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A RANDOMIZED STUDY ON CLINICAL EFFICACY OF RESVERATROL IN MANAGING THE SYMPTOMS OF HYPERTENSION

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ABSTRACT

Hypertension, also called as high blood pressure, is long standing in which the pressure of blood in the arteries is repeatedly increased. High BP generally will not cause indications. Longstanding high BP, however, is an important risk factor for coronary artery disease, heart failure, peripheral vascular disease, stroke, vision loss, and CKD. The aim of this trail is to assess the efficiency of resveratrol in managing blood pressure in sufferers diagnosed with prehypertension and stage 1 HTN. The primary objectives of this study are to assess the BP-lowering action of resveratrol on SBP, DBP, and mean arterial BP in subjects diagnosed with prehypertension and stage 1 HTN. The study was conducted at the Prime Hospital Hyderabad, Prehypertensive (the mean of two measurements in a 15-minute interval; diastolic and systolic BP, 80-89 mmHg and 120-139 mmHg) and stage-1 hypertensive (the average of 2 measurements in a 15-minute interval; DBP and SBP, 90-99 mmHg and 140-159 mmHg, respectively) males or females, aged between 20 and 60 years will be enrolled for the trial. The sufferers for this trail will be allotted through health care provider referral at the clinic and take their voluntary consent. HTN is a condition that needs long-standing medicine in take. Because the study period is only 6 months, longer-term studies need to be directed to assess the efficiency of resveratrol as a sustained therapy option. In this trail, subjects took daily a single, higher dose of resveratrol, which will be taken BD throughout the trail (a high dose that is well tolerated).

Key Words: Hypertension, peripheral vascular disease, Resveratrol.

1. INTRODUCTION

Hypertension also called as high blood pressure, is longstanding in which the pressure of blood in the arteries is repeatedly increased. High BP generally will not cause indications. Longstanding high BP, however, is an important risk factor for coronary artery disease, heart failure, peripheral vascular disease, stroke, vision loss, and CKD. High BP is categorized into either primary



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(essential) high blood pressure or secondary high blood pressure. About 90-95% of cases are primary, defined as high blood pressure due to unspecific way of life and hereditary factors. A lifestyle element that elevates the risk involves excessive salt, excessive body weight, smoking, and alcohol. The other 5-10% of cases are classified as secondary elevated BP, defined as high BP due to an identifiable cause, such as CKD, kidney arteries narrowing, an endocrine disease, use of pills for birth control.

BP is communicated by 2 measurements, the systolic BP and diastolic BP, which are the maximum and minimum BPs. Normal BP at rest is within the level of 100-140 (mmHg) SBP and 60-90 mmHg DBP.¹ If the resting BP is repeated at or >140/90 mmHg for most adults it is High BP.² Different numbers apply to children.³ Ambulatory BP observing over a 24-hour period arrives more exact than office best BP measurement.⁴

Lifestyle alters and medicines can decline BP and elevate the risk of health difficulties.⁵ Lifestyle alters involves weight loss, reduced salt intake, physical exercise and healthy diet.⁶ If lifestyle alters are not adequate then BP medicine. Up to three medicines can control BP in 90% of population. The therapy of moderately high arterial BP (defined as >160/100 mmHg) with medicines is correlated with an upgraded life expectancy.⁷ The effect of therapy of BP b/w 140/90 mmHg and 160/100 mmHg is less clear, with some reviews finding benefit⁸ and others results a lack of proof for profit.⁹ High BP affects b/w 16 and 37% of the people globally.¹⁰ In 2010 HTN was trusted to have been a factor in 18% (9.4 million) deaths.

High BP is a usual state in which the long-standing force of the blood in artery walls flow reversely is high enough that it may finally cause health hazards, such as CHDs.

BP is determined both by the amount of blood in heart pumps and the amount of opposite to blood flow in arteries. Pumps more blood in the arteries and narrows heart, the elevated BP. We can have high BP (hypertension) for years without any indications. Even without indications, harm to blood vessels and heart continues and can be detected. Uncontrolled high BP elevates risk of serious health problems, involving heart attack and stroke.

High BP usually develops over many years, and it affects nearly everyone. Fortunately, high BP can be easily

noticed. And once if we know that we have high BP, you can follow your doctor to control it¹¹.

The aim of this trail is to assess the efficiency of resveratrol in managing blood pressure in sufferers diagnosed with prehypertension and stage 1 HTN¹².

2. EXPERIMENTAL SECTION

MATERIALS:

Design Overview and Ethics Approval:

This trail is a single-center trial with an allocation ratio of 1:1. The members, doctors, PIs and physician and statistical consultant will be blinded to the distribution status. The records of allocations will be kept confidential by practice consultant and will be revealed only after blinded statistical analyses or by request from Data and Safety Advisory Board. The trail is approved by the regional research ethics committee.

Study Settings, Population, and Recruitment

The trail was conducted at the Prime Hospital Hyderabad, Prehypertensive (the average of two readings in a 15-minute gap; diastolic and systolic BP, 80–89 mmHg and 120–139 mmHg, correspondingly) and stage-1 hypertensive (the average of two readings in a 15-minute gap; diastolic and systolic BP, 90–99 mmHg and 140–159 mmHg, correspondingly) males or females, aged among 20 and 60 yrs will be registered for the trial. The sufferers for this trail will be enrolled through physician appointment at the clinic and randomized to the therapy arm after the initial screening and with their volunteer consent.

General objective

The objective of this study is to regulate whether resveratrol (99 % pure) therapy for 4 weeks will reduce BP in prehypertensive and stage 1-HTN sufferers.

Primary objectives

The primary objectives of this trail to regulate the BP-reducing effects of resveratrol on systolic, diastolic, and mean arterial BP in participants analyzed with prehypertension and stage 1 HTN.

B. Secondary objectives

The secondary objectives are as follows:

1. To regulate if therapy with resveratrol reduces levels of renin, angiotensin II, endothelin, norepinephrine, tumor necrosis factor- α (TNF- α), and oxidative stress markers and elevates the range of nitric oxide in prehypertensive and stage 1-HTN sufferers.
2. To regulate the effects of resveratrol on hematologic indices in participants with prehypertension and stage 1 HTN.
3. To regulate the effects of resveratrol on lipid profile in these sufferers.
4. To regulate the effects of resveratrol on liver function markers in sufferers with prehypertension and stage 1 HTN.
5. To regulate the effects of resveratrol on renal function markers in sufferers with prehypertension and stage 1 HTN.

Specific procedures

Serum renin, angiotensin II, endothelin, norepinephrine, and TNF- α will be calculated by ELISA kits. Nitric oxide (NO), malondialdehyde and urinary isoprostanes will be calculated by ELISA Kits, spectrophotometry, gas chromatography/mass spectrometry, correspondingly [15]. Hematocrit (HCT) and platelet (PLT) will be expected using a hematology cell counter. Prothrombin time and partial thromboplastin time will be calculated using a blood coagulometer. Examines for biochemical factors, involving fasting blood glucose, will be carried out using a Selectra 2 autoanalyzer [16]. Serum total cholesterol and high-density lipoprotein cholesterol (HDL) will be expected using cholesterol oxidase phenol amino antipyrine enzymatic method and triglyceride (TG) using the glycerol-3-phosphate oxidase phenol amino antipyrine enzymatic method [16]. Serum low-density lipoprotein (LDL) cholesterol will be measured using the Friedewald formula [17]. Creatinine and blood urea nitrogen ranges will be expected using enzymatic method. In order to measure liver function in the sufferers, alkaline phosphatase (ALP), gamma-glutamyl transferase, bilirubin and albumin will be calculated by enzyme kinetic procedures on a Selectra 2

autoanalyzer.

Eligibility criteria

Inclusion criteria are as follows:

- Prehypertensive (mean of two calculations in a 15-minute interval; diastolic and systolic BP, 80–89 mmHg and 120–139 mmHg, correspondingly)
- Stage 1 hypertensive (mean of two calculations in a 15 minute interval; diastolic and systolic BP, 90–99 mmHg and 140–159 mmHg, respectively)
- Male or female
- Age between 20 and 60 years Ability to provide informed consent

Exclusions are as follows:

- Approved or doubtful secondary hypertension
- H/o chronic or acute kidney illness
- H/o heart failure
- H/o chronic or acute liver illnesses
- H/o diabetes mellitus
- H/o prior cardiovascular actions (acute myocardial infarction, cardiovascular illnesses, percutaneous coronary angioplasty or coronary artery bypass graft)
- Pregnancy or breast feeding
- Blood arterial pressure >180/110
- H/o bowel illness of any etiology that may affect absorption/or distribution of any drug administered orally
- H/o electrolyte imbalance during 3 months prior to the registration
- H/o alcohol abuse 4 weeks prior to the acceptance Needful a major surgical process (abdominal, thoracic, neurovascular, urological, or gynecological) during the course of the trail
- Feeding of steroid hormones or nonsteroidal anti-inflammatory drugs 1 month prior to the registration
- H/o hormonal variations (thyroid and adrenal)
- Receiving lipid-lowering drugs
- H/o bleeding illnesses
- Receiving blood thinners
- Regular intake of omega-3 fatty acid, vitamins, and mineral supplements

- Intention of having high intake of table salt or salty foods

Informed Consent

The sufferers will be informed about the trial by their consultant during clinic visit. Interested persons will contact the trail coordinator by phone/email. Interested persons will be requested to attend a first trail visit by the concerned clinicians on a specified day, when a pre-screening will be conducted to exclude members based on the inclusion/exclusion criteria. If members show up with irregular values for laboratory examinations during pre-screening, the tests will be frequent. If examinations show alike outcomes (abnormal values) the members will be excluded from the trails. If the criteria are met, trail coordinator will go through the consent form planned in local language. Finally, clinical study particulars will be outlined and the members will be given an opportunity to ask any questions/concerns. If they agree to the trail, registration will be finished. Members will be registered only with their voluntary informed consent (Appendix 1).

A prospective, randomized, parallel, open-label, comparative, active-controlled clinical trial was performed at the single trail center in India. From November 2016 to July 2017, 60 sufferers of either sex of 20-65 years who had stage I HTN (systolic BP [SBP] 140-159 mmHg and diastolic BP [DBP] 90-99 mmHg), and stable on telmisartan 20 mg single drug therapy were enrolled. Pregnant women, lactating mothers, H/o severe heart illness, hepatic illness and renal dysfunction, eager to use other antioxidant supplementation rather than resveratrol, grapes allergy, the sufferer was receiving drug which affect BP, and regular alcoholics were omitted from this trail. During the screening visit on the day, medical history was obtained; physical test and laboratory surveys were achieved. Medicines considered essential for the sufferer and which does not relate with the trail medicine were allowed. All sufferers were explained the process clearly and written informed consent from each member was obtained before their involvement in the trail. The protocol was accepted by Care, Health and welfare Ethics Committee, registered under Drug controller general of India (Reg No: ECR/632/Inst/MH/2014). The trail was performed in compliance with the Ethical principles of

Declaration of Helsinki; Good Clinical Practices rules issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India; Ethical rules for biomedical research on human members, Indian Council of Medical Research, New Delhi; and International conference on harmonization of technical necessities for registration of pharmaceuticals for human use - standard for good clinical practices. The study was registered with Clinical Trial Registry-India before initiation of the trail. Enrolled sufferers were randomized in 1:1 in 2 groups as per the computer made sheet. The sufferers randomized in the interventional group (test group) were accepted telmisartan 20 mg once daily along with oral resveratrol 500 mg twice a day (a total of 1 g/daily). The sufferers randomized to control group were accepted only telmisartan 20 mg once daily. The therapy period was 12 months for both the groups. Agreement to trail medications was evaluated using pill count method at each valuation visit after dispensing study medication to sufferers. Both systolic and DBP was evaluated twice with 2 minutes apart after a 5-minutes rest in the sitting station, using an auscultator method of calculation with a correctly calibrated and validated mercury sphygmomanometer. Two calculations were made 2 minutes apart. SBP is the point at which the first of two or more sounds is heard (phase 1), and DBP is the point before the evaporation of sounds (phase 5). The mean of the two recordings was taken for examination. Heart rate was measured for 1 minute in the 2-minute interval between BP measurements. Body temperature was calculated by thermometer. BP (SBP and DBP) and heart rate were calculated at starting point (before the beginning of study therapy), end of 2, 4 and 6 months in both the therapy groups.

Statistical analysis:

Based on a power of 80% and a type I error rate of $\alpha = 0.05$ (two-tailed), a sample size of at least 30 sufferers per group was essential to detect a clinically significant difference of 08 mmHg in the change in BP (with standard deviation [SD] of 10.26 [12]) among both groups. Considering dropout rate of 15%, total sample size will be approx. 60 sufferers (30 sufferers in each group). Categorical data were obtainable as absolute number/% of sufferers while quantitative data were presented as mean \pm

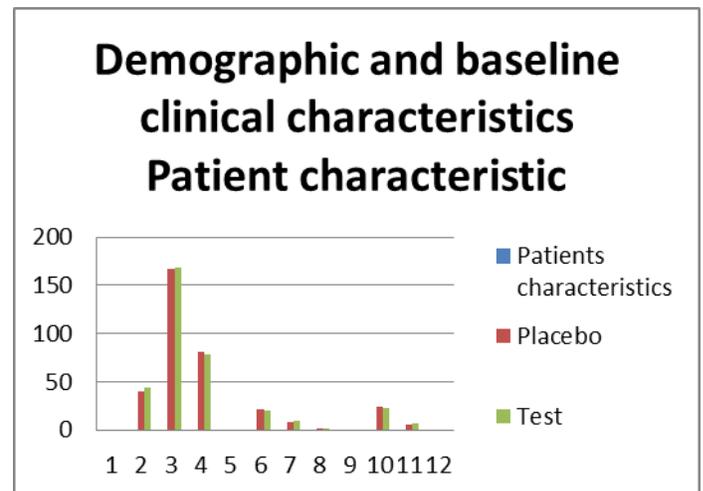
SD. Depending on the distribution of data appropriate parametric or non-parametric test was used to find p value. Unpaired “t”/Man-Whitney test was used to analyze the quantitative data for between group judgments. Within-group assessment was performed using paired t-test or Wilcoxon test for quantitative data founded on the distribution of data. Lost data were handled using Mean replacement or Last observation carried forward method. Chi-square test/fisher exact test was used to relate the categorical or qualitative data of both the therapy groups. Normality tests (KS and SW test) were used to detect supply of data for numerical data.

3. RESULTS AND DISCUSSIONS

There was no sufferer dropout from each group during the trial period. At the end of the trail, totally 30 sufferers in each group (control and intervention group) finished the trail and subjected to statistical examination. A consort diagram is offered showing the flow of contributors through the trail. Demographic and clinical characteristic of sufferers of both the therapy groups were similar (Table 1). At the starting point, there was no notable alteration between both groups regarding age, body weight, gender, duration of illness and smoking, systolic and DBP. The occurrence of HTN in the family was also similar in both the therapy groups (Table 1). Before the start of trail drug therapy (at baseline), SBP and DBP were comparable in both the therapy group. There was gradual decrease in blood SBP and DBP over a period of 12 months hrs in both the therapy groups as practical from the decrease trend in the SBP and DBP from baseline (Table 2). In both the therapy groups, decrease in SBP and DBP was statistically notable when related to starting point (within group comparison). Between-groups assessment showed that decrease in SBP and DBP was significant superior in test group at 2,4 and 6 months when related to control (In this prospective, randomized, parallel, open-label, comparative, active controlled, single center clinical trial, resveratrol as adjuvant therapy significantly reduction SBP and DBP in sufferers with HTN.

Table 1: Demographic and baseline clinical characteristics Patient characteristic

Patients characteristics	Placebo	Test	P value
Demography			
Gender(male/female)	19/11	17/13	0.07
Age	41.7±5.6	41.0±5.3	0.06
Height	142.1±3.4	169.9±2.0	0.07
Weight	75.6±2.8	69.5±3.12	1.02
Smoking			
Yes	17	16	0.05
No	13	14	
Duration of disease	2.4±0.6	1.9±0.4	0.1
Family history of hypertension			
Yes	22	23	0.13
No	8	7	-



Graph-1: Demographic and Baseline Clinical Characteristics Patient Characteristic

Resveratrol as adjuvant therapy having acceptable safety profile and the most common adverse event is a gastrointestinal disturbance. Our study suggested that the addition of resveratrol to gold standard therapy of anti-hypertensive class of drug and significantly improve the efficacy of gold standard treatment due to synergistic action.

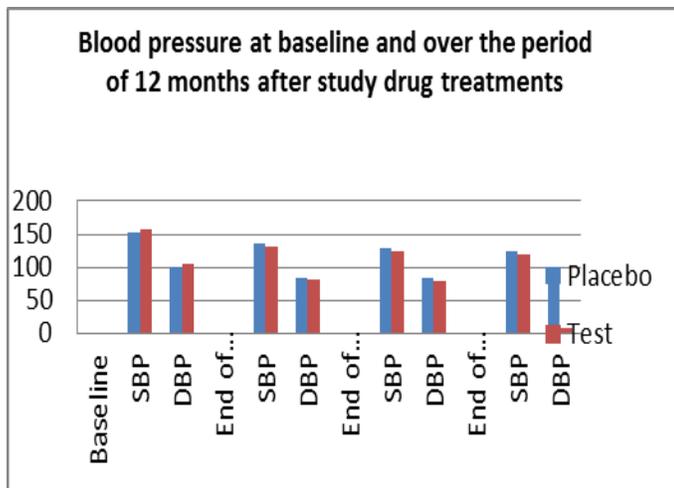
Table 2: Blood pressure (mmHg) at baseline and over the period of 12 months after study drug treatments

Parameters	Placebo	Test	P value
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Baseline			
SBP	162.7±6.3	159.0±6.14	0.1
DBP	112.3±5.5	100.3±4.09	0.08
End of the treatment 2 months			
SBP	117.0±4.1	131.0±5.48	0.02
DBP	78.1±4.8	81.0±3.80	0.03
End of the treatment 4 months			
SBP	115.7±5.3	113.7±3.5	0.01
DBP	78.7±5.3	76.0±3.5	0.04
End of the treatment 6 months			
SBP	110.7±3.8	108.3±2.0	0.01
DBP	73.7±3.5	72.03±2.1	0.01

DBP	-11.6±5.2	-14.2±5.6	0.03
End of the treatment 4 months			
SBP	-19.6±8.3	21.3±8.6	0.01
DBP	-11.3±4.3	12.5±5.2	0.04
End of the treatment 6 months			
SBP	-23.0± 6.3	-25.6±6.9	0.01
DBP	-12.0±4.3	-14.6±5.2	0.01

The potential effect of resveratrol in the management of hypertension has been established in pre-clinical setting. In rodent model, resveratrol was effective in preventing obesity and oxidative stress and reducing the risk of hypertension and dyslipidemia in adult rats¹³. Resveratrol stops monocrotaline-induced pulmonary HTN in rats. Resveratrol apply antioxidant, anti-inflammatory, and antiproliferative actions in the arteries of lungs, which may prevent pulmonary hypertension¹⁴. Prolonged resveratrol ingestion decreases metabolic disturbances and decreases BP in obese rats¹⁵. Chronic resveratrol increases endothelium-dependent distraction in aorta of immediate hypertensive rats¹⁶. Resveratrol has a preventive effect on HTN-induced cardiac hypertrophy in rats¹⁷. Moreover, our study results were also consistent with the previous clinical reports, short-term clinical use of resveratrol 1 g/daily (500 mg BD) was found to be effective in decreasing BP when compared to Placebo after 45 days¹⁸. Another 4 week clinical study (in 10 Fig. 1: Flow of participants through the study Table 2: Blood pressure (mmHg) at baseline and over the period of 12 months after study drug treatments Parameters Control (n=30) Test (n=30) p Baseline SBP 151.7±8.3 156.0±8.14 >0.05 DBP 100.3±8.5 104.3±6.79 >0.05 End of 3 months SBP 135.0±5.1* 131.0±5.48*



Graph-2: Blood pressure at baseline and over the period of 12 months after study drug treatments

Table 3: Change in BP from Baseline to End of 2, 4 And 6 Months

Parameters	Placebo	Test	P value
End of the treatment 2 months			
SBP	-12.4±7.2	-13.0±7.9	0.02

The increasing need for alternative strategies for controlling hypertension can be addressed by identifying promising nutraceutical candidates. In this view, resveratrol has indicated good potential in eradicating or reversing CVD involving HTN in preclinical trails. New meta-analyses¹⁹ that surveyed successful clinical studies²⁰ finalized that resveratrol may be marked as an additional therapeutic person for treating type 2 diabetes. In light of these challenging clinical results and previously

documented preclinical proofs, resveratrol seems to be a potential antihypertensive product. The efficiency of resveratrol has to be clinically assessed in sufferers with HTN. This trial will be the first trail to assess the potential of treatment use of resveratrol for the treating of BP in sufferers with prehypertension and type 1 HTN. The results from this trail will help to assess the efficiency of short-term resveratrol therapy in hypertensive sufferers and bridge the gap with views to the present preclinical and clinical proof. This trail will also help in gathering further data with view to identifying a therapeutically good dose of resveratrol in gathering CVD risk factors. Importantly²¹⁻²³, if a positive result is identified, it will provide us with an effective therapeutic strategy to combat HTN and would pave the way for achieving enormous public health profit²⁴.

4. CONCLUSION

A sensitive & selective RP-HPLC method has been developed & validated for the analysis of Decitabine API. Further the proposed RP-HPLC method has proved for the excellent precision and reproducibility. The results shows the developed method is yet another suitable & stability which can help in the analysis of Decitabine in different formulations.

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