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Original Article

Ivabradine effects on COVID-19-associated postural orthostatic tachycardia syndrome: a single center prospective study

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Abstract: Background: A wide range of cardiac arrhythmias were reported in the setting of active infection or as a complication of COVID-19. The main pathophysiology can be attributed to dysautonomia or autonomic nervous system dysfunction. Postural orthostatic tachycardia syndrome (POTS) is a complex, multisystemic disorder affecting usually younger age with tachycardia at rest or with minimal effort being the main symptom. Data regarding the safety and efficacy of ivabradine in POTS treatment is limited to small studies and case reports. Methods: This prospective observational study included a total of 55 COVID-19-associated POTS patients after the exclusion of other causes of tachycardia. Ivabradine 5 mg twice daily was initiated. Re-assessment of patients' symptoms, heart rate, and heart rate variability (HRV) parameters' changes after 3 days of ivabradine therapy was done. Results: The mean age of the included patients was 30.5±6.9 years with 32 patients being males (58.2%). 43 of 55 (78%) of the included patients reported significant improvement of the symptoms within 7 days of ivabradine therapy. 24-hour heart rate (minimum, average, and maximum) was significantly lower (p-value < 0.0001*, = 0.001*, < 0.0001* consecutively) with a significant difference in HRV time-domain parameters (SDNN, rMSSD) (p-value < 0.0001*) after ivabradine therapy. Conclusion: In a prospective study that evaluated the effects of ivabradine in post-COVID-19 POTS, patients treated with ivabradine reported improvement of their symptoms within 7 days of ivabradine treatment with a significant reduction of 24-hour average, minimum, and maximum heart rate, and improvement of HRV time domains parameters. Ivabradine might be a useful option to relieve symptoms of tachycardia in COVID-19 POTS. Further research is required to confirm the safety and efficacy of ivabradine in POTS treatment.

Keywords: Ivabradine, COVID-19, dysautonomia, postural orthostatic tachycardia syndrome

Introduction

The long-term cardiac electrophysiological consequences of COVID-19 are still not well known but a wide variety of cardiac arrhythmias have been reported [1]. Several pathophysiologic mechanisms were proposed, the most widely accepted is cardiac autonomic dysfunction in active COVID-19 infection or as a complication of a previous infection [2]. Postural orthostatic tachycardia syndrome (POTS) is a poorly understood, complex multisystem clinical disorder that predominantly affects a younger age group. It is characterized by: (1) lightheadedness, palpitations, tremors, weakness, blurry vision, and fatigue upon standing. (2) ≥ 30 beats/minute increase in the heart rate within a 10-minute standing test or a head-up tilt table test. (3) absence of any signs of orthostatic hypotension [3]. Current recommendations for POTS include lifestyle modifications (e.g., exercise, increase water and salt intake, compression stockings). No current approved Class I pharmacological recommendations for POTS, midodrine, and fludrocortisone are Class IIb recommendations [3, 4]. In addition, heart rate-lowering medications such as beta-blockers and calcium-channel blockers may be used but their blood pressure effects might limit their use. Although long-term data on POTS is limited, the prognosis is favorable, especially with younger age at onset with an estimated 50% of

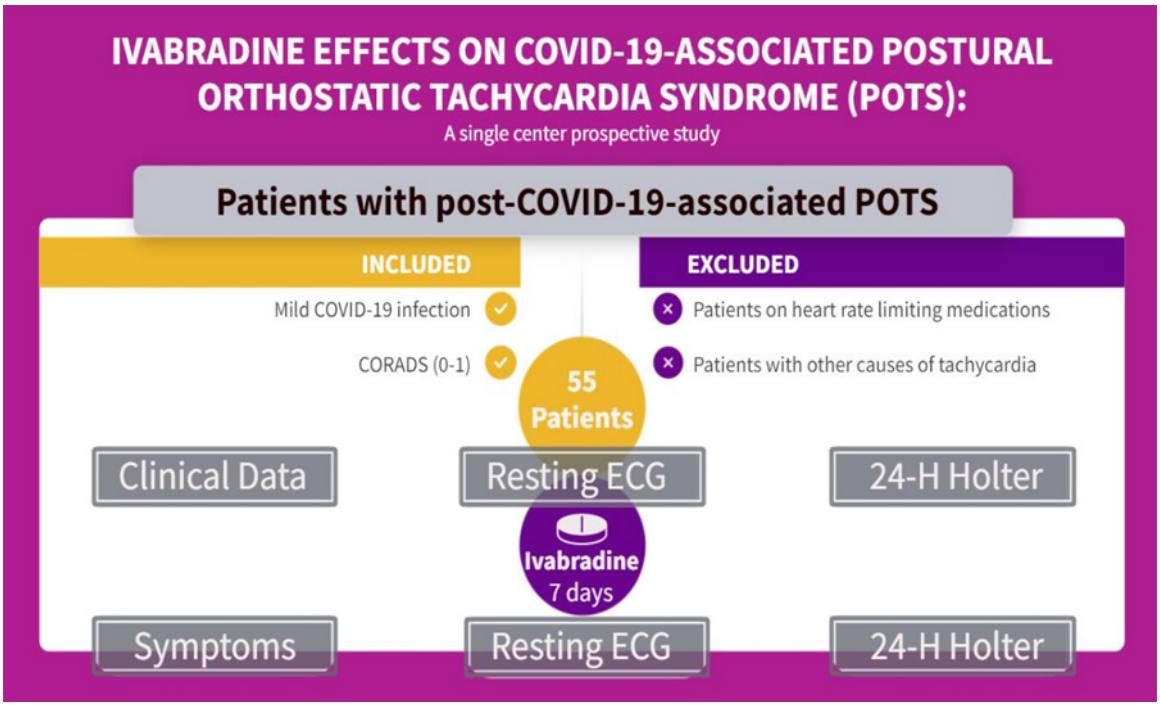

Figure 1. Central illustration demonstrating the study design.

POTS patients spontaneously recovering within 1-3 years [5]. Ivabradine is a selective I_f channel blocker of the sinoatrial (SA) node resulting in a direct reduction of the heart rate with no effects on blood pressure. The SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) study showed that ivabradine was associated with lower heart failure hospitalization rates. Currently, it has a Class IIa recommendation to reduce heart failure hospitalizations in New York Heart Association (NYHA) class II to IV symptoms, left ventricular ejection fraction (LVEF) ≤ 35%, sinus rates ≥ 70 beats/minute despite guideline-directed medical therapy [6]. Although it has a Class IIa recommendation in the treatment of inappropriate sinus tachycardia [3], but so far it is not recommended in POTS treatment due to lack of supporting evidence. Data regarding the safety and efficacy of ivabradine is limited to small studies and case reports. This study aimed to evaluate the role of ivabradine in the management of COVID-19-associated POTS in young patients.

Patients and methods

Study population

This study was a prospective cohort observational study that included a total of 55 patients diagnosed with COVID-19-associated POTS. (Central illustration of the study design is shown in **Figure 1**).

Inclusion criteria

- All included patients had mild COVID-19 disease and normal CT chest (Coronavirus disease 2019 (COVID-19) Reporting and Data System (CO-RADS) 0 or 1) and none of the patients were receiving any heart rate-limiting medications.

- POTS was diagnosed based on a 10-minute standing test and symptoms (episodes of palpitations) with patients having symptoms of orthostatic intolerance with an associated ≥ 30 beats/minute increase in the heart rate in the absence of other conditions associated with orthostatic intolerance.

Exclusion criteria

- Patients with other causes of tachycardia such as anemia, thyroid dysfunction, pheochromocytoma, and hypertension.

Baseline clinical evaluation

Full history, clinical examination, routine laboratory investigations including complete blood

Table 1A. Summary of the used time-domain measures of HRV

Variable	Unit	Description
SDNN	ms	Standard deviation of all normal to normal (NN) intervals
RMSSD	ms	Square root of the mean of the sum of the square of differences between adjacent NN interval

ms = millisecond.

Table 1B. Summary of the used frequency-domain measures of HRV

Variable	Units	Description	Frequency range
LF	ms^2	Low-frequency power	0.04-0.15 Hz
HF	ms^2	High-frequency power	0.15-0.4 Hz
LF/HF		Ratio between low to high-frequency power	

ms^2 = millisecond square.

count (CBC), comprehensive metabolic panel (CMP), troponin, and Brain natriuretic peptide (BNP), a standard 12 lead electrocardiogram (ECG) to exclude any baseline rhythm abnormality, and transthoracic echocardiography (TTE) were acquired from all patients.

Holter electrocardiogram

A baseline and a 7-day 24-Holter ECG were recorded using Meditech CardioMera ECG Holter monitor system. Data was interpreted using Meditech CardioVisions 1.22.0 software with emphasis on heart rate and heart rate variability (HRV) time-domain parameters (SDNN and RMSSD illustrated in **Table 1A**), and HRV frequency-domain parameters (low frequency (LF) and high frequency (HF) illustrated in **Table 1B**) interpreted based on the standard methods for HRV measurement as discussed in the Task Force of the European Society of Cardiology (ESC) and The North American Society of Pacing and Electrophysiology (NAPSE) [7].

Follow-up

Re-assessment of patients' symptoms, heart rate, and HRV parameters changes at 7 days of ivabradine therapy.

Statistical analysis of the data

Statistical analyses were performed using IBM SPSS software version 22 (SPSS Inc., Chicago, IL, USA) and its related materials. Categorical data were presented as frequency and percentages, and the comparison between groups was conducted using Chi-square test or Fisher's Exact correction as appropriate. Continuous data were presented as a mean ± standard deviation for normally distributed variables or as a median and interquartile range for non-normally distributed variables. T-test and Mann Whitney test were used for comparison of continuous data with or without normal distribution between two groups, respectively. Wilcoxon signed ranks test was applied for the comparison of rank data between two groups. A *p*-value of less than 0.05 was considered significant.

The study protocol was approved by the ethics committee and the study is compatible with the Declaration of Helsinki. Informed consent was acquired from all patients before participation.

Results

Baseline patient demographic and clinical data

The mean age of the included patients was 30.5±6.9 years, 32 patients were males (58.2%), and the mean number of days after COVID-19 diagnosis was 13.5±5.6 days. The mean resting heart rate was 84.4±13.8 beats/minute. The mean left ventricular ejection fraction (LVEF) was 66.3±6.8% (Clinical data illustrated in **Table 2**).

Response to ivabradine therapy

Forty-three of the included patients (78%) reported subjective significant improvement of the symptoms (episodes of palpitations) within 7 days of ivabradine therapy (Illustrated in **Table 2**).

Heart rate and HRV

Comparing 24-hour heart rate, and HRV time and frequency domains before and after ivabradine therapy, 24-hour heart rate (mini-

Table 2. Demographic and clinical characteristics

Demographic and clinical data (N = 55)	
Age (Years)	30.5±6.9
Males	32 (58.2)
Smoking	22 (40)
Alcohol	4 (7.3)
Left ventricular ejection fraction (%)	66.3±6.8
Number of days post COVID-19 (days)	13.5±5.6
Resting ECG HR (bpm)	84.4±13.8
Number of patients reported clinical improvement with ivabradine	43 (78%)

Results were represented as numbers (%) or mean ± standard deviation, BPM: Beats per minute.

Table 3. Comparison between heart rate and heart rate variability parameters before and after ivabradine therapy

Heart rate and heart rate variability parameters (N = 55)			
	Before Ivabradine	After Ivabradine	*P*-value
HR data			
Average HR (24 H) (bpm)	82.2±11.2	75.1±11	0.001*
Min. HR (24 H) (bpm)	63.5±5.8	58.4±5.1	< 0.0001*
Max. HR (24 H) (bpm)	146.9±15.3	118.7±18.1	< 0.0001*
HRV data			
SDNN (ms)	123±21.6	177.6±45.1	< 0.0001*
rMSSD (ms)	100.4±19.4	157.2±34.6	< 0.0001*
LF (ms^2)	633.1±197.7	656.8±181.1	0.51
HF (ms^2)	1848±229.1	1881.4±225.1	0.44

Results are represented as numbers (%) or mean ± standard deviation, BPM: Beats per minute, HR: Heart rate, HRV: Heart rate variability, LF: Low frequency, HF: High frequency. *P value ≤ 0.05.

mum, average, and maximum) was significantly lower (p-value < 0.0001*, = 0.001*, < 0.0001* consecutively) (Illustrated in **Table 3** and **Figure 2**). There was a significant difference in HRV time-domain parameters (SDNN, rMSSD) (p-value < 0.0001*) while there was no difference in HRV frequency-domain parameters (LF, HF) (p-value = 0.51, 0.44 consecutively) (Illustrated in **Table 3** and **Figure 3**).

Discussion

Postural orthostatic tachycardia syndrome (POTS) is a poorly understood, complex multisystem clinical disorder that predominantly affects a younger age group. It is characterized by: (1) lightheadedness, palpitations, tremors, weakness, blurry vision, and fatigue upon standing. (2) ≥ 30 beats/minute increase in the heart rate within 10 minutes of standing with postural changes (recumbent to an upright position). (3) absence of any signs of orthostatic hypotension [3]. Current guideline-approved recommendations for POTS include lifestyle modifications (e.g., exercise, increase water and salt intake, compression stockings) with no approved Class I pharmacological recommendations for POTS, but midodrine, and fludrocortisone can be used (Class IIb recommendation) [3, 4]. Our data suggested that ivabradine was associated with subjective significant improvement of the symptoms (episodes of palpitations) and objective evidence of heart rate improvement with a significantly lower 24-hour heart rate and improved HRV parameters within 7 days of ivabradine therapy. A few studies addressed the effect of Ivabradine on POTS patients. A retrospective case series studied the effects of ivabradine on POTS-related symptoms showing that 60% of patients treated with ivabradine report a symptomatic improvement [8]. A retrospective study evaluated 49 patients diagnosed with POTS who received ivabradine. The most common reported symptoms were palpitations and lightheadedness, and both improved significantly, with 88.4% and 76.1% response rates, respectively. A total of 38 patients reported improvement in their symp-

Figure 2. A box and whisker plot showing the differences in heart rate (minimum, average, and maximum) before and after ivabradine therapy.

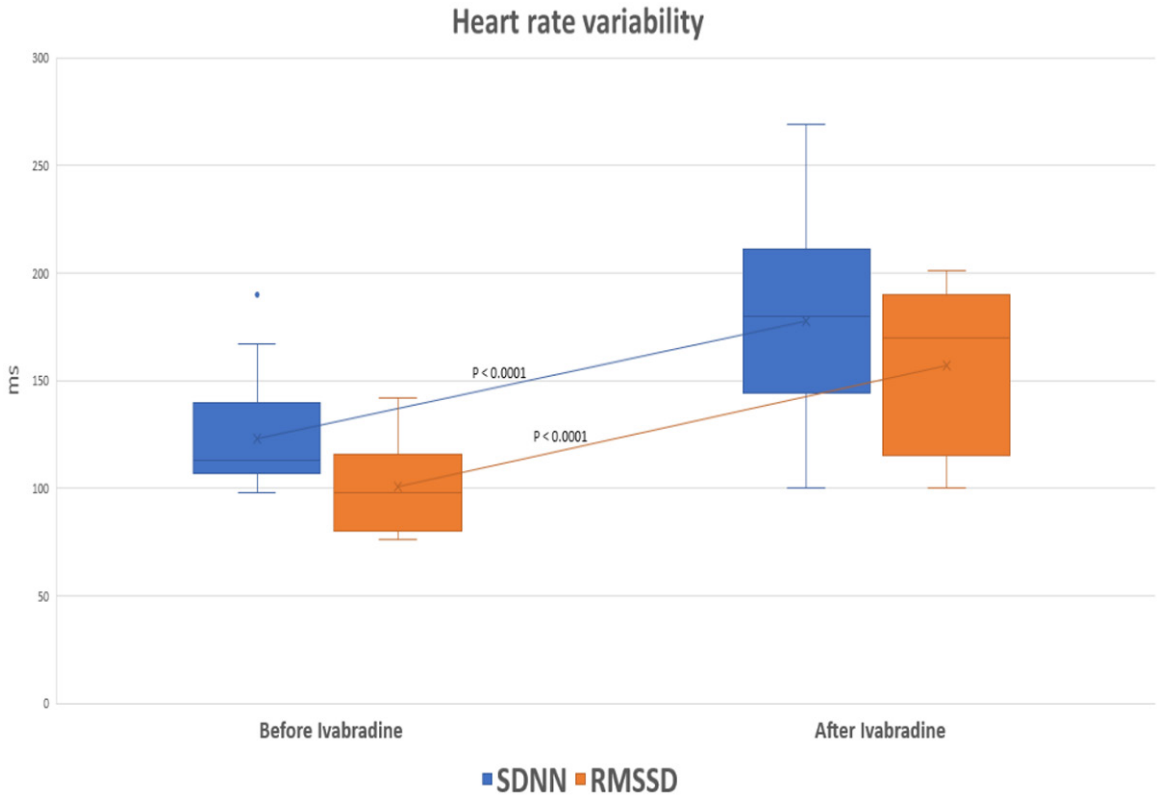

Figure 3. A box and whisker plot showing the differences in HRV time domain parameters before and after ivabradine therapy.

toms. Additionally, ivabradine resulted in a decrease in sitting and 2 standing heart rates (P = 0.01 and P < 0.001 respectively). The study concluded that nearly 78% of patients reported a significant improvement in symptoms with ivabradine therapy with no major adverse effects reported [9]. A randomized parallel blinded crossover-controlled trial compared ivabradine with placebo among hyperadrenergic POTS patients. Patients were started on either ivabradine twice daily or placebo (n = 22 in each group) for 1 month, followed by a 1-week washout period, then crossed over to the other treatment for 1 month. The study concluded that among patients with hyperadrenergic POTS, ivabradine was associated with an improvement in heart rate (*p*-value = 0.001) and some quality-of-life measures (physical functioning and social functioning *p*-value = 0.008) and social functioning (*p*-value = 0.021). Standing norepinephrine levels were also marginally improved with ivabradine (*p*-value = 0.056) [10].

Study limitations

The study had some limitations, this was an observational study limited by the lack of a control group or placebo effect. Due to the small sample size and specific patient population, the differences between responders and non-responders might be overestimated and the generalizability of the results might be affected.

Study recommendations

Large-scale randomized placebo-controlled trials are required to confirm the safety and efficacy of ivabradine in POTS treatment.

Conclusion

In conclusion, in this prospective observational study that evaluated the effects of ivabradine in COVID-19-associated POTS, patients treated with ivabradine reported subjective improvement of their symptoms within 7 days of ivabradine therapy with objective significant reduction of 24-hour average, minimum, and maximum heart rate, and improvement of HRV time domains. Traditionally, POTS management is difficult, and usually, many patients have persistent symptoms. Ivabradine might be a useful option to relieve symptoms of tachycardia in COVID-19-associated POTS or POTS in general.

Disclosure of conflict of interest

None.

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