Original Article

Randomized Control Trial to Study the Effect of Coded Unani Formulation UNIM-904 and Amlodipine on Serum Lipid Profile and Electrolyte Level in Patients with Essential Hypertension

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Abstract

Essential hypertension, is a major health problem in developed countries, affecting nearly one billion people worldwide. It has a strong association with cardiovascular disease and contributes greatly to morbidity, mortality economic burden, Accounting for about 57% of all deaths due to stroke and 24% of all deaths due to coronary heart disease in India. By 2025, the number of hypertensive individuals may rise to 213 million from 118 million in 2000. Herbal medicines origin has been extensively used in the therapeutic management of hypertension for a long time.

Aim of the study: To study the Effect of coded Unani formulation UNIM-904 on serum Lipid profile and electrolyte level with allopathic drug amlodipine before and after treatment in patients with essential Hypertension.

Materials and methods: Randomized and open-level clinical trials were conducted on UNIM-904 and amlodipine cases at the Regional Research Institute of Unani Medicine, Mumbai, from 2014-2018. The participants of the treatment group were treated with coded Unani formulation UNIM-904 5 gm BD/day) and Amlodipine 5 mg OD/day) was given to the control group for 84 days once at night daily.

Results: We observed a significant reduction (treatment group versus control group) in mean serum potassium by 4.91 versus 4.45, Calcium9.34 versus 8.52, Cholesterol 169.93 versus 198.87, HDL-Cholesterol 47.97 versus 44.29 levels was statistically significant after Treatment in both Groups. Thus, it is concluded that both the drugs do possess the anti-hypertensive activity and reduce systolic, and diastolic blood pressure respectively, there were no significant changes in liver function tests as well as kidney function tests. yet the Unani-coded drug has shown a comparatively better rate of safety and without side effects and, therefore, recommended for use in essential hypertension cases. Further studies are suggested on a larger group of essential hypertensive patients to develop safe, effective, viable, and cheap herbal drug to combat hypertension evading satisfactory cure in modern medicine.

Keywords: Essential hypertension, blood pressure, precision medicine, Lipid profile

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Introduction:

Hypertension or high blood pressure (BP) defined as systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg has a significant role in developing heart, brain, kidney, and other diseases and is a significant cause of premature death around the globe.[8]High BP directly does not cause symptoms.[9] Long-term hypertension is a significant risk factor for certain health problems such as coronary artery disease, stroke, heart failure, atrial diseases, chronic kidney disease, and dementia. [10] Epidemiologically it was estimated that 1.13 billion people have hypertension worldwide.[8]According to a systemic review and meta-analysis, the prevalence of hypertension in high-income countries is higher than in low-income countries. However, awareness, treatment, and control substantially are also more in high-income countries than in LMIC.[11]As a result, now, two-thirds of hypertensive people live in the LMICs.[8]India is one of the LMICs. It is also a substantial public health problem in India.[12,13] Hypertension was responsible for 53.8%, 55.7%, and 54.3% of deaths due to heart disease, stroke, and chronic kidney disease, respectively in India in 2016.[14]In 2010, the Government of India launched a program named the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS) to prevent noncommunicable disease-related deaths in India[15] to achieve the global target of reducing 25% hypertension-related premature deaths by 2025.[8]

Many variable risk factors for hypertension have been discovered, including being overweight or obese [16,17], not attending in physical activity [18, 24] and taking a poor diet [11], large amount of alcohol intake [24], use of nonnarcotic analgesics [12, 13], insulin resistance, high salt intake [26] and low folic acid intake [23, 24] have been detected as self-dependent original and changeable risk factors for developing hypertension among women.

In the Unani system of medicine, several single as well as compound drugs have been used in the therapeutic management of hypertension for centuries such as:

Dawa-us-Shifa, Habb-e-Mudirr, Sharbat-e-Buzoori Motadil, Asrol (Rauwolfia serpentine L.), Lahsan (Alium sativum Linn.), Parshi-aoshan (Adiantum capillus Linn.), Tukhm-e-Kharpaza (Cucumis melo Linn.) etc. have proven their efficacy in controlling blood pressure [25, 26, 27]. Keeping these in view the present work deals with the Effect of coded Unani formulation UNIM-904 and Amlodipine on serum Lipid profile and electrolyte leveland the safety of Unani-coded drug UNIM-904 with allopathic drug amlodipine in the treatment of essential hypertension and results are presented.

Objective:

This study aims to analyse the effect of coded Unani formulation UNIM-904 and Amlodipine on serum Lipid profile and electrolyte level in patients with essential Hypertension.

Materials and Methods

Study population

Comparative Randomized open clinical trial. The study was carried out at the Regional Research Institute of Unani Medicine (RRIUM), Mumbai. Unani-coded drug UNIM-904 and amlodipine were obtained from the Central Council for Research in Unani Medicine, New Delhi. One hundred two patients, aged 18-65 years of either sex were selected from the lot of patients attending the outpatient department (OPD) of the institute following the predesigned inclusive/exclusive criteria. General physical and clinical examination, symptoms regarding hypertension, and vital parameters like blood pressure and heart rate have also been studied. Patients were randomly divided into two treatment groups, test and control following the block randomization method. The total registered cases in the trial group were 100, with completed cases 31 and dropout cases 69. The total registered cases in the control group were 105, completed cases 41, and dropout cases 64. The Effect of coded Unani formulation UNIM-904 and Amlodipine on serum Lipid profile, electrolyte level, and safety of Unani coded drug UNIM-904 and amlodipine was evaluated based on symptomatic, vital parameters (blood pressure and pulse rate and electrocardiogram (ECG)), biochemical and hematological parameters.

Ethical consideration:

The study was approved by the RRIUM's institutional ethics committee, f.no RRIUM/MUM/2012-13/IEC/25.The Institutional Ethics Committee (IEC) approved this study's protocol, informed consent form, and case record form on **20.12.2012**. This study was, thereafter, registered in Clinical Trial Registry-India (CTRI) number: (TRI/2013/10/004091) (registered on 23/10/2013). Each participant submitted a signed written informed consent form before enrolment into the study.

Study design: A prospective, randomized, open-label, active-controlled, and parallel-group clinical trial.

Subject selection criteria:

Patients were enrolled based on the following inclusion and exclusion criteria:

Inclusion criteria:

Patients of either sex in the age group of 18-65 years, patients of hypertension with SBP 160-179 mmHg and DBP 90-100 mmHg, presence of any of the following symptoms and signs viz; Headache (suda), vertigo (duwar), palpitation (khafqan), laziness (kasal), anxiety (qalaq), breathlessness (usr al-tanaffus), diminished alertness (takaddur fi'l hawas), subconjunctival haemorrhage (jiryan al-dam zer multahima), epistaxis (ru'af), pulsus plenus (nabz mumtali), were included.

Exclusion criteria:

Patients with SBP ≥180 mmHg and diastolic BP >100 mmHg and secondary hypertension, pregnant and lactating women, females using oral contraceptive pills regularly, patients taking any other medication affecting blood pressure like NSAIDs, patients with abnormality in investigations done at baseline (SGPT >105 IU). Obese subjects – BMI >30, patients with disorders requiring long-term treatment, e.g., diabetes mellitus, drug addicts, alcoholics /malignancy /epilepsy /CAD/CKD, patients with sinus bradycardia, i.e., pulse rate less than 60/min, were excluded.

Drug, Dose, and mode of administration

The trial Unani-coded drug UNIM-904 was given orally to the patients in the form of a sachet in a dose of 5.0 gm granules twice a day before 30 minutes of lunch and dinner and the control allopathic drug amlodipine was given orally in a dose of one tablet (5 mg) once a day to the patients for a period of 12 weeks-days.

Estimation of biochemical markers:

Blood was collected from the participants after 12 hours of fasting. The collected blood was allowed to clot for 15–30 min in a yellow gel vacutainer kept at room temperature. The serum separated from the clot by Remi centrifuging at 2000–2500 rpm for 5–10 min was used for estimation of biochemical markers.

Kits purchased from Erba Mannheim manufactured by Transasia Biomedical Pvt Ltd India were used for the estimation of biochemical markers using ERBA-EM 200 Fully Automatic Biochemistry Analyzer, Electrolyte using EasyLyte Automated Electrolyte Analyzerand Haematology Analyser ERBA H360 for estimation of Haematology Profile.

Statistical analysis

The data was analyzed as per protocol (i.e., the participants who completed the trial were included in the data analysis). The continuous data were measured in mean and standard deviation. The categorical data were measured in the frequency distribution. Inferential statistics were applied using parametric student's paired t-test.

Results and Discussion

Demographic Study

Table 1: Sex-wise distribution of Group-I (n=31) and Group-II (n=41)

Sex			
UNIM-904 (T/C)		**Frequency**	**Percent**
Group-I	F	11	35.5
	M	20	64.5
	Total	31	100.0
Group-II	F	13	31.7
	M	28	68.3
	Total	41	100.0

In the trial group, out of 31 patients with essential hypertension, 20 (64.5%) were male and 11 (35.5%) female, whereas in the control group, 28 (68.3%) were male and 13 (31.7%) female, which shows that male has higher incidence as compared to female.

Table 2: Age-wise distribution of Group-I (n=31) and Group-II (n=41)

Age				
UNIM-904 (T/C)			**Frequency**	**Percent**
Group-I	Valid	(30-40) Years	5	16.1
		(40-50) Years	8	25.8
		(50-60) Years	12	38.7
		Above 60	6	19.4
		Total	31	100.0
Group-II	Valid	(30-40) Years	7	17.1
		(40-50) Years	12	29.3
		(50-60) Years	13	31.7
		Above 60	9	22.0
		Total	41	100.0

In both trials as well as the control group 50-60 years Age group 12 (38.7%) and 13 (31.7%) respectively, have higher incidence followed by age group 40-50 years 08 (25.8%) and 12 (29*.3%) respectively. Risk factors comprise family history, body mass index (BMI), smoking, tobacco chewing, and alcohol intake.

Analysis of Safety Parameters

Table 3: Effect on liver and kidney function tests in Group-I (n=31) and Group-II (n=41)

Name of Parameter	**Treatment Group Group-1**		**P-value**	**Control Group Group-2**		**P-value**
	Before Treatment	**After Treatment**		**Before Treatment**	**After Treatment**	
SGOT IU/l	20.88 ±4.69	22.58 ±6.60	0.182	22.74 ±6.10	23.39 ±6.23	0.595
SGPT IU/L	26.18 ±18.34	20.40 ±9.58	0.100	21.43 ±14.03	20.19 ±10.70	0.624
Alkaline Phosphatase IU/L	79.61 ±34.25	79.90 ±22.03	0.967	82.30 ±26.76	82.86 ±23.19	0.891
B. Ureamg%	22.28 ±8.67	19.22 ±8.60	0.038	19.30 ±8.72	19.03 ±9.82	0.844
Creatinine mg%	0.96 ±0.17	1.40 ±2.61	0.285	1.01 ±0.25	1.10 ±1.36	0.639
Uric Acid mg%	5.90 ±1.36	5.44 ±1.81	0.127	5.64 ±2.24	5.30 ±1.27	0.360

SGOT =serum glutamic oxaloacetic transaminase; SGPT =serum glutamic pyruvic transaminase; Alkaline Phosphatase (ALP)

Comparative effect of Unani coded drug UNIM-904 and amlodipine in the SGOT, SGPT, alkaline phosphatase, blood urea (BU), serum creatinine, and uric acid levels in hypertensive patients. Biochemical studies undertaken have indicated that there were no significant changes in liver function tests as well as kidney function tests. Therefore, it can be inferred that the test drug UNIM-904 did not induce any adverse reaction. Thus, the drug's safety has been complied upon.

Effect of UNIM 904 on Hemogram

Table 4: Comparative change in Hemogramin Group-I (n=31) and Group-II (n=41)

Name of Parameter	Treatment Group		P-value	Control Group		P-value
	Before Treatment	After Treatment		Before Treatment	After Treatment	
Haemoglobin (gm%)	13.25 2.69	13.17 1.66	0.849	13.30 1.55	13.20 1.58	0.595
RBC (10^6 /mm3	4.99 0.53	4.97 0.59	0.845	5.01 0.45	4.92 0.40	0.116
E.S.R. (mm /hr)	25.16 16.02	21.81 13.84	0.206	24.90 14.82	25.56 15.61	0.751
Platelet counts (lac/ mm3)	278.61 64.63	300.06 88.18	0.307	286.93 59.63	295.39 68.93	0.512

RBC= Red blood corpuscles, ESR= erythrocyte sedimentation rate

No significant changes in the level of haemoglobin, red blood corpuscles (RBC), total leucocyte count (TLC), platelets count, polymorphs, lymphocyte, eosinophils, and erythrocyte sedimentation rate (ESR) respectively had been observed in both UNIM-904 and amlodipine treated patients after 12 weeks

Assessment of the effect of UNIM 904 and Amlodipine on systolic and diastolic blood pressure.

Table 5: shows the effect of Blood Pressure in Group I (n=31) and Group II (n=41)

Group	Parameter	Baseline	After Treatment	P-value
UNIM-904	SBP n=31	162.34	144.52	0.000
Amlodipine	SBP n=41	162.95	149.71	0.000
UNIM-904	DBP n=31	97.41	88.65	0.000
Amlodipine	DBP n=41	96.39	88.37	0.000

SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure

Effect on systolic blood pressure

A significant reduction of diastolic blood pressure after the 12th week of treatment of test drug UNIM-904 144.52 versus162.34 (P<0.000) had been observed and these were compared with the values of baseline and follow-up treatment

Effect on diastolic blood pressure

A significant reduction of diastolic blood pressure after the 12th week of treatment of test drug UNIM-904 88.65 versus97.41 (P<0.000) had been observed and these were compared with the values of baseline and follow-up treatment

Objective parameters

Effect on lipid and electrolyte profiles

Table 6: shows the Effect on lipid and electrolyte profiles in Group I (n=31) and Group II (n=41)

Name of Parameter	Treatment Group Group-I (n=31)		P-value	Control Group Group II (n=41)		P-value
	Before Treatment	After Treatment		Before Treatment	After Treatment	
T. Cholesterol	198.87 ±25.69	169.94 ±26.79	0.000	188.25 ±34.16	168.01 ±24.80	0.000
HDL-Cholesterol	44.29 ±6.58	47.97 ±7.79	0.019	43.14 ±7.67	49.90 ±9.17	0.000
Calcium	8.52 ±1.20	9.35 ±0.55	0.000	8.37 ±1.33	9.35 ±0.55	0.000
S. potassium	4.45 ±1.12	4.91 ±0.62	0.001	4.40 ±1.01	4.85 ±0.73	0.000

A significant reduction in mean serum Total cholesterol by 169.94 versus 198.87 in the treatment group and from 168.01 versus 188.01in the control group, serum HDL cholesterol was raised by 47.97 versus 44.29 in the treatment group and by 49.90 versus 43.14 in the control group, Serum Calcium was raised by 9.35 versus 8.52 in the treatment group and by 9.35 versus 8.37 in the control group, serum potassium was raised by 4.91 versus 4.45 in the treatment group and by 4.85 versus 4.40 in the control group respectively after 12 weeks of treatment.

The outcome of this study supports that UNIM-904 is a safe and effective formulation in reducing Total Cholesterol, HDL cholesterol, Serum Potassium and raising the Serum Calcium levels significantly from baseline and after 84 days of treatment. UNIM-904 did not show any adverse effects during the study. No issue of non-adherence and intolerance in the participants of the two groups was observed.

This study had certain limitations. The sample size was not very large. It had strict inclusion criteria and did not include co-morbid cases. The duration of the treatment was not long. There was no diet and lifestyle modification as part of the therapy. This study was designed to have minimum bias. Selection bias was minimized by random allocation of the participants and concealment of the computer-generated sequence of allocation of the participants. This study was an open-label study. Because masking (blinding) was not possible due to the different physical features of the test and control drugs.

Conclusion

Hypertension burdens the community with early mortality and disability. Moreover, its expensive treatment along with the side effects of drugs compels people to be irregular with their prescriptions. Hence, alternatives to cope with this problem are required. Unani system of medicine provides a full regimen for the control and prevention of hypertension. Each regimen of the Unani system of medicine has its benevolent effects. The present study concludes that Unani coded drug UNIM 904 is effective and safe in hypertensive patients as compared to the allopathic drug amlodipine. We, therefore, recommend this drug for further investigations on a larger group of patients to develop a viable herbal drug of choice to combat hypertension, a disease thus far, eluding a satisfactory cure in modern medicine.

Ethical Clearance: The study was approved by the RRIUM's institutional ethics committee, f.noRRIUM/MUM/2012-13/IEC/25**.**

Conflict of Interest: There are no conflicts of interest

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