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Studying the Effect of Spironolactone Treatment on Right Ventricular Function in Patients with Pulmonary Hypertension Group 1

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Abstract:

Objectives

Despite the evidence showing the effect of vasoactive hormones including aldosterone in the pathophysiology of pulmonary arterial hypertension (PAH), few clinical reports are available about the effect of treating PAH with aldosterone antagonists, so in this study, the effect of treating patients with idiopathic PAH with the drug Aldosterone inhibitor spironolactone was discussed.

Methodology

This study was conducted as a randomized clinical trial with a double-blind control group. All patients diagnosed with PAH referred to Imam Reza (AS) hospital in Mashhad from the beginning of August 2015 to the beginning of August 2016 were included in this study. The patients were randomly treated with the standard treatment of tadalafil 10-20 mg once a day plus bozentan 125 mg, once or twice a day or standard treatment plus spironolactone (25 mg) daily for three months. Before the start and after three months, the patients were evaluated. After collecting the data, they were analyzed using SPSS version 16 software, and $p>0.05$ was considered as a significant level.

Results

Routine treatment in the control group and routine treatment plus spironolactone in the intervention group had little effect on the severity of dilatation of the patients participating in the study but it had significant effect on TAPSE.

Conclusion

After the intervention a significant increase in the TAPSE index was observed compared to the control group. Significant difference in other echocardiographic and clinical indicators examined after the intervention in the intervention groups and the witness was not identified.

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Introduction

Pulmonary hypertension (PH) is a pathophysiological disorder that may cause several clinical conditions and can cause complications in most cardiovascular and pulmonary diseases (1-4) It is estimated that the prevalence and incidence of PAH is 15 cases per million and 4.2. be one in million (4).

An increase of more than 25 mm Hg (mmHG) in mean pulmonary arterial pressure (mPAP) at rest is considered (PH). The classification is as follows (5) Group 1 pulmonary arterial hypertension, Group 2 PH caused by left heart disease, Group 3: PH caused by lung diseases or hypoxia, Group 4 of chronic thromboembolic PH, Group 5: PH with unknown multifactorial mechanisms.

Different treatments have been suggested for these patients. In some patients who respond quickly to the vasodilator test, calcium channel blockers can be considered a very effective drug (6).

For nearly 2 decades, the administration of prostanoids was considered as the main element in the treatment of PAH. Endothelin receptor antagonists selectively block endothelin-A receptors or dually block endothelin A and B receptors. Sildenafil was investigated in PAH patients, and Sildenafil is currently approved at a dose of 20 mg 3 times a day (7-10).

In addition to medical treatments, some surgical treatments are also available for selected patients with PAH, including lung transplantation and atrial septostomy, which are out of the scope of this study. (11,12)

In rat models with PAH, treatment with mineralocorticoid receptor antagonists such as spironolactone and eplerenone reduces the number of prominent vessels, increases the luminal cross-section, decreases vascular collagen deposition and fibrosis, decreases pulmonary artery systolic pressure, and decreases right ventricular hypertrophy (46). Also, spironolactone has prevented the deformation of pulmonary vessels and dysfunction of the right ventricle in a mouse model with PAH (13-15).

Spironolactone is a very available and cheap drug from the group of mineralocorticoid receptor antagonists, which acts non-selectively and requires liver metabolism to produce its active metabolites. The maximum response of the drug is observed around 48 hours after the first dose. It is with progesterone and this drug has cross effects with some sex steroid receptors. This phenomenon leads to anti-progesterone and anti-androgenic effects in some patients who are treated with spironolactone, however, this treatment is still not accepted in the treatment process of PAH, and as a result, an optimal dose of this drug has not been reported in the treatment of PAH (16-18).

Considering the appropriate theoretical mechanisms as well as limited laboratory and clinical studies in the field of treating patients with PAH with spironolactone and considering the very limited clinical studies in the world and the lack of studies in this field in the country, we decided to investigate the clinical effects of spironolactone alongside standard treatment of idiopathic PAH in a randomized clinical trial.

Method

At first, sampling was done by diagnosing patients with idiopathic PAH based on European international guidelines and by performing right catheterization echocardiography and examination by a fellow pulmonologist, and after systemic examination to rule out secondary causes of pulmonary hypertension.

At the beginning of the study, an interview was conducted with all the patients, and the objectives of the study and its process were fully explained to them, and the patient was assured that all necessary diagnostic and treatment measures will be taken for him if he does not participate in the study. Finally, if they wish, informed consent forms were given to the patients, in which all the study information was mentioned again, so that they could participate in the study if they wished. Demographic information was recorded.

To standardize the treatment process, the patients were included in the study after at least 3 months of routine and standard treatment of pulmonary hypertension in Imam Reza Hospital and by the organizers of the project. To check the severity of clinical symptoms, a complete history was taken

from the patient and the functional class of the patient was determined based on the NYHA classification. Also, the 6MWD test was performed on all patients in the rehabilitation department and the results were recorded.

Then, to evaluate the mentioned echocardiographic variables, all the patients were subjected to echocardiography by one of the project managers with General Electric Vingmed Ultrasound AS, Horten, (Vivid 7 Dimension Norway) device, and all the functional and structural variables of the patients' heart, including the middle diameter of the right ventricle, PAP and TAPSE) was registered.

The main outcome of this study is the 6MWD variable, which indicates the general state of heart function. Also, PAP TAPSE NYHA functional class variables and right ventricular median diameter were considered as secondary outcomes of the study. It is also worth mentioning that initially the pro BNP variable was also part of the studied variables, but due to unforeseen problems and lack of acceptance. Patients with pro BNP measurement were excluded from the analysis in this study.

Patients were randomly assigned to two groups using PASS randomization software. To one group of standard treatment tadalafil 10-20 mg once a day plus bosentan 125 mg, once or twice a day (recommended in the guideline) and to another group of standard treatment plus spironolactone at a dose of 25 mg daily to It was given for a period of three months. It should be noted that in the control group

After three months, all variables, including clinical and echocardiographic variables, were evaluated, and recorded. Before these re-examinations, the patients of the group of patients were unknown to the examiner (executive of the project) and after the completion of the history, the patient's information was recorded based on their code that was assigned to them from the beginning of the study. The exercise test to check (MWD and echocardiography) was done by other operators of the project who were not aware of the type of treatment of the patients and their information was recorded based on the same code. Also, the patients of each group were visited on separate days and were not informed about the treatment status of the opposite group. The patient and the data collection researcher were not aware of the type of treatment.

It should be noted that the serum levels of potassium and creatinine of the patients were monitored one week after the start of spironolactone and three months after the start of the treatment, so that in case of side effects or drug intolerance, the patients would be excluded from the study, Although the patient was not excluded from our study for this reason.

This study was conducted in full form from the beginning of August 2015 to the beginning of August 2016 and according to the estimate made in the year before the start of the study of the number of referrals who met the entry criteria, this number of 25 people was determined for each group. The data related to the demographic and clinical observations of the patients were entered into the SPSS software, version 16, and statistical analysis was done using this software. Descriptive statistical methods were used to describe the data, including the central indices of dispersion and frequency distribution, to compare the variables. The independent T test was used to compare the two groups. In case of not having a normal distribution, its non-parametric equivalent was used, although in our study, the distribution of no variable was non-normal.

Chi-square test was used to compare the qualitative variables of two groups. Paired t test or its non-parametric equivalent was used to compare quantitative variables before and after drug administration, and McNemar's test was used to compare qualitative variables before and after drug administration. In all tests, $p>0.05$ was considered as a significant level.

Ethics committee authorization code and date

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Code and date of registration in IRCT

IRCT20171120037376N1

Result

In total, among the patients who agreed to participate in the study, only 45 patients (23 patients in the intervention group, 22 patients in

the control group) completed the treatment process and follow-up after that. All the patients who entered the study and completed the study. and they were fully involved in the follow-up. There were no drug complications for the patients that caused them to be excluded from the study. However, during the study period, the number of patients who were eligible to enter the study in this center was more than this number. In total, there were only 3 male patients, 2 patients in the intervention group, 1 patient in the control group, and the other 43 patients were female. At first, to check the normality of the data distribution, quantitative data was analyzed separately for the studied groups with We used the Kolmogorov-Smirnov test.

Considering the normality of the data distribution, the independent T-test was used to compare the two intervention control groups, and as can be seen in Table 1, there was not significant difference in the distance traveled in 6 minutes (6MWD), right ventricular diameter, PAP and TAPSE between the two groups.

According to the statistical analysis, it was observed that 3 months after the study in both control and intervention groups, the percentage of patients who had different degrees of right ventricular dilatation was like the percentages before the study. In fact, routine treatment in the control group and routine treatment plus spironolactone in the intervention group had little effect on the severity of dilatation of the patients participating in the study but it had significant effect on TAPSE (table 2).

Table 1: Variable before treatment in case and control group

variable	case	control	P Value
6MWT m	370.23±21	338.1±22	0.149
RVD cm	4.07±0.5	4.09±0.6	0.919
TAPSE cm	1.78±0.4	1.76±0.5	0.181
PAP mm Hg	73.5±12	73.4±16	0.986

Table 2: Variable after treatment in case and control group

variable	case	control	P Value
6MWT m	378.23±21	348.1±22	0.235
RVD cm	4.06±0.5	4.07±0.6	0.817
TAPSE cm	1.66±0.3	1.76±0.4	0.041
PAP mm Hg	72.5±12	71.4±16	0.967

Discussion

The main finding in this study, we tried to investigate the effect of spironolactone along with the standard treatment of idiopathic PAH in a randomized clinical trial. In our study, it was observed that there was no significant difference in any of the studied indicators in any of the two case groups after the completion of the research period (3 month). significantly more than the group study, the witness was observed. So far, very limited studies have been conducted in the field of investigating the effect of aldosterone receptor antagonists around the world, all of which are less than a decade ago. Also, no study in this field had been conducted in the Islamic Republic of Iran.

In a study published by Maron et al. in 2013, it examined the effect of simultaneous use of spironolactone and ambrisentan in patients with PAH. ARIES and 2-ARIES, which compare the doses of ambrisentan in the treatment of PAH, have been investigated and the patients who randomly received spironolactone in these studies were selected and evaluated. Finally, 21 patients in the placebo group and 10 patients in the ambrisentan group. Spironolactone was taken at the same time. In this study, it was observed that in the spironolactone and ambrisentan group, as well as in the ambrisentan group with a dose of 10 mg per day), there was a significant improvement in the 6MWD variable compared to the placebo group after 12 weeks of treatment. However, it should be noted that in the study of Maron et al.

(19) it was also observed that there is no significant difference between ambrisentan and spironolactone in the 6MWD variable after 12 weeks of treatment. Another noteworthy point in this study is the significant difference of 6MWD between spironolactone and spironolactone and ambrisentan group patients, which confirms the more effective role of ambrisentan in the treatment of patients with PAH. Unfortunately, the difference between spironolactone and placebo groups has not been determined; However, this difference does not seem to be significant.

In the study of Maron et al., it was observed that spironolactone alone could not make a significant difference in any of the investigated variables, so it is emphasized in this study that it is in accordance with the hypotheses raised in other studies (19,20.21). The clinical manifestation of PAH is the result of many pathobiological mechanisms independent of aldosterone, and most single-drug treatment regimens are not sufficient in the treatment of PAH. It should be kept in mind that due to the retrospective nature of this study; it may suffer from recall and patient selection errors; In addition, the low sample size and lack of assessment of spironolactone side effects are other limitations of Maron et al.'s study (19).

This study was the only study that is clinically like our study, and other studies in the molecular and laboratory animal fields are discussed. In the past, of course, in a study that Eshtredi et al. (21) presented in the form of a poster in 2014, they reviewed 2194 patients with severe pulmonary hypertension and left ventricular ejection fraction more than 50% in 3 hospitals in New York City. The study of patients based on the consumption of spironolactone for 12 consecutive months after the diagnosis of PH, were divided into two groups. In this study, it was stated that there was a significant difference in the one-year mortality rate between the two groups of spironolactone users and non-users, respectively 3.25 in 6.32, 70.0 RR) no re-admission to the hospital due to acute PH or corpulmonary disease (6.6 vs. 0.4.3, 70.0 RR) was observed. The results of this study are also consistent with result of our study.

Conclusion

In this randomized, double-blind, clinical trial, we examined the effect of treating patients with idiopathic PAH with spironolactone alongside its standard treatment, after the intervention a significant increase in the TAPSE index was observed compared to the control group. Significant difference in other echocardiographic and clinical indicators examined after the intervention in the intervention groups and the witness was not identified.

Source of Funding

Mashhad University of Medical Sciences

Conflict of Interest

We have no conflict of interest

Disclosure(s)

Thanks to Mashhad heart failure group

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