OB caused any serious AEs.

P-PVC group In the P-PVC group, both the TB and OB significantly decreased the total PVC density (\( P < 0.001, P = 0.029 \) respectively) and PVC density during the daytime (\( P < 0.001, P = 0.029 \) respectively). The TB also significantly decreased the P-PVC density during the night-time (\( P = 0.017 \), while the OB did not (\( P = 0.17 \)) (Table II). The responder rate to the treatment did not differ significantly between the TB and OB groups (TB: 12/22, versus OB: 12/20, \( P = 0.76 \)). Also, there was no significant difference in the improvement rate of subjective symptoms between the TB and OB groups (TB: 4/8, versus OB: 6/10, \( P = 1.0 \)). The change in the P-PVC density within a 24-hour period in each group is shown in Figure 2. Significant reductions were observed during each time period for the changes within 24-hours in the hourly P-PVC density from baseline in the TB group, while the hourly P-PVC burden from baseline during the hours in the middle of the night (11 PM to 6 AM) did not signifi-
AEs that were considered treatment-related were observed in 1 patient (application site pruritus) in group TB and in 1 patient (bradycardia with lightheadedness) in group OB, which was not statistically significant ($P = 1.0$).

**NP-PVC group** In contrast, in the NP-PVC group, neither the TB nor OB made any significant change in the total PVC density ($P = 0.051$, $P = 0.064$ respectively), PVC density during the day-time ($P = 0.59$, $P = 0.064$ respectively), or PVC density during the night-time ($P = 0.12$, $P = 0.69$ respectively) (Table II). The responder rate to the treatment did not differ significantly between the TB and OB groups (TB: 4/21, versus OB: 3/15, $P = 1.0$). Also, there was no significant difference in the improvement rate of subjective symptoms between the TB and OB groups (TB: 7/11, versus OB: 9/11, $P = 0.64$).

AEs that were considered treatment-related were observed in 3 patients (1 patient, with application site pruritus and 2 with application site dermatitis) in the TB group and in 1 patient (bradycardia with lightheadedness) in the OB group, which was not statistically significant ($P = 0.5$).

**Discussion**

**Main findings:** Compared with OB, the TB could be used with the same efficacy in reducing the total PVC density. Both the TB and OB were particularly effective in reducing the PVCs in the P-PVC group. The TB resulted in a significant reduction in the P-PVC density during not only the day-time but also the night-time, while OB did not significantly decrease the P-PVC density during the night-time. The AEs at the application site in the TB group were mild, and the incidence of AEs excluding the patch application site were similar for both drugs.

**Treatment with β-blockers for idiopathic PVCs:** There are 3 indications for treatment in patients with idiopathic PVCs: 1) symptoms related to PVCs, 2) frequent PVCs associated with a reversible form of cardiomyopathy, and 3) polymorphic VT/ventricular fibrillation due to malignant PVCs. Asymptomatic patients with a low PVC burden do not require specific therapy. For patients, the treatment options include medical therapy or catheter ablation. β-Blockers are a reasonable initial option for a PVC reduction because of their sympatholytic effect and safety profile. However, the literature examining the effect of β-blockers on idiopathic PVCs is limited, and several
The hourly PVC density at baseline (solid circle) and after therapy (open circle) with the TB and OB in the P-PVC patients. The OB did not significantly decrease the P-PVCs density from baseline during the hours between 11 PM and 6 AM, even though the TB significantly decreased the P-PVC density during each time period for the changes within 24 hours. **P < 0.05 versus baseline.

Table II. PVC Reduction Effect of the TB and OB

|                        | Group TB |                       |                       | Group OB |                       |                       |
|------------------------|----------|------------------------|------------------------|----------|------------------------|------------------------|
|                        | Pre      | Post                   | Pre                    | Post     |                        |                       |
| PVC density (per 24 hours) | 14.6 (9.9-19.2) | 7.6 (1.7-15.8)     | < 0.001*               | 13.2 (7.6-21.9) | 4.6 (0.5-17.0)     | 0.0041* 0.73**         |
| Day-time PVC density (per 14 hours) | 14.4 (10.3-19.3) | 5.9 (1.5-17.9)     | 0.041*                | 13.9 (8.6-21.0) | 4.4 (0.7-16.6)     | 0.0027* 0.30**         |
| Night-time PVC density (per 10 hours) | 13.6 (7.1-19.7) | 6.9 (1.0-14.6)     | < 0.001*              | 12.5 (5.6-22.2) | 3.9 (0.2-21.1)     | 0.081* 0.66**          |
|                        | 13.9 (8.7-20.7) | 3.7 (0.5-14.7)     | < 0.001*              | 13.3 (7.7-26.7) | 1.2 (0.4-16.6)     | 0.029* 0.96**          |
| Day-time PVC density (per 14 hours) | 15.8 (10.2-21.7) | 4.4 (0.5-15.6)     | < 0.001*              | 17.3 (8.8-29.2) | 1.6 (0.5-19.0)     | 0.029* 0.81**          |
| Night-time PVC density (per 10 hours) | 11.2 (6.1-16.8) | 2.3 (0.2-13.2)     | 0.0017*               | 8.6 (5.7-21.8)  | 0.5 (0.2-16.5)     | 0.17* 0.83**           |
|                        | 16.4 (9.9-18.1) | 8.7 (4.8-15.4)     | 0.051*                | 13.2 (8.0-18.8) | 6.4 (2.8-16.6)     | 0.064* 0.71**          |
| Day-time PVC density (per 14 hours) | 13.8 (10.6-17.7) | 9.4 (3.0-18.4)     | 0.59*                 | 12.3 (9.5-16.2) | 5.2 (2.6-13.0)     | 0.064* 0.22**          |
| Night-time PVC density (per 10 hours) | 15.3 (10.4-20.2) | 7.8 (5.8-15.5)     | 0.12*                 | 11.7 (7.0-20.7) | 11.2 (1.9-21.4)     | 0.45* 0.69**          |

PVC indicates premature ventricular contraction; TB, transdermal bisoprolol patch and OB, oral bisoprolol. Data are expressed as the median (25%-75%). The P values were determined by the *Wilcoxon signed-rank test, or **repeated-measures-ANOVA.
studies have shown that β-blockers are not sufficient to suppress idiopathic PVCs. In most cases, sympathetic activation could trigger the occurrence of idiopathic PVCs, but a few studies have shown that PVCs develop when the parasympathetic activation is increased in some patients. β-Blockers might provide insufficient suppression of idiopathic PVCs owing to the presence of PVCs not facilitated by sympathetic activation. He, et al. suggested that the HR dependency of idiopathic PVCs revealed different autonomic mechanisms. Thus, we analyzed the relationship between the hourly PVC density and hourly mean HR to estimate the HR dependency of PVCs following the method of He, et al, and investigated the comparison between the TB and OB for decreasing idiopathic PVCs by considering their HR dependency.

**Comparison between TB and OB:** The TB had an idiopathic PVC-reducing effect similar to that of OB. This finding indicates that the TB was considered to provide a new means of treatment for a PVC reduction as an alternative to OB in patients with a condition that made them unsuitable for oral administration (such as patients with difficulty swallowing due to advanced age or an ischemic stroke) as well as ordinary patients.

He, et al showed that PVCs with their density positively related to HR might be facilitated by sympathetic activation estimated by using the HR variability (HRV), and β-blockers (oral bisoprolol or metoprolol) decreased the PVC density in patients with positive HR-dependent PVCs. Our study also demonstrated that both the TB and OB significantly reduced the P-PVC density. However, the effect of OB in reducing the P-PVC density did not last during the night-time when it was administered once in the morning. The TB was designed to maintain a sustained plasma concentration of bisoprolol by a lower peak plasma bisoprolol concentration and higher trough concentration than OB. One of the important advantages of the TB over OB is that it can provide a constant release of the drug for long periods of time. A phase III trial on the TB revealed that the TB demonstrated stable HR-reducing effects during a 24-hour period, and the Bisono-AF study conducted in Japan also demonstrated that the TB significantly decreased the hourly mean HR during atrial fibrillation over 24-hours. Further, a previous study conducted to compare the TB and OB using HRV demonstrated that the circadian pattern of the autonomic modulation according to the HRV parameters varies between the TB and OB. This difference was attributed to a more stable sympatholytic effect and more decreased autonomic fluctuation resulting from the administration of the TB, which was seen during the middle of the night when both drugs were administered once in the morning.

According to the phase II trial on the TB, the TB achieved approximately twice as high a blood level as OB more than 12 hours after the drug initiation. That period of time was equivalent to the night-time in the present study because both drugs were administered once in the morning on the basis of the Japanese custom. A significant difference in the blood level of bisoprolol between the TB and OB may explain our main findings. It is not clear that suppression of the P-PVC density during the night-time is clinically relevant, but patients with P-PVCs and symptoms over 24 hours could be the most likely candidates for treatment with the TB because it can keep the drug’s blood level and sympatholytic effect constant.

Overall, the TB was well tolerated. When using the TB in clinical practice, it is assumed that not only AEs at the application site but also those specific for β-blockers such as hypotension and bradycardia will occur. However, a transdermal drug removal enables a rapid decrease in the drug’s circulating level. Especially, this advantage seems to be important for elderly patients with the risk of developing AEs due to physiological dysfunction, polypharmacy, or multiple comorbidities.

**Limitations:** This study had some potential limitations. First, it was a single center, retrospective, non-randomized, and observational study. The statistically significant results might not reflect a true effect and should be interpreted carefully. Treatment with the TB or OB was selected by the attending physician, and the patients may have influenced the choice of medication. Similarly, the timing of the 24-hour Holter ECGs after treatment were determined by the attending physician. Second, the number of patients was small. Third, the treatment period was 1-3 months, so the long-term effect and prognosis could not be clarified. Fourth, we did not perform an HRV analysis. We need further studies using HRV analysis to clarify the differences in the cardiac autonomic fluctuation between the TB and OB. Fifth, as we did not measure the bisoprolol blood level, the aforementioned explanation considering blood level of bisoprolol may be a matter of speculation. Future large-scale randomized studies should be conducted.

**Conclusions**

Compared to OB, the TB could be used with the same efficacy and safety for reducing idiopathic PVCs. The TB could be a more useful therapeutic agent for PVCs during the 24-hour period than OB.

**Disclosure**

**Conflicts of interest:** T.I. has received grant support through his institution from Daiichi Sankyo and Bristol-Myers Squibb and honoraria for lectures from Bayer Healthcare, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Tanabe-Mitsubishi, and Ono Pharmaceutical. Regarding this study, all authors declare that there are no potential conflicts of interest.

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