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Original Research Article

Effect of C-type natriuretic peptide and amiodarone in Chinese patients with arrhythmia

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Abstract

Purpose: *To compare the effect of C-type natriuretic peptide and amiodarone in Chinese patients with arrhythmia.*
Method: *Chinese men and women aged 18 to 65 years with premature ventricular complexes (PVCs), were administered C-type natriuretic peptide (CNP) - test group or amiodarone (study group) in ratio of 1:1 for 96 h. Patients in CNP group received infusion of synthetic human CNP (10 pmol/kg/min) for an initial 2 h, and then for 30 min every day until discharge. Patients in amiodarone group received initial dose of 1000 mg over the first 24 h. Change in PVCs from baseline was the primary efficacy endpoint. Secondary efficacy endpoint includes: change in PVCs-related symptom scores from baseline, change in ejection fraction of left ventricle (LV), end-diastolic diameter of LV, and cardiac events as composite outcome (CCE). The effect of both treatments on hemodynamic and electrocardiography parameters, and safety were evaluated. Data from 200 patients were analyzed.*
Results: *The CNP showed significantly greater decrease in the number of PVCs when compared to amiodarone ($p < 0.005$). Moreover, CNP was superior in alleviating PVCs- related symptoms when compared to amiodarone ($p < 0.005$). A similar trend of favorable effect of CNP was observed for other endpoints.*
Conclusion: *The C-type natriuretic peptide offers significantly greater benefits of suppressing PVCs and related symptoms, and demonstrates significantly greater improvement of cardiac function and clinical outcome. Thus, CNP can be considered for further investigation as a suitable alternative in the management of ventricular arrhythmia with PVC among Chinese patients.*

Keywords: *C-type natriuretic peptide, Amiodarone, Ventricular arrhythmia, Premature ventricular complexes*

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INTRODUCTION

Premature ventricular complexes/contractions (PVCs) are quite common among patients with ventricular arrhythmias [1-6]. Untreated cases of PVCs usually cause remodeling of ventricle, and associated with deterioration of left ventricle systolic function. It has been reported that PVCs are being observed in at least 6 % of the healthy population. In patients with heart diseases, the prevalence of PVCs is approximately 50 % [7-12]. The use of anti-arrhythmic drug has been recommended by physicians in managing PVCs [7-12]. Currently, anti-arrhythmic drugs are

widely used to manage PVCs and other related adverse conditions such as remodeling of ventricle and deterioration of left ventricular systolic function. Amiodarone induces prolongation of cardiac relaxation phase and block calcium and sodium channel, with β-receptor blocking properties [5-13]. Being a lipid-soluble molecule, the half-life of amiodarone is very long, which makes it suitable for once daily formulation. It has been reported that amiodarone prevents early ventricular strokes, and incidents of non-continuous ventricular tachycardias among subjects with low ejection fraction [7-16]. It has been reported that amiodarone reduced the incidence of PVCs in patients with cardiomyopathy/associated ventricular arrhythmia. Although amiodarone is the standard treatment option, its long-term use could result in adverse events such as skin discoloration, thyrotoxicosis, microdeposits in cornea, neuropathy, radiosensitivity, ocular neuritis, and respiratory toxicity. The most common adverse events of amiodarone long term usage are hepatic and renal damage [17,18]. Therefore, there is need for safe and effective option in management of PVCs in patient with arrhythmias/CCF. Effect of C-type natriuretic peptide in rodent model of arrhythmia have been investigated [19-22]. However, there is no clinical study evaluating the efficacy and safety of C-type natriuretic peptide versus amiodarone in premature ventricular complexes among patients with arrhythmia. The present investigation was designed to compare the effect of C-type natriuretic peptide and amiodarone in Chinese patients with arrhythmia.

METHODS

Patients

Chinese men and women aged 18 to 65 years with premature ventricular complexes (Lown's score: 2 - 4) were enrolled at the study site after obtaining written informed consent from them. This study was conducted in accordance with the guidelines of Declaration of Helsinki [23]. The study was approved by the Institutional Ethical Committee of BaoJi Central Hospital (approval no. IRB/2021/29-12/09-2187). To assess the eligibility of participants, each subject was visited and screened, and blood samples collected for complete laboratory assessment including chest x-ray and electrocardiogram.

Exclusion criteria

Patients with (1) heart rate < 50 per min; (2) single/second/3rd degree heart blockage; (3) duration of QTc > 480 ms were excluded. The patients had history of peripheral neuropathy, fibrosis, hepatitis, bleeding disorder, hypokalemia, uncontrolled diabetes, severe heart diseases, mental disorder, chronic renal disease, sleep disorder, asthma, heart failure, non-cardiac illness, pleural adhesions, and underwent ipsilateral thoracic surgery were excluded. The patients with deformity in airways or spinal, or chest wall were also excluded. Patients with suspected carcinoma or a history of carcinoma were excluded. Patients with any other pathology, which the consulting physician feels may affect the outcome of the study or patients who received prohibited concomitant medications that affect bone metabolism or undergoing any other surgery, considering the impact of the study outcome and subject's safety, were also excluded from the study.

Treatments

All eligible patients received an infusion (2 h) of synthetic human C-type natriuretic peptide or amiodarone in the ratio of 1:1 for approximately 96 h. Patients in CNP group received infusion (2 h) of synthetic human C-type natriuretic peptide (10 pmol/kg/min) for 30 min every day until discharge. Patients in amiodarone group received an initial dose of 1000 mg over the first 24 h of therapy. After the first 24 h, the maintenance infusion rate of 0.5 mg/min was continued.

Efficacy and safety assessments

The primary efficacy endpoint was changed in PVCs from baseline. Secondary efficacy endpoint include change in PVCs-related symptom scores from baseline, change in ejection fraction of left ventricle (LV), end-diastolic diameter of LV, and cardiac events as composite outcome (CCE). Moreover, the effect of both the treatment on hemodynamic and electrocardiography parameters was evaluated. Safety of each patient was evaluated throughout the study period.

Statistical analysis

No formal sample size calculation was performed due to the pilot nature of this study. However, at least 200 evaluable patients were included in the present study. The data which belonged to numerical variable or quantitative variable was analyzed using appropriate statistical method such as student *t*-test for parametric data, and Man Whitney test for non-parametric data. Categorical variable or qualitative variable was analyzed using appropriate statistical method such as Chi-square and Fisher exact based on

the number of patients in each category. Data related to variables with greater variation in response were analyzed using non-parametric test. Graph Pad prism was used to analyze the data. Quantitative data were expressed as mean ± standard deviation (SD).

RESULTS

Patient disposition and baseline characteristics

A total of 220 patients were screened out of which 200 patients were enrolled. Data for 200 patients were analyzed using appropriate test. Demography and baseline characteristics were comparable (Table 1).

At baseline, NIS score for PVCs-associated symptoms was comparable in both treatment groups. After treatment, significantly greater reduction in NIS score of each PVCs-associated symptom was observed from baseline in each treatment group (within group comparison) (Table 2). This indicates that both treatments (CNP and amiodarone) were effective in reducing PVCs-associated symptoms. Moreover, reduction in NIS score of each PVC-associated symptom was significantly greater in patients treated with CNP when compared to patients treated with amiodarone. This indicates that CNP treatment were statistically superior to amiodarone in reducing PVCs-associated symptoms.

Overall composite endpoint of treatment effectiveness is summarized in Table 3. Significantly greater proportion of CNP treated patients had clinical benefit as compared with amiodarone. As indicated in Table 3, CNP was effective in 90 % of patients, whereas amiodarone was effective in 62 % of patients. In CNP group, only 10 % of patients showed no meaningful effect, whereas 38 % of patients in amiodarone group did not benefit.

The clinical outcome is summarized in Table 3. At baseline, beats per 24 h was similar for both treatment groups. Patients treated with CNP had significantly lower beats per 24 h as compared to patients treated with amiodarone throughout the study.

The proportion of patients with 90 % reduction in PVCs from baseline was significantly higher in patients treated with CNP when compared to amiodarone. In addition, for the proportion of patients with 30, 50 and 70 % reduction in PVCs from baseline. The CNP treated patients had significantly greater reduction in PVC.

Table 1: Demography and baseline characteristics

Parameter	CNP	Amiodarone	*P*-value
Age (years)	56.2±3.1	55.7±4.3	>0.05*
Sex, F/M (%)	58/42	55/45	>0.05**
Weight (kg)	67.2±3.2	68.2±4.5	>0.05*
BMI (kg/m^2)	24.2±2.8	23.4±1.5	>0.05*
Duration of PVCs (months)	17.16±3.37	16.31±4.17	>0.05*
Numeric rating scale score for each PVCs-related symptom			
Heart palpitations	5.32±1.6	5.43±2.3	>0.05*
Chest stiffness	3.43±2.6	3.36±1.8	>0.05*
Breathing problem	4.67±2.1	4.34±2.5	>0.05*
Insomnia	3.74±2.3	3.86±1.9	>0.05*
Fatigue	4.87±1.8	4.23±2.8	>0.05*
% of patients with hypertension	68.2	67.5	>0.05**
% of patients with CCF	73.2	74.5	>0.05**
Pulse rate, hr/min	72.7±5.2	73.8±6.3	>0.05*

**P*-value was calculated using Mann Whitney test; ***P*-value was calculated using Chi-square test. (values are mean ± SD, n = 100)

Table 2: Summary of NIS score for PVCs-related symptoms after treatment at the end of study

Parameter	CNP	Amiodarone	*P*-value*	*P*-value**
Heart palpitations	1.36±0.8	4.43±0.3	<0.05	<0.05
Chest stiffness	1.21±0.6	2.83±0.8	<0.05	<0.05
Breathing problem	1.42±0.4	3.34±0.5	<0.05	<0.05
Insomnia	1.32±0.3	2.86±0.9	<0.05	<0.05
Fatigue	1.23±0.2	3.23±0.8	<0.05	<0.05

**P*-value was calculated using Mann Whitney test (between group comparison); ***P*-value was calculated using Wilcoxan test (within group comparison). (Values are mean ± SD, n = 100)

Table 3: Summary of clinical outcomes (treatment effectiveness)

Parameter	CNP (%)	Amioda-rone (%)	*P*-value
Noticeable effective	48	32	<0.05
Effective	42	30	<0.05
Ineffective	10	38	<0.05

**P*-value was calculated using Chi-square test, n = 100

At baseline, the left ventricular end-diastolic diameter was similar in both treatment groups (Figure 1). After treatment, there was a decrease in left ventricular end-diastolic diameter among the patients treated with amiodarone when compared with CNP. However, the difference was not statistically significant. Thus, the effect of CNP and amiodarone was similar on left ventricular end-diastolic diameter.

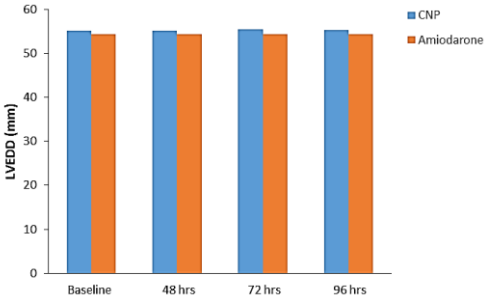

Figure 1: Left ventricular end-diastolic diameter (LVEDD) in patients treated with CNP and amiodarone

At baseline, the left ventricular ejection fraction was similar in the treatment groups (Figure 2). After treatment, there was marginal increase in the left ventricular ejection fraction as observed in patients treated with CNP when compared to amiodarone after 72 h of treatment. However, the difference was not statistically significant ($p > 0.05$). There was significant increase in left ventricular ejection fraction among the patients treated with CNP when compared to amiodarone after 96 h of treatment, and the difference was statistically significant.

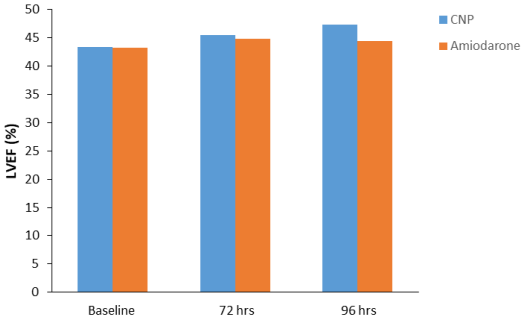

Figure 2: Left ventricular ejection fraction (LVEF) in patients treated with CNP and amiodarone

The proportion of patients with New York Heart Association (NYHA) I, II and III in both treatment groups is displayed in Figure 3. Proportion of patients with NYHA I was significantly lower in CNP group when compared to amiodarone. The proportion of patients with NYHA II was significantly higher in CNP group when compared to amiodarone while the proportion of patients with NYHA III was significantly lower in CNP group when compared to amiodarone. Moreover, CNP treated patients had lower incidence of symptoms when compared to amiodarone. Therefore, CNP treated patients had significantly greater reduction in PVC and associated symptoms.

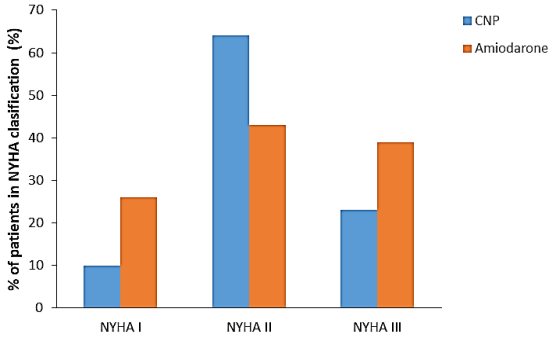

Figure 3: Proportion of patients with NYHA classification

Electrocardiogram data (24 h) before and after treatment are summarized in Table 4. At baseline, beats per 24 h (PVCs) was comparable. Both study drugs significantly improve beats per 24 h (PVCs) when compared to baseline (before treatment). On comparing both the treatments, significantly greater improvement in beats per 24 h (PVCs) was observed in patients treated with CNP when compared to amiodarone ($p < 0.05$). Similar trend of significantly greater improvement in PVCs reduction was observed in patients treated with CNP when compared to amiodarone.

Electrocardiography parameters after treatment is summarized in Table 5. Both study drugs significantly increased the interval/duration of action potentials when compared to baseline (before treatment). On comparing both treatments, interval/duration of action potentials was higher in patients treated with CNP than amiodarone, the difference was statistically significant ($p < 0.05$), indicating that CNP is an effective treatment alternative for Chinese patients with ventricular arrhythmia with premature ventricular complexes by increasing action potentials.

Table 4: Summary of electrocardiogram data (24 h) before and after treatment

Parameter	CNP	Amiodarone	*P*-value
Beats per 24 h (PVCs)			
Baseline	3571±2145	3575±2122	>0.05
At 48 h	1523±2145	1892±2122	<0.05
At 72 h	1231±639	1434±632	<0.05
At 96 h	1102±612	1297±542	<0.05
Patients with PVCs reduction			
90%	40%	20%	<0.05
70%	35%	15%	<0.05
50%	15%	35%	<0.05
30%	10%	30%	<0.05

**P*-value was calculated using Mann Whitney test (between group comparison). Values are mean ± SD (n = 100)

Table 5: Effect on electrocardiography parameters

Parameter	CNP	Amiodarone	*P*-value
PR interval (ms)			
Baseline	134±12	132±11	>0.05
End of study	208±15	198±13	<0.01
QRS duration (ms)			
Baseline	78±7	74±9	>0.05
End of study	132±5	118±8	<0.01
QTc interval (ms)			
Baseline	62±6	61±9	>0.05
End of study	72±6	69±8	<0.01
JTc interval (ms)			
Baseline	401±23	404±19	>0.05
End of study	487±18	452±16	<0.01

P-value was calculated using Mann Whitney test (between group comparison). (Values are mean ± SD, n = 100)

DISCUSSION

The present study has been designed to compare the effect of C-type natriuretic peptide and amiodarone in Chinese patients with arrhythmia. The results of this study will serve the basis of future clinical investigation and may give a new treatment option to the scientific community/researchers in the management of ventricular arrhythmia with PVC. Amiodarone is the standard treatment option. However, long term use of amiodarone exerts several adverse events. The most common adverse events of amiodarone after long term usage are hepatic and renal damage, which are life threatening situations. Therefore, there is need for safe and effective treatment option for management of PVCs in patients with arrhythmias/CCF.

In the present study, CNP demonstrated significantly greater decrease in number of PVCs as compared to amiodarone ($p < 0.005$). The CNP was superior in alleviating PVCs- related symptoms when compared to amiodarone. Similar trend of favorable effect of CNP for other efficacy endpoints was observed. This study results showed that CNP demonstrate significantly greater benefits of suppressing PVCs and related symptoms, and it also demonstrated significantly greater improvement of cardiac function and clinical outcome. It also significantly produced greater reduction in NIS score of each PVCs-associated symptom from baseline in each treatment group (within group comparison). This indicates that both treatments (CNP and amiodarone) were effective in reducing PVCs-associated symptoms.

Between group comparison showed that reduction in NIS score of each PVC-associated symptom was significantly greater in patients treated with CNP when compared to patients treated with amiodarone. This indicates that CNP treatment is statistically superior to amiodarone in reducing PVCs-associated symptoms. The CNP was effective in majority of patients, whereas amiodarone was effective in 60 % of patients. In CNP group, only 10 % of patients did not benefit and showed no meaningful improvement, whereas 38 % of patients in amiodarone showed no meaningful improvement. Overall, CNP was more effective in the treatment of PVCs when compared to amiodarone. The results of present study are consistent with the previous published studies [19-22] in which CNP was found to be effective in suppressing ventricular arrhythmias in rodent model. In the present study, both the treatment groups significantly reduced beats per 24 h when compared to baseline throughout the study period. However, the patients treated with CNP had significantly lower beats per 24 h when

compared to the patients treated with amiodarone throughout the study. Moreover, majority of CNP-treated patients had 90 % reduction in PVCs from baseline when compared to amiodarone. The CNP treated patients had significantly greater reduction in PVC, that indicates effective treatment alternative. Electrocardiography investigation suggested that interval/duration of action potentials was higher in patients treated with CNP ($p < 0.05$) indicating that CNP is an effective treatment alternative for ventricular arrhythmia with PVC by increasing action potentials.

Limitations of this study

Since the present trial was conducted at a single hospital in China, the findings of this present study cannot not be generalized to the Chinese population. Due to lower sample size, a clinical trial with appropriate sample size is needed to confirm the present findings. Since the duration of study was short, a long-term study will be needed to evaluate safety and efficacy of CNP to be designed in patient's ventricular arrhythmia with premature ventricular complexes.

CONCLUSION

Compared to amiodarone, CNP shows significantly greater benefits of suppressing PVCs and related symptoms, and it also demonstrates significantly greater improvement in cardiac function and clinical outcomes. This indicates that CNP is superior to amiodarone, but should be considered for further investigation as a suitable alternative in the management of ventricular arrhythmia with premature ventricular complexes among Chinese patients.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

This study was approved by the Institutional Ethical Committee of BaoJi Central Hospital, China (approval no. IRB/2021/29-12/09-2187).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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