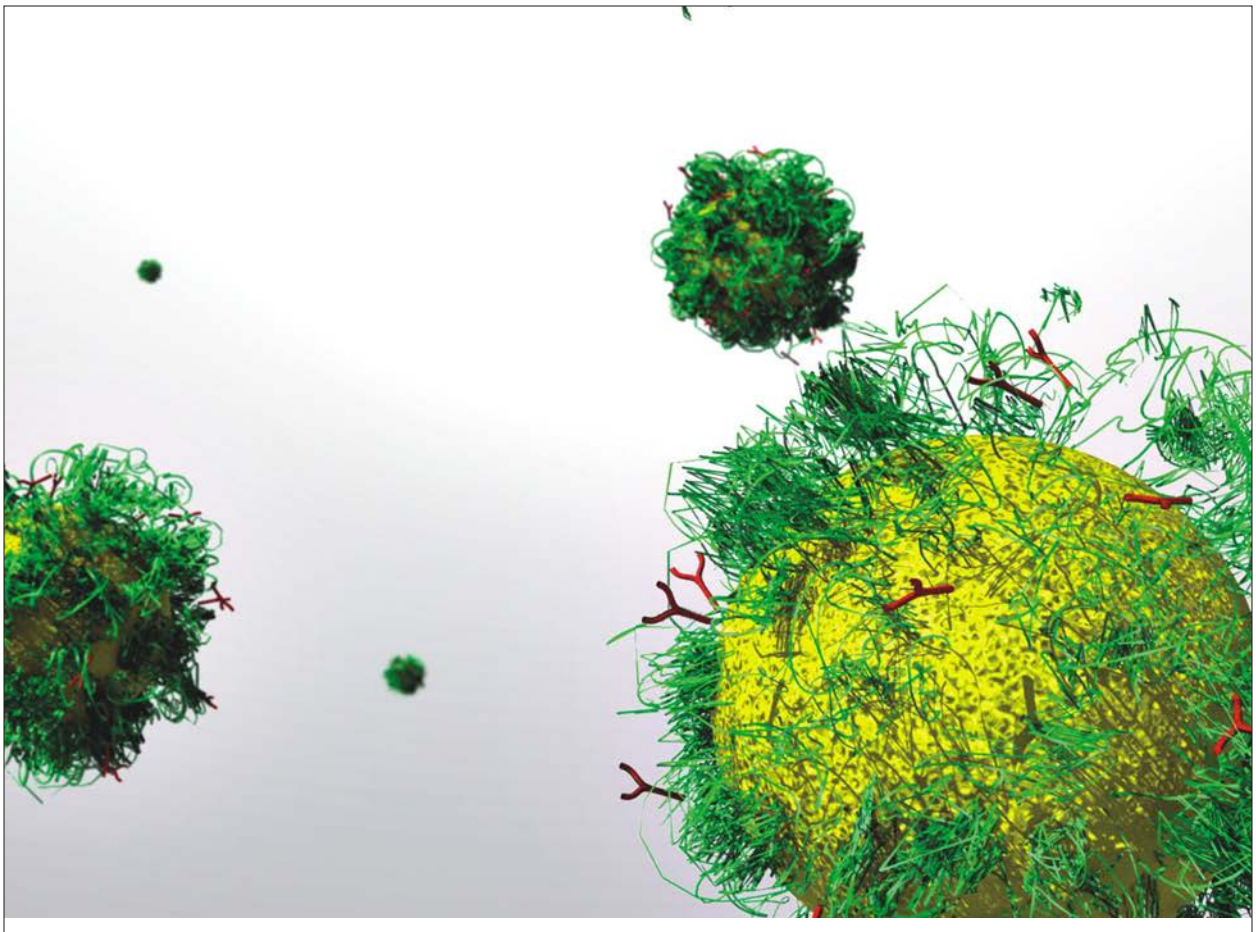

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Research Article
Two-week Treatment with Diuretics as Add on Therapy is Enough to Control the Blood Pressure in Patients Presented with Uncontrolled-resistant Hypertension

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Abstract

Background and Aim: Diuretics used as a first line therapy in the management of hypertension. Spironolactone is the fourth drug that indicated in the management of resistant hypertension. This study aimed to clarify the importance of using short term therapy for 2 weeks as add on therapy in the management of uncontrolled-resistant hypertension. **Materials and Methods:** A total number of 120 patients were enrolled in open label clinical study. The patients are assigned to receive 2 week therapy of a single daily dose of amiloride (5 mg) plus hydrochlorothiazide (50 mg) (Group I), or 50 mg spironolactone (Group II) or 50 mg hydrochlorothiazide (Group III). The following measurements, including the anthropometric measurement, blood pressure, lipid profile and serum electrolytes were considered. **Results:** Diuretics produced significant reduction of the blood pressure of systolic and diastolic that amounted 23 and 14.2% (Group I), 24.3 and 14.4% (Group II) and 25.4 and 13.0% (Group III) of the baseline value. They induced alterations in serum electrolytes in Group II and III. **Conclusion:** Two- week therapeutic regimens of diuretics are enough to achieve the control of blood pressure and the logic drug for resistant hypertension is spironolactone.

Key words: Diuretics, uncontrolled resistant hypertension, short term regimen, add on therapy, serum electrolytes, lipid profile, anthropometric measurements

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diuretics prescribed in the management of hypertension as primary drugs or as add-on- therapy or used in combination with other antihypertensive agents like calcium entry blockers or angiotensin receptor blockers. These medications act at different sites of actions and they differed in their efficacy and inducing adverse reactions. In adult hypertensive patients, the diuretics effectively reduced the blood pressure as well as the risk of adverse cardiovascular complications[1]. Thiazides (e.g., hydrochlorothiazide) reduced the blood pressure in a dose dependent manner and it reduced 11 mm Hg (systolic) and 5 mm Hg (diastolic) by using 50 mg day^{-1} for eight weeks[2]. Single low dose of chlorthalidone (6.25 mg) but not hydrochlorothiazide (12.5 mg) reduced the day time and night time blood pressure over 24 h monitoring which indicated that chlorthalidone is a useful remedy as monotherapy in management of hypertension[3]. Thiazide-type diuretics are useful first-line agents because they reduced the cardiovascular mortality and co-morbidities in hypertension (systolic and diastolic subtype)[4]. Long-term therapy with thiazides (at least more than 4 weeks) reduced the total peripheral resistance and reduced the blood pressure independent of natriuresis[5]. Loop diuretic class, as a monotherapy, reduced the blood pressure by 8 mmHg (systolic) and 4 mmHg (diastolic) after 8 weeks treatment with a fixed dose (e.g., frusemide 40-60 mg day^{-1})[6]. This class of diuretics is preferable to treat hypertension that associated with renal impairment[7]. Potassium sparing diuretics notably spironolactone usually prescribed as the fourth drug for treatment of uncontrolled-resistant hypertension[8].

It is estimating that 20% of hypertensive patients were resistant to at least three antihypertensive drugs and those patients have a primary aldosteronism. In one study, Verdalles *et al.*[9] found that the resistant hypertension increased significantly with age, degree of chronic kidney disease and albuminuria and the blood pressure was controlled in about 47.5% of patients who used $\geq$4 antihypertensive agents. The efficacy of amiloride (an epithelium-sodium channel blocker) in controlling the resistant form of hypertension is inferior to the spironolactone[10]. The rationale of this study that diuretics usually indicated as a first line therapy in the management of hypertension and their effects observed after 4 weeks but they can reduce the blood pressure within a short period with variable efficacy and minimal adverse reactions.

Therefore, this study aimed to clarify the benefit of using different modalities of diuretics as 'add on therapy' and not as first line therapy for two weeks to treat uncontrolled hypertensive patients used antihypertensive drugs other than diuretics.

MATERIALS AND METHODS

This study was reviewed by the Scientific Committee at the Department of Pharmacology and approved by the Council of College of Pharmacy at Hawler Medical University in Kurdistan region in Iraq as a part of postgraduate study. Each patient was asked to enroll in this study, according to the ethical guideline that approved by the General Directorate of Health, Erbil. The patients who are eligible for the study are adult hypertensive patients of both genders. The criteria of inclusion are hypertensive patients treated with antihypertensive drugs. Therefore, the patients included in this study were on the different antihypertensive modalities gave a picture of the variability in the number of medications at the time of entry into the study. The criteria of exclusion are end stage renal failure, emergency hypertension, preeclampsia, pregnant or lactated mother and confirmed diagnosis of secondary hypertension (polycystic kidney, Conn's syndrome and Cushing's syndrome).

The patients recruited from the Consultant Clinics of Internal Medicine at Rizgary Hospital. A total number of 120 patients who fulfilled the above criteria were enrolled in this open-labeled clinical study and they are assigned to the following treatments for two weeks according to their clinical conditions:

- **Group I (n = 45):** Patients treated with a combined therapy of amiloride (5 mg) plus hydrochlorothiazide (50 mg) in the pharmaceutical preparation of Moduretic tablet, single oral dose per day
- **Group II (n = 44):** Patients treated spironolactone (50 mg) single oral dose per day
- **Group III (n = 31):** Patients treated hydrochlorothiazide (50 mg) single oral dose per day

Each patient was clinically assessed by the consultant internal medicine before assignment to the diuretic treatment. Then each patient was subjected to the following measurements and laboratory investigations.

Blood pressure measurement: Mercury sphygmomanometer was used to measure both systolic and diastolic blood pressure manually. The patient asked to relax on chair for 5 min and then blood pressure was by the palpatory method followed by ausculatory method. The pulse and mean arterial pressure were determined by using the following formula:

Pulse pressure (mmHg) = Systolic BP-diastolic BP
Mean arterial BP (mmHg) = Diastolic $BP + \frac{1}{3}$ pulse pressure

Two measurements of blood pressure were recorded, the first measurement on the admission and the second measurement after two weeks of treatment.

Anthropometric measurements: The anthropometric measurements included weight (kg) and height (m). The Body Mass Index (BMI) was calculated according to the Quetlett's equation:

$$BMI\ (kg\ m^{-2}) = \frac{Weight\ (kg)}{Height^2\ (m)}$$

Laboratory investigations: The following biochemical tests were determined in the laboratories of the hospital as a part of routine investigations of the patient's assessment. A venous blood was obtained from each patient (fasting state) by venipuncture and the serum was separated by centrifugation (3000 rpm for 5 min) and collected for determination of fasting glucose and lipid profile Total Cholesterol (TC), triglycerides (TG) and High Density Lipoprotein cholesterol (HDL-c)), uric acid, creatinine and electrolytes (sodium and potassium). Fasting serum Low Density Lipoprotein-cholesterol (LDL-c) was calculated by using the following equation:

$$\text{Fasting serum LDL-c} = TC - ((0.2 \times TG) + (HDL\text{-}c))$$

Serum electrolytes were determined by a direct method using i-Smart Electrolyte Analyzer (serial number 30551, Korea). The principle of this testing is electrochemistry, by which a serum sample of 60 µL was aspirated and the voltage potential of sodium and potassium was simultaneously recorded and calculated accordingly to the reference values. The results expressed in mmol L^{-1}. At the time of the entry into the study, the mean levels of serum creatinine and uric acid were 0.87 and 3.91 mg dL^{-1}, respectively and no patient have abnormal levels.

Statistical analysis: The results are expressed as number, percentage and mean±SD. The data were analyzed using Student's t test (two tailed, paired), one way analysis of variance (ANOVA) *post hoc* Tukey (HSD) test and the difference between percentage test using XLSTAT 2015 program. The lower limit of significance is $p \leq 0.05$.

RESULTS

Table 1 showed the characteristics of the patients enrolled in this study. There was insignificant differences between treated groups regarding the age, duration of hypertension, current smoking, history of taking contraceptive pills or the presence of co-morbidities e.g. diabetes mellitus or dyslipidemia. Significant high frequencies of uncontrolled hypertension (patients used < 3 antihypertensive drugs) were found in the Group I and III compared with Group II (Table 1). The patients of Group II were included uncontrolled (43.2%) and resistant (56.8%) hypertension. The cardiometabolic risk factors were observed in all patients enrolled in the study and did not show significant differences between studying groups except the mean arterial blood pressure, which attended significant low value in Group III compared with Group I and Group II (Table 2). The mean value of BMI was in the range of overweight and the mean value of fasting serum triglycerides was above the normal cutoff level of 150 mg dL^{-1} (Table 2).

Figure 1 showed that two-week treatment with diuretics significantly reduced both systolic and diastolic blood pressures. Combined therapy of hydrochlorothiazide and

Table 1: Characteristics of the patients enrolled in the study

Characteristics	Group I (n = 45)	Group II (n = 44)	Group III (n = 31)
Gender (Male: Female ratio)	11:34	13:31	5:9
Age (year)	51.2±9.1	54.5±9.3	50.1±16.0
Current smoking	8 (17.8)	8 (18.2)	4 (28.6)
History of contraceptive pills	15 (33.3)	14 (31.8)	4 (28.6)
Duration of hypertension (year)	5.8±4.5	7.0±5.1	4.9±3.7
Number of antihypertensive			
<3 drugs	45 (100)	19 (43.2)*	14 (100)†
≥3 drugs	(0.0)	25 (56.8)	0 (0)
Co-morbidities			
Diabetes mellitus	7 (15.6)	8 (18.2)	2 (14.3)
Dyslipidemia	14 (31.1)	15 (34.1)	7 (50.0)

The results are expressed as number (percentage) and Mean±SD. Group I: Patients treated with hydrochlorothiazide and amiloride, Group II: Patients treated with spironolactone, Group III: Patients treated with hydrochlorothiazide, *p<0.001 compared with Group I, †p<0.001 compared with Group II

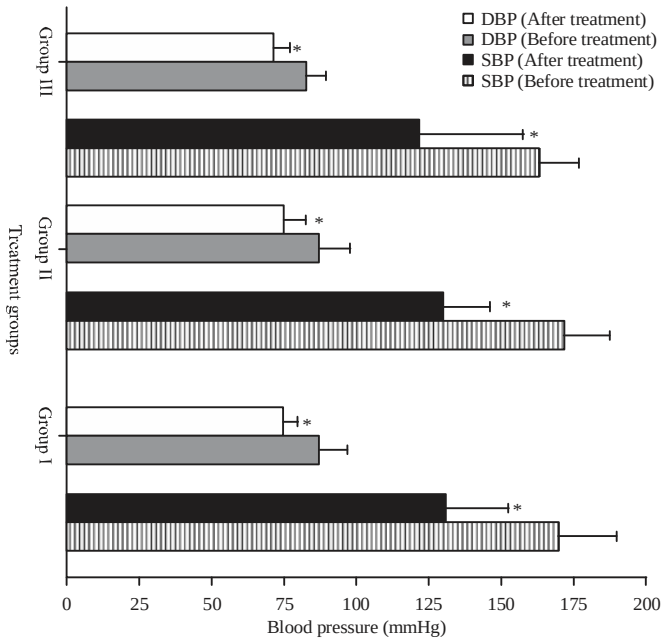

Fig. 1: Effect of 2 week treatment with diuretics on the blood pressure. The results are expressed as Mean±SD. Group I: Patients treated with hydrochlorothiazide and amiloride, Group II: Patients treated with spironolactone, Group III: Patients treated with hydrochlorothiazide, *p<0.001 was calculated by using paired Student's t test

Table 2: Cardio-metabolic risk factors

Characteristics	Group I (n = 45)	Group II (n = 44)	Group III (n = 31)
Body mass index (kg m^{-2})	28.5±3.6	28.0±3.0	27.6±2.4
Fasting serum levels of:			
Glucose			
Total cholesterol	184.2±43.3	190.7±36.1	187.1±34.4
Triglycerides	181.5±122.0	215.0±99.7	185.5±76.9
High density lipoprotein cholesterol	43.8±12.5	45.5±12.2	47.9±14.5
Low density lipoprotein cholesterol	108.8±45.4	102.0±58.2	102.0±44.2
Blood pressure (mmHg)			
Systolic	169.4±14.6	171.4±15.5	162.9±13.3
Diastolic	87.2±9.5	87.0±10.5	82.1±7.0
Mean	114.6±9.5	115.1±10.8	98.8±13.8*†

The results are expressed as Mean±SD Group I: Patients treated with hydrochlorothiazide and amiloride, Group II: Patients treated with spironolactone, Group III: Patients treated with hydrochlorothiazide, *p<0.001 compared with Group II, †p<0.001 compared with Group I

Table 3: Effects of diuretic on the serum electrolytes levels

	Serum potassium (mmol L^{-1})			
Groups of patients	Before treatment	After treatment	Before treatment	After treatment
Group I (n = 45)	137.7±4.4	135.2±4.6**	4.21±0.55	4.24±0.56
Group II (n = 44)	136.4±4.4	135.9±4.2	4.20±0.35	4.53±0.73***
Group III (n = 31)	134.8±3.7	132.9±3.3***	4.36±0.5	4.00±0.43*

The results are expressed as Mean±SD. Group I: Patients treated with hydrochlorothiazide and amiloride, Group II: Patients treated with spironolactone, Group III: Patients treated with hydrochlorothiazide. Statistical differences were calculated by using paired Student's t test. *p<0.02, **p<0.005, ***p<0.001

amiloride reduced the systolic and the diastolic blood pressures by 23 and 14.2% of the baseline value, respectively in Group I patients. In Group II, spironolactone reduced the systolic and the diastolic blood pressures by 24.3 and 14.4% of the baseline value, respectively. Hydrochlorothiazide reduced the systolic and the diastolic blood pressures by 25.4 and 13.0% of the baseline value, respectively. All diuretics reduced the blood pressures to the within normal levels, that is, systolic

(<140 mm Hg) and the diastolic (<90 mm Hg). Two week treatment with diuretics significantly altered the serum electrolytes. Serum sodium level significantly reduced by 1.9 mmol L^{-1} from the mean baseline level in patients of Group III (Table 3). Potassium level significantly increased by 0.33 mmol L^{-1} from the mean baseline level in patients of Group II and significantly decreased by 0.36 mmol L^{-1} from the mean baseline level in patients of Group III (Table 3).

DISCUSSION

The results of this study highlight three important observations. First, diuretics of whatever class, they reduced the blood pressure when they prescribed as add on therapy instead of using these compounds as a first line therapy. Second, the magnitude of blood pressure reduction is so high and achieved within a short period. Third, the significant alterations of the serum electrolytes do not manifest clinically. Previous studies reported that a fixed dose of the aldosterone inhibitor (amiloride) and thiazide diuretics (hydrochlorothiazide) reduced the blood pressure by 31 mmHg (systolic) and 15 mmHg diastolic after 3 weeks of treatment of resistant hypertension[11]. Our results are in agreement with that study except Group I represented patients with uncontrolled (used <3 medications) and only one patient presented with resistant hypertension. Literature review did not disclose the benefit of such therapy as add on therapy. Corea *et al.*[12] reported that fixed dose of moduretic for 4 weeks did not achieve a satisfactory reduction of the blood pressure in hypertensive patients resistant to atenolol therapy. In Group II, spironolactone therapy is effective to reduce the blood pressure to the normal levels in both uncontrolled and resistant hypertension. Our results are in agreement with Oliveras *et al.*[13] study that finds the effectiveness of spironolactone, as add on therapy for 6 months, in reducing the ambulatory 24 h systolic and diastolic blood pressure in resistant hypertension patients and such therapy was adversely affecting the glomerular filtration rate. Batterink *et al.*[14] explored that spironolactone can reduce the blood pressure in a dose up to 50 mg day^{-1} but the significant reduction of blood pressure in patients with a primary hypertension can achieve with 100-500 mg day^{-1}. In respect of duration of antihypertensive prescription, Chaturvedi *et al.*[15] reported a range of 3-24 weeks is enough to evaluate the antihypertensive effect of a drug as a monotherapy or combined with other medications. Williams *et al.*[16] found that spironolactone was the most effective add on drug for the treatment o f resistant hypertension compared with α or β-adrenoceptor blocking agents and it induced insignificant and occasionally increased serum potassium levels. Accordingly, our results add new information, including short term therapy a fixed dose of 50 mg is enough to reduce the blood pressure and a routine testing of serum electrolytes is essential to detect subclinical hyperkalemia. The third treatment option that used in our study is hydrochlorothiazide. There is no doubt that most hypertensive patients were preferred a combined therapy of a small dose of hydrochlorothiazide and calcium entry blockers or angiotensin receptor blockers[17,18] or the patients used chlorthalidone[19] as a first line therapy and those patients. Therefore, the use of single dose of 50 mg hydrochlorothiazide may be carried a certain limitations. The results of our study showed that hydrochlorothiazide as add on therapy is effective as other diuretics in uncontrolled hypertension while Roush and Sica[19] mentioned in their review that hydrochlorothiazide was less effective than antihypertensive agents in decreasing the systemic blood pressure. The explanation for this discrepancy is due to the methodology of assessment of hypertension in which in home 24 h reduction of the blood pressure was an index of the effectiveness of antihypertensive agents in the Roush and Sica study[19]. The limitations of the study included small sample size of resistant hypertension, serum renin levels did not measure and 24 h changes of the blood pressure at home or in the office did not practice.

CONCLUSION

It is conclude that a therapeutic short term (only two weeks) regimen of diuretics of whatever class is enough to reduce the blood pressure to the normal levels in uncontrolled hypertension and spironolactone therapy is a logic the fourth drug that used as add on therapy to control resistant hypertension. It is necessary to measure the serum electrolyte in patients who are currently on diuretics therapy.

SIGNIFICANCE STATEMENTS

- Short-term therapy (two weeks) is enough to control high blood pressure in patients used anti-hypertensive drugs without getting the goal of control
- It is not necessary to use diuretics for long time and they can used whenever there is resistant or uncontrolled hypertension
- Diuretics of whatever mechanism of action can reduce the blood pressure without clinical adverse reactions
- It is necessary to measure the serum electrolytes when diuretics are used. The laboratory findings of serum electrolyte alteration are usually not manifested clinically

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