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Role of Ivabradine in Treatment of Pulmonary Hypertension

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Abstract

Pulmonary arterial hypertension is a devastating disease, which if not interrupted, leads to progressive right-sided heart failure and death within 2 to 3 years after diagnosis**.** Ivabradine is the first of a heart rate-lowering medication that specifically inhibits the f ion channels in the sinus node. Lowering heart rate with ivabradine has been reported to be safe and free from unpleasant collateral side effects in a case series of pulmonary arterial hypertension patients. This study was conducted aiming to assess the clinical effect of treatment with ivabradine in pulmonary hypertension patients. The current study is an observational study that was carried out on 50 patients suffering from pulmonary hypertension with sinus rhythm during the period from November 2019 to November 2020. These patients received a therapeutic dose of Ivabradine and had basic investigations as 12 leads ECG, 2D ECHO study and 6 MWT performed as baseline and after 3 months of ivabradine therapy. High statistically significant differences were found between baseline and after 3 months clinical characteristics including HR and 6MWT results as well as in NYHA class. Also, comparison of baseline and after 3 months right sided echo parameters revealed statistically significant differences as regards RV mid diameter, TAPSE and PASP. It can be concluded that ivabradin can be used in pulmonary hypertension patients to reduce heart rate and may provide functional capacity in those patiants. However, the exact biological role of ivabradin in pulmonary hypertension need more in-depth investigation. Large scale multi-center studies are recommended to evaluate the prognostic efficacy of Ivabradin in patients with pulmonary hypertension.

Key words: Echo, Ivabradine, Pulmonary arterial hypertension, 6 minute walk test**.**

1. Introduction

Pulmonary hypertension (PH) is defined as mean pulmonary arterial pressure (mPAP) >25 mmHg as assessed by a right-heart catheterization [1]. Pulmonary arterial hypertension (PAH) is a devastating disease, which if not interrupted, leads to progressive right-sided heart failure and death within 2 to 3 years after diagnosis [2].

The treatment process of PAH patients cannot be limited to mere prescription of drugs but is characterized by a complex strategy that includes the initial evaluation of severity and the subsequent response to treatment [3]. And the overall goal of treatment is to achieve a low-risk status whereby a patient is maintained in the WHO-FC II which is usually accompanied by near-normal 6-min walk distance (6MWD) [4].

Ivabradine is the first of a heart rate (HR)-lowering medication that specifically inhibits the ion channels in the sinus node. Ivabradine selectively lowers the HR without affecting cardiac conductivity and repolarization, improves left ventricular diastolic filling, reduces myocardial oxygen consumption and increases the time of coronary perfusion [5].

Correale et al. [6] reported that lowering heart rate with ivabradine has been reported to be safe and free from unpleasant collateral side effects in a case series of PAH patients.

We therefore in this study seek to assess the clinical effect of treatment with ivabradine in PH patients.

2. Materials and Methods

Time frame and study design

The current study is an observational study that was carried out on 50 patients suffering from PH with sinus rhythm for demonstrating the effects of ivabradine therapy given for three months on functional capacity. Patients were selected from inpatient and outpatient clinic of cardiology Department of Mabra Masr El Kadima Hospital and Benha university hospital, during the period from November 2019 to November 2020.

2.1. Inclusion criteria

1. Age: 40-60 years old.
2. Sex :both sex
3. Patients complaining of pulmonary hypertension (with a systolic pulmonary artery pressure more than 40 mmHg and mean pulmonary artery pressure more than 25 mmHg under rest) with normal sinus rhythm [7].

2.2. Exclusion criteria

1. Patients with atrial fibrillation.
2. Patients with ventricular arrhythmias.
3. Patients with severe hepatic dysfunction.
4. Patients with sick sinus syndrome and sinoatrial block.
5. Patients with pacemaker dependence.

2.3. Methods

1. **Clinical data (History and clinical examination):** All patients were subjected to complete clinical assessment (full history and clinical examination), for the presence of risk factors for PH, previous medications and associated co-morbidity. Attention was directed to features that fulfill our inclusion criteria and to exclude patients who have any of the exclusion criteria. Heart rate assessment was performed before and after ivabradine therapy.

2. **Electrocardiogram (ECG):** Each patient underwent 12 leads resting standard ECG to confirm the rhythm.
3. **Transthoracic Echocardiography (TTE) :** A comprehensive echocardiographic study was performed for all patients including:

Left ventricle study: Left ventricular End-systolic volume (ESV), End-diastolic volume (EDV) and fractional shortening (FS), were measured in parasternal long axis (PLAX) 2D/M mode just distal to the mitral valve tip. Left ventricular ejection fraction (LVEF) was measured using M mode [8].

Right ventricular (RV) dimension: RV dimension is best estimated at end-diastole from a right ventricle–focused apical 4-chamber view. Care should be taken to obtain the image demonstrating the maximum diameter of the right ventricle without foreshortening. This can be accomplished by making sure that the crux and apex of the heart. Diameter > 42 mm at the base and > 35 mm at the mid-level indicates RV dilatation. Similarly, longitudinal dimension > 86 mm indicates RV enlargement [9].

RV systolic function: RV systolic function was evaluated using mainly TAPSE. TAPSE is easily obtainable and is a measure of RV longitudinal function. TAPSE < 16 mm indicates RV systolic dysfunction [9].

Pulmonary Systolic Pressure (RVSP): TR velocity reliably permits estimation of RVSP with the addition of Right atrial (RA) pressure, assuming no significant right ventricular outflow tract obstruction. It is recommended to use the RA pressure estimated from IVC and its collapsibility, rather than arbitrarily assigning a fixed RA pressure. In general, tricuspid regurge velocity > 2.8 to 2.9 m/s, corresponding to SPAP of approximately 36 mm Hg, assuming an RA pressure of 3 to 5 mm Hg, indicates elevated RV systolic and PA pressure [9].

6-minute walking test (6 MWT) : The test was performed according to American Thoracic Society (ATS) statement 2002, after history taking, examination, ECG & performing an Echocardiography for the patient, immediately after stabilization of the patient, the test was performed [10]. 6MWT was done for every patient before starting ivabradine intake and 3 months after starting ivabradine intake to measure the distance that can be walked by patients. The object of this test is to walk as far as possible for 6 minutes.

Instructions given to patients: Patient was informed to walk back and forth in this hallway. Six minutes is a long time to walk, so you would be exerting yourself. You would probably get out of breath or become exhausted, you are permitted to slow down, to stop, and to rest as necessary. You could lean against the wall while resting, but resume walking as soon as you are able. You might be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. I was going to show to show the patient. Please watch the way I turn without hesitation. We would avoid having a conversation so that you could save your wind for walking. You could begin when I say 'go'". At the end of the 6 minutes: Have participant sit down (portable chair).

After that, vital signs were assessed, starting with HR (resting &maximum) (because it drops more quickly than SBP and Recovery time (Time taken for heart rate to return to resting HR) should be taken. Calculate and record the distance walked, dyspnea at rest or with minimal exertion, auscultate the lung bases for new or increased crackles and also auscultate the heart apically to detect an S3 heart sound [11].

New York Heart Association Functional Classification

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and/or angina pain [12].

Class I: Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs, etc.

Class II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

Class III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m).Comfortable only at rest.

Class IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

2.4. Statistical analysis

Data were collected, revised, coded and entered to the statistical package for social science (SPSS) version 17. Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges. The comparison between two groups with qualitative data was done by using Chi-square test and Mann Whitney test and Wilcoxon signed rank test. The comparison between two paired groups with quantitative data and normally distributed was done by using paired sample t-test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as follows: $P > 0.05$: Non significant, $P < 0.05$: Significant and $P < 0.01$: Highly significant .

2.5. Ethical considerations

A brief appropriate explanation of the aim of the study was given to patients stressing on the importance of data they are going to offer. Personal consent was obtained to enroll patients in the study.

Safe guards were taken to protect the confidentiality of personal & clinical data. No risk to the patients enrolled in the study.No obligation on patient to participate in the study.

3. Results

The current study was conducted on 50 cases whose age distribution is shown in table (1) and baseline and clinical characteristics is shown in table (2).

The most prevalent cause of PH in the studied population was chest causes and collagen causes were the least prevalent as shown in table (3), their baseline ECG parameters are shown in table (4) and their baseline left sided echo parameters are shown in table (5).

High statistically significant differences were found between baseline and after 3 months clinical characteristics including HR and 6MWT results as shown in table (6) as well as in NYHA class as shown in table (7).

Comparison of baseline and after 3 months right sided echo parameters revealed statistically significant differences as regards RV mid diameter, TAPSE and PASP. Meanwhile, no statistically significant differences were found between baseline and after 3 months right sided echo parameters as regards as RV basal or long diameters shown in table (8).

Table (1) Age distribution of patients.

Age (years)	No.	%	Min. – Max.	Mean ± SD.	Median (IQR)
40 –	22	44.0			
50 –	23	46.0	40.0 – 60.0	50.68 ± 5.93	50.50 (46.0–55.0)
60 –	5	10.0			

Table (2) Baseline and clinical characteristics of patients.

Clinical characteristics		Number (n=50)	%
Sex	**Male**	28	56.0
	Female	22	44.0
Smoking	**Non smoker**	24	48.0
	Smoker	26	52.0
Hypertension	**No**	20	40.0
	Yes	30	60.0
Diabetes mellitus	**No**	13	26.0
	Yes	37	74.0
Coronary artery disease	**No**	15	30.0
	Yes	35	70.0

Table (3) Causes of pulmonary hypertension in the included patients**.**

Item	Number(n:50)	Percent (%)
Chest disease		
- **Yes**	23	46
- **No**	27	54
IHD		
- **Yes**	35	70
- **No**	15	30
Collagen disease	9	19
Non collagen	41	82

Table (4) Baseline ECG parameters of the included patients.

ECG parameters	Yes	No.
Coronary artery disease	35 (70.0 %)	15 (30%)
Sinus rhythm	50 (100%)	0 (0%)
P-pulmonale	37 (74%)	13 (26%)
RVH	13 (26%)	37 (74%)
RBBB	39 (78%)	11(22%)

Table (5) Baseline left sided echo parameters of the included patients**.**

Baseline	Min. – Max.	Mean ± SD.	Median (IQR)
LVESV	35.0 – 42.0	38.26 ± 1.51	38.0 (38.0–39.0)
LVEDV	50.0 – 56.0	52.68 ± 1.41	53.0 (52.0–54.0)
LVEF	56.0 – 65.0	60.36 ± 1.85	60.0 (59.0–62.0)
FV (FS)	27.0 – 33.0	30.20 ± 1.23	30.0 (29.0–31.0)
SV	68.0 – 86.0	76.58 ± 3.48	77.0 (74.0–78.0)
LA diameter	33.0 – 46.0	39.26 ± 3.22	39.0 (37.0–42.0)

Table (6) Comparison between baseline and after 3 months clinical parameters.

		baseline	After 3 months	T	P
Heart Rate	**Min.-Max.**	81.0 –119.0	69.0 – 75.0	19.955*	<0.001*
	Mean ±SD.	101.26 ± 10.08	72.64 ± 1.41		
	Median(IQR)	100.50 (93.0–110.0)	73.0 (72.-74.0)		
6-min walking distance (m)	**Min. – Max.**	103.0 – 307.0	278.0 – 298.0	9.110*	<0.001*
	Mean ± SD.	221.50 ± 50.38	287.06 ± 4.23		
	Median (IQR)	214.0 (184.0–264.0)	287.0 (284.0–290.0)		

T: Paired t-test

Table (7) Comparison between baseline and after 3 months NYHA class.

NYHA class		n = 50 No.	%	X^2	P
Baseline	**I**	1	0.02	9.859*	<0.001*
	II	26	0.52		
	III	21	0.42		
	IV	2	0.04		
3 months after	**I**	23	46.0		
	II	25	25.0		
	III	1	0.020		
	IV	1	0.020		

X^2: Chi-square test

Table (8) Comparison between baseline and after 3 months right sided echo parameters.

		Baseline	After 3 months	T	P
RV mid diameter	**Min. – Max.**	26.0 – 52.0	33.0 – 44.0	2.524*	0.015*
	Mean ± SD.	41.02 ± 5.91	38.84 ± 2.25		
	Median (IQR)	42.0 (37.0–46.0)	39.0 (38.0–41.0)		
RV basal diameter	**Min. – Max.**	30.0 – 61.0	35.0 – 55.0	0.356	0.723
	Mean ± SD.	46.62 ± 5.71	46.98 ± 4.62		
	Median (IQR)	47.0 (44.0–51.0)	48.0 (43.0–51.0)		
RV long diameter	**Min. – Max.**	50.0 – 95.0	56.0 – 90.0	0.429	0.669
	Mean ± SD.	73.42 ± 8.76	72.72 ± 7.70		
	Median (IQR)	75.0 (69.0–80.0)	73.0 (67.0–79.0)		
TAPSE	**Min. – Max.**	16.0 – 27.0	22.0 – 35.0	9.193*	<0.001*
	Mean ± SD.	21.56 ± 2.02	25.80 ± 2.65		
	Median (IQR)	21.0 (20.0–23.0)	25.50 (24.0–27.0)		
PASP	**Min. – Max.**	42.0 – 93.0	46.0 – 88.0	3.384*	0.001*
	Mean ± SD.	75.36 ± 11.17	68.46 ± 8.51		
	Median (IQR)	76.0 (68.0–84.0)	69.0 (63.0–74.0)		

T: Paired t-test

4. Discussion

Ivabradine uniquely reduces the heart rate without affecting myocardial contractility [13]. Ivabradine has been approved in Europe by European Medicines Agency (EMA) for chronic stable angina in 2006 [14] and was approved for patients with chronic stable HF in 2012 [15].

The direct effect of ivabradine on PH have not been studied carefully. However, it was reported that the use of ivabradine in patients with PH is safe and with no unpleasant side effects [6].On the other hand, many reports showed a relation between HR and mean pulmonary artery pressure (mPAP) in cases with pre-capillary PH [16]. That raise a possibility of potential benefit from the HR-lowering effect of ivabradine on patients with PH [17].

In this study we followed 50 adult patients with normal sinus rhythm and with pulmonary artery systolic pressure more than 40 mmHg. These patients received therapeutic dose of ivabradine and were followed for 3 months. Changes on heart rate clinical indices of functional capacity, ECG, and echocardiography changes of right ventricle were recorded pre- and post-treatment. The aim was to determine the effects of ivabradine on the clinical and functional parameters of patients with pulmonary hypertension.

In the study, the average age was 50.6 years old, 56% of sample were males and 44% were females. 48% of the patients were nonsmoker, 26% patients (52%) were smoker, 60% were hypertensive, 35% had coronary artery diseases, and 74 %were diabetics. The assessment of functional capacity of patients' in this study was accomplished by monitoring changes in heart rate, NYHA classification daily symptoms and six-minute walk test.

In this study, there was statistically significant reduction in mean heart rate from Mean± SD of 101.26 ± 10.08 to Mean± SD of 72.64 ± 1.41 after 3 months of Ivabradine intake.

This was in agreement with Correale et al.,[6] who reported five case reports in term of role of Ivabradine in PAH and found that Ivabradine may be of help in improving the hemodynamics of patients with higher sinus rates through reducing heart rate. They also reported that the first case was about a 75-year-old woman with systemic sclerosis-related PAH, she lives alone and suffering from dyspnea. After treatment with Ivabradine 10 mg/day, her functional status improved with a resting heart rate of 80 bpm and improvement of dyspnea which made him reported that whether the effect of ivabradine is direct or indirect, he said that many studies showed that functional improvement in patient with PH under Ivabradine therapy reported significant reduction in heart rate .

As well as in this study there was statistical significant reduction in NYHA classification where it changed from Mean ± SD of 2.68 ± 0.59 to Mean ± SD of 1.58 ± 0.57 after 3 months of Ivabradine intake.

This was in agreement with De Santis et al. [17] who studied 40 patients (20 asthmatic patients and 20 COPD patients) who received Ivabradine 7.5 mg twice daily for 5 days and placebo twice daily for 5 days in a crossover manner, in one of the two arms of the study, with at least 2 days of washout between treatments and they documented that there was marked reduction in cardiac a NYHA classification which proved beneficial to patients with major cardiovascular disability and critically ill patients.

As well this was in agreement with Correale et al. [6] who documented that in a report, more than 90% of cases showed reduced NYHA classification with 50% of these cases reduced to NYHA class II

In this study that there was a high statistically significant difference between baseline and after 3 months 6 minute walk test where P<0.001.

This was in concordance with Correale et al. [6] who reported that improvement of functional capacity in patients complaining of pulmonary hypertension who treated with Ivabradine ,as well he documented that this was in agreement with many authors who showed that significant increased mean six minute walk test (6MWT) in patient with PH for respiratory or cardiac causes.

And this was in agreement with Akhmetzianova et al., [18] who tested use of Ivabradine in patients with chronic obstructive pulmonary disease (III-IV stages) showed that tolerance to exercise is significantly enhanced in patients with PH due to COPD**.**

Also, Correale et al. [6} documented that in a report, more than 90% percentage of cases reduced NYHA classification with 50% of these cases reduced to NYHA class II. Interestingly, the basal heart rate and 6MWT distance as predictors for the reduction of NYHA classification to class II**.**

Kolomoets et al. [19] tested Ivabradine in patients with systolic heart failure and found improvement in total arterial compliance and ventricular-arterial coupling, resulting in a higher stroke volume so ,he reported that Ivabradine intake in patients with PH is associated with increase in circadian index, blood oxygen saturation and partial tension.

In conclusion, Ivabradine is associated with mprovement in multiple factors that give a clue to a role in improving the total functional capacity of patients with PH.

In this study, the echocardiographic parameters of right ventricle showed significant changes among the follow up period of the study.

As regard to RV function, there was a high statistically significant difference between baseline and after 3 months according to TAPSE where there was a significant increase in the average tricuspid annular plane systolic excursion (TPASE) (from 21.56 to 25.80) with P<0.001.

This was in agreement with Reil et al. [20] Who tested Ivabradine in patients with PHT and showed reduction in total arterial compliance as well as ventricular arterial coupling, resulting in higher stroke volume. However, there was increase pulmonary arterial pressure

However, this was against what reported by Suresh-Babu et al. [21] Who documented that some reports showed that Ivabradine has no effect on

cardiac contractility, repolarization or atrio-ventricular conduction

As regard to RV dimension, there was statistically significant difference between baseline and after 3 months according to right sided echo parameters RV mid diameter and PASP where $P<0.05$.

This was in concordance with Akhmetzianova et al. [18] who tested use of Ivabradine in patients with chronic obstructive pulmonary disease (III-IV stages) and found a statistically significant lowering of pulmonary pressure without negative effects.

On the other hand, Chemla et al. [16] showed that this effect is not related to cause of PH (respiratory or cardiovascular). The heart rate lowering effect of ivabradine showed a linear relation with lower mean pulmonary artery pressure in patients with pre-capillary PH

In addition, some reports showed no effect of ivabradine intake on the pulmonary artery pressure. PASP showed no reduction in series of PH patients under Ivabradine regimen for 3 months [6] . [6

In this study there was no statistically significant difference between baseline and after 3 months according to right sided echo parameters RV basal diameter and RV long diameter.

In addition, this was in agreement with Reil et al. [20] who reported that there is possible role of Ivabradine in improving right ventricular function by affecting arterial compliance and ventricular arterial coupling.

As long as there no control group to control for dose, cause, or other factors affecting ventricular contractility, the finding of this study cannot be used to prove either side of the controversy about effect of Ivabradine on right ventricular function.

However, there is a much suggestive data with Ivabradine being positive role reducing right ventricular dilatation and enhancing contractility, directly via reducing heart rate tor indirectly by enhancing blood flow to myocardium and improving oxygen saturation.

5. Conclusion

Patients with PAH and either having rest Heart rate more than 100 bpm or symptomatic for palpitations may be safely treated with ivabradine. Three-month treatment with ivrabradine coincided with significant improvements in functional capacity of PAH patients. This deserves additional investigation, perhaps via a small randomized study, for confirmation and to understand possible mechanisms of benefit.

6. Recommendations

The exact biological role of Ivabradin in PH need more in-depth investigation. Large scale multi-center studies are recommended to evaluate the prognostic efficacy of Ivabradin in patients with pulmonary hypertension. The use of Ivabradin in these patients may help to reduce heart rate and may provide functional capacity of those patiants.

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