

(RESEARCH ARTICLE)



Influence Spironolactone on blood glucose, heart arrhythmias and arterial blood pressure

Almir Jagodic ¹, Elvedin Osmanovic ^{1,*} and Irma Ikanovic ²

¹ Public Health Center Zivinice Zip code 75270, Bosnia and Herzegovina.

² Emergency Medical Care, Institute of Emergency Medicine, Sarajevo Zip code 71000, Bosnia and Herzegovina.

Magna Scientia Advanced Research and Reviews, 2022, 06(01), 051–057

Publication history: Received on 09 August 2022; revised on 21 September 2022; accepted on 23 September 2022

Article DOI: <https://doi.org/10.30574/msarr.2022.6.1.0063>

Abstract

Spironolactone is a diuretic and is often used in the treatment of hypertension. This medicine is very good when it comes to lowering the blood pressure, and this is also a drug of choice when it comes to the stage of hypertensive urgencies and emergencies. It can be administered intravenously, and the effects reach a maximum within 30 minutes. Due to the fact that this medicine can cause higher level of potassium ions it can affect blood glucose and arrhythmias. A prospective random study was carried out in Hemodialysis center of Public Health Institution Center “Zivinice”, where we analyzed 120 patients which were suffering from hypertension heart disease, and diabetes. We included all 120 patients whom suffering from hypertension and diabetes. Clinical and laboratory data of patients were collected during period from February to August 2022. Looking at all the three groups of patients, it can be noticed that the maximum value of arterial blood pressure upon arrival at the Hemodialysis center had patients suffering from hypertension and diabetes, where the average value of arterial blood pressure was 173/113 mmHg. According to analysis for all three observed groups of patients, after treatment with spironolactone there is no statistical significance in the incidence of arrhythmias between the groups where. Looking at the summary for all three groups of patients, the average value increase of blood glucose after treatment with spironolactone is 0.9 mmol/l. Spironolactone is safe for the treatment of hypertension in diabetic patients.

Keywords: Spironolactone; Arrhythmias; Hypertension; Diabetes

1. Introduction

Spironolactone is a diuretic and is often used in the treatment of hypertension. This medicine is very good when it comes to lowering the blood pressure, and this is also a drug of choice when it comes to the stage of hypertensive urgencies. It can be administered intravenously, and the effects reach a maximum within 30 minutes, don't affect the reduction of blood glucose and arrhythmias [1].

Spironolactone is an aldosterone antagonist and a potassium-sparing diuretic. It is widely used in the management of congestive heart failure and other edematous states. Its use in the treatment of hypertension is limited to an adjuvant therapy for resistant hypertension. There are some studies on spironolactone in the treatment of resistant hypertension. Spironolactone reduces morbidity and mortality in severe heart failure, and effectively lowers blood pressure in hypertensive patients with and without hyper aldosteronism. Small uncontrolled studies have also demonstrated its effectiveness in patients with resistant hypertension. This is reflected in the latest British Hypertension Society guidelines, which recommend spironolactone as fourth-line therapy when other drugs have failed to control blood pressure [2].

* Corresponding author: Elvedin Osmanovic
Public Health Center Zivinice Zip code 75270, Bosnia and Herzegovina.

Spironolactone reduces the body's elimination of potassium, causing blood potassium levels to rise. Potassium levels that are too high (hyperkalemia) can affect the heart, leading to irregular heartbeats (arrhythmias) and, in severe cases, heart attack.

Diabetes mellitus is a group of metabolic disorders where there are high blood sugar levels over time. Prolonged elevations in sugar levels lead to a number of health complications including cardiovascular disease and kidney disease [3].

Diabetes mellitus is one of the most common concomitant diseases in patients with atrial fibrillation. In a survey of hospitalized patient, atrial fibrillation occurred in 14.9% of diabetes mellitus patient's vs 10.3% in control group with hypertension but no diabetes mellitus. High blood glucose levels has been cited as the risk factor for atrial fibrillation. The Framingham study indicated diabetes mellitus to be an independent risk factor for heart arritmias [4].

Aims

The aims of this manuscript is:

- To determine arterial hypertension in patients suffering from diabetes.
- To determine the frequency of arrhythmic heart disorders in patetien how have diabetes.
- To determine the frequency of arrhythmic heart disorders before and after antihypertensive treatment of spironolactone.

2. Material and methods

A prospective random study was carried out in Hemodialysis center of Public Health Institution Center "Zivinice", where we analyzed 120 patients which were suffering from hypertension heart disease, diabetes or they had high blood pressure without diagnosed hypertension heart disease and diabetes. Patients were divided into 3 groups, each group of 40 persons.

The following groups were formed:

- The first group of patients which were suffering from hypertension;
- The second group which includes hypertensive patients who suffered from co-morbidities diabetes;
- The third (control) group of patients are patients which suffered from high blood pressure, but they have not been diagnosed with hypertension and diabetes.

All three groups of patients in the treatment of hypertension were treated with spironolactone once a day 50 mg pills.

Demographic, clinical and laboratory data of patients were collected during period from February to August 2022.

Criteria for inclusion in the study for both sexes were: highblood pressure, high blood glucose levels, 18 – 80 years of age, non-smokers, not drinking alcohol, last meal consumed before 6 or more hours. Criteria for exclusion from the study was: a disease that can cause disturbance of potassium and glucose levels (except for diabetes), surgical procedures on theheart and blood vessels, diseases of the pancreas, the existenceof recent acute stress reactions, use of medicines that can affectthe level of blood glucose and cardiac arrhythmias.

Data were collected upon patients' arrival in the Hemodialysis center, as well as 30 minutes after administration of spironolactone.

Patients were selected consecutively, and analysis was carried out as follows:

- Clinical evaluation of each patient included a medical history about the presence of the aforementioned associated symptoms: chest pain, shortness of breath, headache, nausea and vomiting, epistaxis, anxiety, convulsions, focal neurologic deficit (numbness or weakness in the extremities, speech disorder, balance disorder, confusion, and loss of consciousness) and visual disturbances. Also, data was collected from the patients regarding the duration of hypertension and antihypertensive treatment.
- An analysis of the arterial blood pressure values were measured in the Hemodialysis center. Arterial blood

pressure was measured to all patients using sphygmomanometer (apparatus for measuring blood pressure) "Riester diplomat" which is produced in Germany. Arterial blood pressure was measured, in the sitting position after resting for 5 minutes, using standard equipment and techniques. A check of blood pressure was performed 30 minutes after application of therapy.

- An analysis of electrocardiography (ECG) was performed in the Emergency Medical Service. Electrocardiogram was performed to all patients on electrocardiograph "Schiller AT-2 plus" produced in Switzerland with 12 conventional drains under optimal conditions (shooting speed of 25 mm / s, a calibrated gauge deflection of 1 mV / 10 mm). We analyzed arrhythmia (tachycardia, bradycardia, AV block, premature, atrial and ventricular flutter and flicker) and ischemia.
- We analyzed results of hypertension therapy (30 minutes after the administration of the therapy was performed a control measurement of arterial blood pressure and on the basis of that was assessed the success of the therapy).
- A comparison of ECG was performed before and after treatment.
- Blood glucose was measured before and after the treatment, and it has been performed evaluation and statistical analysis of an impact of medicines on the blood glucose levels. The measurement was performed using glucometer "Wellion Calla Light" and using strips produced in Austria. Blood was taken from the fingertip and finger disinfection was carried out using Asepsol.

Medicines which were used in the study were: Spironolactone pills 50 mg per oral (Aldactone, manufacturer Esteve Pharmaceuticals GmbH, Germany).

All data were analyzed using descriptive statistics, where numerical data was presented using appropriate measures of the central tendency and measures of dispersion, also alfanumerical data are presented in appropriate tables and graphs.

Nonparametric methods and tests were used in order to calculate statistical significance and those are: for calculation of differences within groups was used χ^2 test, while for calculation of difference between groups besides χ^2 test was also used Kruskal-Wallis test, and if there was a statistically significant difference between the groups, an additional testing was carried out between groups using the Mann-Whitney U test; for parametric data a difference between groups was calculated using single-factor analysis of variance (ANOVA) followed by Tukey's HD test if there were differences between the groups, and also Student's "t" test for dependent samples; for calculation of the testing before and after prescribed therapy was used Wilcoxon rank test; while for calculation of correlation where it was necessary it was used Pearson and Spearman correlation test.

The statistical hypotheses were tested at the level of $\alpha = 0.05$, i.e the difference between groups in the sample is considered significant if $p < 0.05$. Statistical analysis was performed using programmatic support of biomedical application software called " MedCalc for Windows version 12.4.0 " Copyright © 1993 to 2013, and for the most part using the software "SPSS Statistics 17.0," Copyright © 1993-2007.

3. Results

The study included a total of 120 patients, of whom 59 were men (49.1%) and 61 women (50.9) (Figure 1.)

This difference in the frequency of men and women was not statistically significant ($\chi^2 = 11.025$; $df = 1$; $p = 0.7$). The average age of men is 52 years of age while of women is 50.8 years of age.

BMI in all observed patients ranged from 19 to 38, with an average value of 26.98 and a standard deviation of 4.297.

The majority of patients had BMI 30 and 22 of them had BMI (18.3%). There was no statistically significant difference in the frequency of certain values of BMI between men and women ($\chi^2 = 53.665$; $df = 54$; $p = 0.487$). The high blood pressure was higher when the value of $BMI > 25$, while it was lower when the value of $BMI < 25$. It was determined a statistically significant correlation of the elevated BMI and hypertension ($p < 0.001$).

Looking at all the three groups of patients, it can be noticed that the maximum value of arterial blood pressure upon arrival at the Hemodialysis center service had patients suffering from hypertension and diabetes, where the average value of arterial blood pressure was 173/113 mmHg. Patients suffering from hypertension had an average value of

arterial blood pressure 166/105 mmHg, while patients with high arterial blood pressure without diagnosed hypertension had an average value of arterial blood pressure 159/103 mmHg.

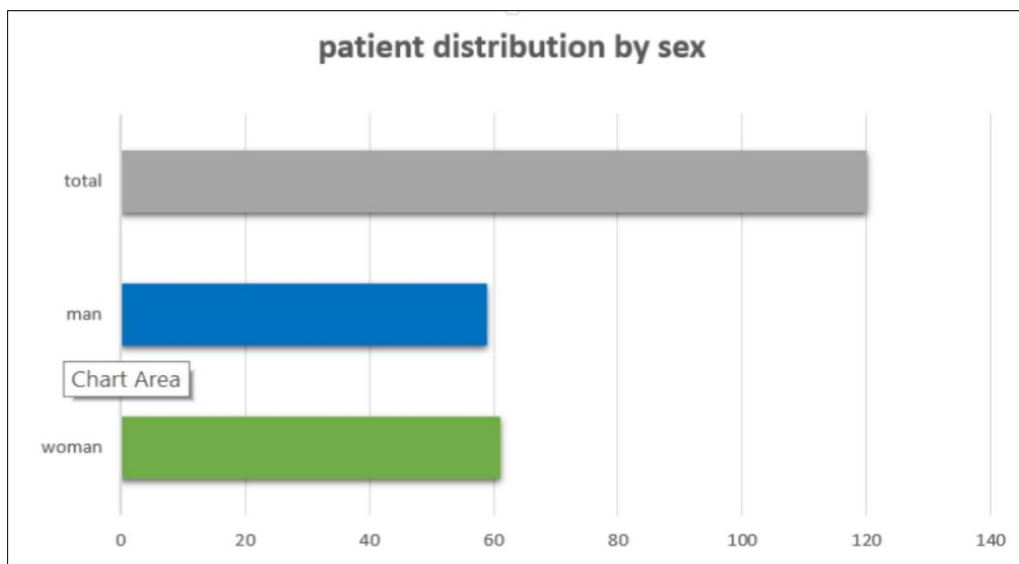


Figure 1 Distribution patients by sex

After treatment with spironolactone, the lowest value of arterial blood pressure had patients with an elevated arterial blood pressure without diagnosed hypertension with an average value of 118/80 mmHg.

The largest number of hypertensive crisis was in a group of patients suffering from hypertension (8 cases), while in the group of patients who are suffering from hypertension and diabetes were 4 cases. In the group of patients who had high blood pressure without diagnosed hypertension and diabetes there were no cases of hypertensive crisis.

Additional comparisons using the Tukey HSD test solar of some examined groups showed that the group of patients suffering from hypertension is significantly different from the other groups when it comes to the hypertensive crisis (Table 1).

Table 1 Differences between the groups regarding values of blood pressure after treatment

Mann-Whitney U		Significance level	The average value of arterial blood pressure
Patients suffering from hypertension	Z = -5.286	p<0.001	130/93
Patients suffering from hypertension and diabetes	Z = -1.516	p=0.074	140/103
Patients suffering from high blood pressure without diagnosed hypertension	Z = -3.990	p<0.001	1121/80

($\chi^2=10.021$; $df=1$; $p=0.7$)

It is observed that after treatment with spironolactone, there is no statistically significant difference in blood glucose values between the two sexes, inside each group $p < 0.0823$.

Observed between groups there is no statistically significant difference in an increase of blood glucose after treatment with spironolactone ($p < 0.09$). Looking at the summary for all three groups of patients, the average value increase of blood glucose after treatment spironolactone is 0.9 mmol / l, which is not statistically significant ($p = 0.3$) (Table 2).

Table 2 Demonstrates a value of blood glucose upon arrival to the Hemodialysis center

The group of patients	Medium value	Standard deviation	The lowest value	The highest value
Patients suffering from hypertension	7.9	4.840	4.0	8.2
Patients suffering from hypertension and diabetes	10.9	3.039	6.1	19.4
Patients suffering from high arterial blood pressure	5.7	4.201	3.2	6.8

ANOVA: F (2.951) = 7.264; p=0

After admission to the Hemodialysis center, the highest level of blood glucose was noticed in the group of patients who are suffering from hypertension and diabetes, with an average value of 11.2 mmol/l, while in the group of patients who are suffering from high arterial blood pressure without diagnosed hypertension and diabetes, the average blood glucose value was the lowest 6,5mmol / l (p = 0.08)

Additional calculations of Mann-Whitney's U-test between individual test groups, using Bonferroni's adjustment of statistical significance ($\alpha = 0.05 / 3 = 0.017$) it was determined a statistically significant difference ($\alpha < 0.017$) among all observed groups.

According to ANOVA analysis for all three observed groups of patients, after treatment with spironolactone there is no in the group of patients who are suffering from high arterial blood pressure without diagnosed hypertension and diabetes, the average blood glucose value was the lowest 6,7mmol / l (p = 0.09). When looking within each group between men and women, there is no statistical significance in the incidence of arrhythmias before and after therapy, where p = 0.709. The most common arrhythmic disorder was supraventricular tachycardia and a total of 7 cases (5.7%) (Table 3).

Table 3 ECG results in the examined groups of patients

	Normal results	Arrhythmia	Ischemia
Patients suffering from hypertension	38	5	0
Patients suffering from hypertension and diabetes	34	4	0
Patients suffering from high arterial blood pressure	36	3	0
Total	108	12	0

($\chi^2=31.549$; df=8; p=0.332)

4. Discussion

An arterial hypertension represents permanent increase of systolic and/or diastolic blood pressure above the established limits for physiological or normal arterial blood pressure. Hypertension often makes no discomfort to the patient, and it can remain uncovered for a very long time. Hypertension is the most severe cardiovascular disorder in European countries with high national income, where hypertension was observed in 20% to 50% of the adult population [5].

A study conducted in the UK during period from 1994 to 1998, says that the incidence of hypertension is around 37% in the population. Male gender and age were closely associated with hypertension. It was determined that half of the respondents knew that they are suffering from hypertension, but they do not use antihypertensive therapy (Webeer, 2005). In our study, men make up 49.1% of patients suffering from hypertension with average age of 52 years. Women make up 50.9% of patients suffering from hypertension, with an average age of 50.8 years [6].

In the UK, about half of the middle aged people have high blood pressure. Most patients have a value of blood pressure up to 160/100 mm Hg, however 1 of 20 patients suffering from hypertension have a blood pressure value greater than

160/100 mmHg (Kenny, 2012). In our study, the average value of arterial blood pressure was 173/113 mmHg, which is little bit higher than it was presented in a study conducted in the UK [7].

The dose of 25 mg spironolactone daily, chosen to be administered in our trial, seems optimal to us for use in resistant hypertension, as it offers good antihypertensive efficacy and a low number of adverse effects, comparable to placebo in the short-term. With the 25 mg dose, the long-term occurrence of adverse events is low, about 13%, leading to the discontinuation of spironolactone only in 6% of patients [8].

There may be a dose-response effect with spironolactone up to 50 mg/day in patients with essential hypertension and higher doses >50 mg/day do not produce further reductions in blood pressure.²⁶ In patients with primary aldosteronism, increasing the dose of spironolactone (up to 75–225 mg/day) may have a greater antihypertensive effect [9]. It is possible that the increase of spironolactone dose to 50 mg/day or more could have led to a more substantial decrease of blood pressure, but would be likely to also cause a higher occurrence of adverse events [10].

In all three groups, spironolactone is administered through parenteral therapy and a dose of 50 mg is injected intravenously. In the study, which we conducted, a group of patients which had a high arterial blood pressure without diagnosed hypertension and diabetes, had a systolic blood pressure reduced by 41 mmHg and diastolic pressure by 23 mmHg. In our study, diabetes was the most common co-morbidity in 33% of patients. Diabetes and obesity were the most present co-morbidities either individually or in combination in hypertensive patients, while significantly less present were in normotensive patients.

A study conducted in the UK during period from 1994 to 1998, says that the incidence of hypertension is around 37% in the population. Male gender and age were closely associated with hypertension. It was determined that half of the respondents knew that they are suffering from hypertension, but they do not use antihypertensive therapy (Webeer, 2005). In our study, men make up 49.1% of patients suffering from hypertensive heart disease with average age of 52 years. Women make up 50.9% of patients suffering from hypertensive heart disease, with an average age of 50.8 years [11].

Number of hypertensive crisis has been increased among people of younger age (18-35 years of age). Cerebrovascular complications of hypertensive crisis happen to patients depending on their age, among male patients it was noticed maximum value between 36 – 74 years of age while in female patients older than 75 years. The largest number of hypertensive crisis in our study was noticed in a group of patients suffering from hypertensive heart disease without diagnosed diabetes [12].

In our study, supraventricular tachycardia is the most common disorder of the heart rhythm (5.7%), which is less in relation to the study conducted in the USA where out of 81.11 patients only 189 (0,22%) of them had paroxysmal supraventricular tachycardia after use of spironolactone. This paper shows that spironolactone does not significantly affect on to the frequency of cardiac arrhythmias.

In our study, an increase of blood glucose levels observed in all three groups after treatment with spironolactone is only 0.9 mmol / l on average, which has no statistical significance. A study conducted by Lind shows that spironolactone increases the concentrations of blood glucose by 0.3 mmol / l. Our study compared to Lindov showed a 2.5 times greater increase in blood glucose, but still does not have statistical significance [13]. In our study it is concluded that use of spironolactone does not lead to a significant increase in blood glucose levels, and it can be safely used in the case of fast reduction of the high arterial blood pressure in both sex.

Diabetic patients are more likely to develop high blood pressure. There are several reasons for such a high frequency of hypertension in diabetic patients. Among the most common reasons are gender, age, combination of essential hypertensive heart disease with diabetes, hyperinsulinemia and proteinuria, obesity. Around 30% of people suffering from diabetes have high blood pressure [14].

5. Conclusion

As spironolactone decreases the pressure within the blood vessels, it is often used to treat high blood pressure, usually when other blood pressure lowering medicines have not been effective enough. Spironolactone is therapy of choice for antihypertensive medicine so patients who use it to treat hypertension.

Compliance with ethical standards

Disclosure of conflict of interest

All authors of the manuscript have no conflict of interests to declare.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors'.

Statement of informed consent

No information about any individuals.

References

- [1] Attar A, Sadeghi AA, Amirmoezi F, Aghasadeghi K. Low Dose Spironolactone Monotherapy in the Management of Stage I Essential Hypertension: A Pilot Randomized, Double-Blind, Placebo-Controlled Trial. *Acta Cardiol Sin.* 2018, 34(1):59-65.
- [2] E Merck. Blood glucose level and arrhythmias. *Canadian Int. J.*, 2011, 5: 103-105.
- [3] Van Belle T. L., Coppieters K. T., von Herrath M. G. Type 1 diabetes: etiology, immunology, and therapeutic strategies. *Physiol. Rev.* 2011, 91(2):79–118.
- [4] Zhou Z, Hu D. Epidemiological study on the prevalence of atrial fibrillation in the Chinese population of mainland China. *Journal Epidemiol.* 2008; 18:209–16
- [5] P. Kumar. Effect spironolactone on blood glucose levels. *Clinical Medicine Journal.* 2012, 11:1243-1250.
- [6] JH. Bauer and WC. Gauntner. Effect of potassium chloride on plasma renin activity and plasma aldosterone during sodium restriction in normal man. *Kidney Int.* 1999; 3:246-30.
- [7] E. Osmanovic. Urgent conditions and complications of patients on chronic hemodialysis. *Atrial fibrillation.* 2013, 1: 64-67.
- [8] LS. Webber and AL Bedimo-Rung. The obesity epidemic: incidence and prevalence. *Medical Soc.* 2005, 11:157-159.
- [9] L. Lind, C. Berne, T. Pollare and H. Lithell,.Metabolic effects of anti-hypertensive treatment with nifedipine and diuretics: a double-blind, cross-over study, *Journal of Human Hypertension.* 2005, 9(2):137-141.
- [10] Calhoun DA et al. Resistant hypertension: diagnosis, evaluation, and treatment. *World Health J.* 2016, 51:143.
- [11] Pollare T, Lithell H, Selinus I, Berne C. Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *Geriatric J.* 2014, 125:456-459.
- [12] FM. Sacks et al.. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *New York Urgent Medicine J.* 2015, 344: 3-10.
- [13] Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. *Hypertension Journal.* 2008, 51:1403–1419.
- [14] Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension.* 2017, 49(4):839-45.