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Original Article

Vasoclear in the Remedial of Cardio Vascular Problems by Natural Means: An Open Label Study

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ABSTRACT

Aim: The present work is to evaluate the safety, efficacy and tolerability of Vasoclear, a uniquely blended syrup from the extracts of Arjuna, Garlic, Ginger, Grape seed, Citrus, Ashwagandha, in patients with cardio vascular problems. **Method:** A total of 66 patients were screened, 41 of them who met all the inclusion criteria and did not meet any of the exclusion criteria were enrolled and out of which 40 completed the study. This was an open label, two centered trial wherein eligible patients were enrolled post consenting to participate in the study on an institutional ethics committee approved informed consent form. Patients were instructed to administer orally 3 to 4 table spoons of Vasoclear in empty stomach daily, half an hour before going to bed for 6 consecutive weeks. Patient blood samples were collected on baseline and after week 6 for assessment of LDL, HDL and total cholesterol levels. Together with blood pressure lowering, Vasoclear's cardio vascular effect was evaluated. Safety and tolerability were assessed through the vitals, adverse effects and Investigator and patient global improvement scales. **Results:** Vasoclear demonstrated statistically significant change ($p<0.01$) in the TGs, LDL, HDL and blood pressure on week 6 (visit 8) when compared to their respective visit 1 values. It showed no changes in other vitalsand Adverse Events, and proved to be completely safe and tolerable when administered orally. **Conclusion:** Vasoclear syrup is found to be a trusted alternate to the allopathic drugs with very good patient compliance in decreasing the elevated cholesterol and blood pressure, clinically proving it asa remedy for cardio vascular problems by natural means.

KEYWORDS: Vasoclear; cholesterol; safety; tolerability; efficacy.

1. INTRODUCTION

Terminalia arjuna: Found commonly in the Himalayan region, the bark of the plant is used by traditional Indian medicine for a number of herbal preparations to treat cardiac disorders. *Terminalia arjuna* is a miracle herb which was used during ancient times to cure heart problems. In ancient

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Ayurvedic literature, Vaghbata and others have described the juice of Arjuna bark as a tonic and astringent. They have recommended it for the treatment of heart diseases. Arjuna is reported to be a beneficial herb in treating heart problems since 1200 B.C. Vaghbata was the first to cite this in his book AstangHridayam' written
some 1200 years ago.[1] Subsequently, Chakradutta and also Bhawa Mishra, described its use in chest pain. [2, 3] However, papers concluded that clinical trials should be conducted to support its therapeutic value.[4,5]

Garlic (*Allium sativum*): Since ancient era of 1550 BC, garlic has been used as a medicinal product and an important dietary component of food enhancing flavor and taste. Garlic is a herb with complex action Daily intake of garlic is useful in fat metabolism and lowering of blood cholesterol levels. Garlic increases high-density lipoprotein (HDL) (good cholesterol), which protects heart and blood vessels, and lowers Low-density lipoprotein (LDL) (bad cholesterol) along with triglycerides (TGs).[6]

Ginger (*Zingiber officinale*): It is a natural dietary component, which has hypolipidemic, antiplatelet aggregation, antioxidant and anticarcinogenic properties.[7] Results of a study with ginger demonstrated lower plasma lipids and body weight significantly, eventually preventing development of coronary artery disease in primary and secondary hyperlipidemic patients.[8]

Grape seed: Phenolic compounds in the extract of grape seeds exhibit antioxidant properties and reduce the concentration of Ox-LDL in plasma. These extracts have also been shown to activate endothelial nitric oxide synthase (eNOS) [9-11], up-regulate eNOS in cultured endothelial cells, and cause an endothelium-dependent relaxation (EDR) of blood vessels.[11] This could be potential source for decreasing the elevated systemic blood pressure.

Citrus sinensis:As gary et al concluded that a single blind randomized trial on 22 healthy subjects when consumed *citrus sinensis* juice for a 4 week period decreased blood pressure significantly.[12] Similarly, Guangning Kou et al concluded that a meta-analysis on 282 participants showed that in taking the citric fruites can reduce the TC and the LDL-C and the effect. [13]

Ashwagandha (*Rauwolfia serpentina*): The derived alkaloids have a direct effect on hypertension and are widely used in preparation of medicine. According to the data, root powder of *R. serpentina* has hypotriglyceridemic and hypocholesterolemic effects with undetectable side effects on liver and cardiac functions.[14]

2. METHODS

Objective and Rationale: In view of existing data and literature on these ayurvedic herbal extracts in the treatment of cardiac diseases, essentially elevated hypertension and cholesterol levels, no clinical data exists on a single formula like vasoclear which is a combination of aforesaid six herbal extracts. Therefore, the present study was initiated to evaluate the safety, tolerability and efficacy of vasoclear in patients with a history of hypertension and hypercholesterolemia.

Ethics: The study was conducted in two institutes, Dr. B R Ambedkar Medical College Hospital, Bangalore and Rathna Ayurveda Hospital, Chittoor. The two institutional Ethics Committees provided favorable opinion in writing for the conduct of this study in respective clinical sites. No further changes or amendments were made to the approved protocol and was executed in its complete form. This study was conducted in accordance with the clinical research guidelines established by the Drugs and Cosmetics Act, 1940 of India, Drugs and Cosmetics Rules, 1945 of India, Ethical Guidelines for Biomedical Research on Human Participants, 2006 of Indian Council of Medical Research (ICMR) in India, the principles enunciated in the Declaration of Helsinki (Edinburgh, 2000) and the ICH harmonized tripartite guideline regarding Good Clinical Practice (GCP).

Subject Information and Consent: Written and oral information about the study in a language understandable by the subject was provided to all subjects. Each subject was informed by the investigator, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and documented the informed consent process in the subject's chart. Ample time was provided for each subject to decide whether to participate in the study and all the questions and clarifications regarding the study were clarified by the investigator.

Study Design and Selection of Study Subjects: This was an open label study design; subjects who met all of the inclusion criteria and did not meet all of the exclusion criteria were included in the study. Inclusion Criteria: 1. Male and female outpatients between 18-75 Years of age, 2. Patients having i. LDL cholesterol>130mg/dl, 3. Serum triglycerides > or equal to 150mg/dl and < or equal to 500mg/dl, 4. Serum creatinine of <3.0mg/dl, 5. Willingness and able to give informed consent and comply with requirements for participation in the study. Exclusion criteria: 1. Subject who is pregnant or Lactating, 2. Any of the following is regarded as a criterion for exclusion from the study: (a). History of serious adverse effect or hypersensitivity reactions to the medication used in the treatment. (b) Pregnant women and breast feeding (c). History of malignancy (d). Active liver disease or hepatic dysfunction as defined by elevations of AST or ALT greater than1.5times ULN. (e). Uncontrolled serum CK greater than3 times ULN (f) Serum creatinine greater than 2.5mg/dl (g). Participation in another investigational drug trial within the previous 4 weeks. A total of 66 patients were screened, 41 of them who met all the inclusion criteria and did not meet any of the exclusion criteria were enrolled and out of which 40 completed the study. The first patient was enrolled on 20 Jun 2017 and the last patient completed the study 29 Sep 2017.

Methodology and Study Procedures: Patient who fulfilled the eligibility criteria was included into the study, and were advised to administer the study medication (Vasoclear) orally 3 to 4 table spoons of in empty stomach daily, half an hour before going to bed for 6 consecutive weeks. Subjects were called for follow up every week. Safety and tolerability were assessed through the adverse effects as mentioned by the patient and evaluated by the investigator. Tolerability was assessed by the investigator based on a 4-point scale on baseline visit and at every subsequent visit as follows: Excellent = No adverse event reported; Good = Mild adverse event(s) reported which subsided with or without medication and did not necessitate stoppage of study medication; Fair = Moderate to severe adverse event(s) reported which subsided with or without medication and did not necessitate stoppage of study medication and Poor = Severe or serious adverse event(s), which necessitated stoppage of study medication. Efficacy was assessed through measurement of vitals having systolic and diastolic blood pressures at every visit, starting from screening to Week 6; cholesterol (TGs, LDL and HDL) values on screening and final visit (Week 6) and also through Investigator and Patient rated 4-point scale global improvement scales, wherein 1 is poor and 4 is excellent. Prohibited Interventions include topical treatment for diabetic foot ulcer other than study medication is allowed during the course of study. A protocol violation was defined as any change, deviation, or departure from the study design or procedures of protocol OR deviation from standard operating procedures, Good Clinical Practices (GCPs).Data was captured using case report forms (CRF). All the fields in the CRF were filled. Any missing fields were explained. All entries were legible and on the CRF of every subject, no information was provided that reveal the identity of the patient. Only the code numbers (screening numbers, patient ID) were written on the paper based CRF. Sequence of activities performed during every visit is illustrated in Table 1. The first patient was enrolled on 20 Jun 2017 and the last patient completed the study 29 Sep 2017.

Safety and efficacy outcomes:

The safety outcomes were abnormal vitals, adverse events and non-tolerability to the study investigational product. Efficacy outcomes were decrease in elevated blood pressure, TG, LDL and increase in HDL values when compared to their respective screening visit values. Also, ratings on global investigator and patient improvement scales were also considered as efficacy outcomes for subjective assessments.

Statistical Analysis:

Statistical comparisons were evaluated at the 5 % ($p<0.05$) significant level. Comparison of means between treatment groups was performed and Student's't' test was employed.

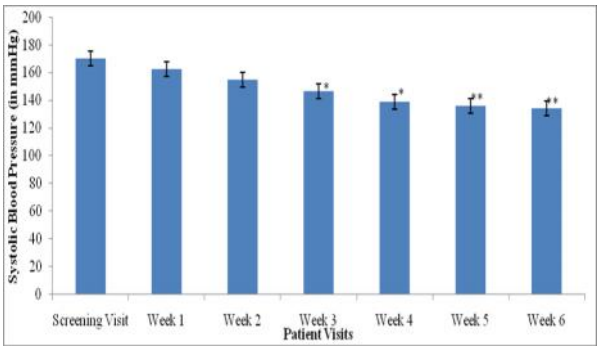

Fig 1: Change in systolic blood pressure levels from screening (visit 1) to last visit (visit 8), *p<0.05 & **p<0.01

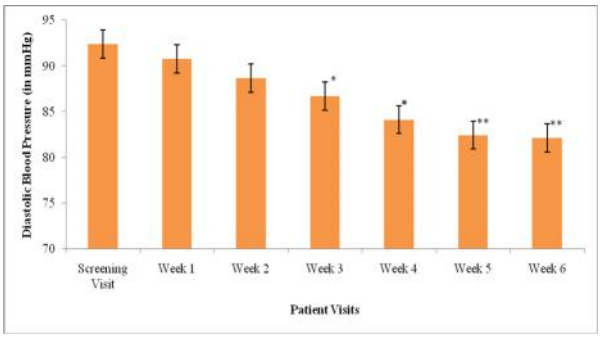

Fig 2: Change in diastolic blood pressure levels from screening (visit 1) to last visit (visit 8), *p<0.05 & **p<0.01

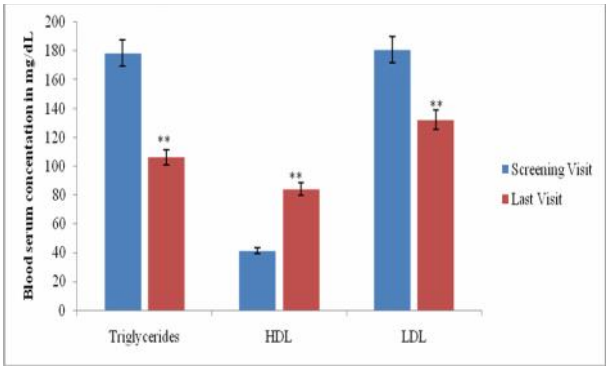

Fig 3: Change in serum biomarker levels from screening (visit 1) to last visit (visit 8), **p<0.01

3. RESULTS AND DISCUSSION

Almost similar number of male and female patients participated in the study, with female participants on a bit higher side. Average age, height and weight of the patients are depicted in Table 2. Approximately 35% of the enrolled subjects were smokers and 27.5% were alcoholics for atleast 3 years prior to participation of the study. Vital signs like temperature, pulse rate, heart rate, blood pressure were measured and recorded from screening till last visit, week 6. Combined with vital parameters, adverse events and tolerability, the product Vasoclear exhibited a very good safety profile with no adverse events and was found to be well tolerated (Table 3) by all the study subjects. No statistical significant changes observed in other vital parameters but the elevated blood pressures demonstrated through systolic and diastolic blood pressures on the

screening visit was found to have a decreasing trend from the first week itself. However, it reached statistical significance ($p<0.05$) from week 3 until week 6. From week 5 onwards the blood pressure remained consistent in the normal range amongst the study participants (Fig 1 and 2). The TGs, HDL and LDL final visit (week 6) values when compared to their respective screening visit (Fig. 3) were found to be statistically significant ($p<0.01$). Investigator and patients' global improvement scale measured on a 4 point scale was found to be encouraging (Table 4).Compliance with study supplement was reviewed at each visit by examination of the returned used bottles. All accountability records were incorporated into the investigator's study file. As the dosage regimen is syrup, the patient compliance was almost 98% (data not shown).

Well-performed, internally valid RCTs may not provide the evidence clinicians need to justify changing practice.[14] This is one of the reasons this study was not randomized controlled trial, also as Vasoclear is already a marketed product across India and in various other countries with proven therapeutic efficacy of individual component (herbal extracts), a placebo control trial was not targeted. Together with this small sample size with no power calculation was one of the limitations of this study. The percentage of individual herbal extract of Vasoclearis proprietary and confidential information of Rathna Biotek, hence they are not disclosed here. Nevertheless, the final product that was used for the trial has passed all the required QC, Quality Control, procedures. All the investigational products used in this study were from three different batches manufactured in a GMP compliant plant in India during the period of January to May 2017 with a shelf life of 2 years. The results indicate that there were no batch to batch variations and the product exhibited consistently good results throughout the clinical trial study duration. The results of overall investigator and patient global improvement, one of the subjective efficacy assessments, were overwhelming.

Table 1: Schedule of Observations

Activities	**Screening (Day -1)**	**Baseline (Day 0)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Eligibility criteria	X	X	-	-	-	-	-	-
Informed consent	X	-	-	-	-	-	-	-
Demographic data	X	-	-	-	-	-	-	-
Vital signs	X	X	X	X	X	X	X	X
Medical history	X	-	-	-	-	-	-	-
Medication history	X	-	-	-	-	-	-	-
Lab investigations	X	-	-	-	-	-	-	X
IP dispensing and reconciliation	-	X	X	X	X	X	X	
Investigator Global Improvement Scales	-	X	X	X	X	X	X	X
Patient Global Improvement Scales	-	X	X	X	X	X	X	X
Concomitant medications	-	X	X	X	X	X	X	X
Adverse events	-	X	X	X	X	X	X	

Table 2: Patient demographics on screening visit

Item	**Mean values**
Age (yrs)	66.26
Height (feet)	5.38
Weight (kgs)	72.3
Male	19
Female	21
Smoking (Yes)	14
Alcohol (Yes)	11

Table 3: Tolerability of the product at various study visits

Tolerability	**Points**
Baseline Visit	3.8
Week 1	3.7
Week 2	3.9
Week 3	4
Week 4	3.8
Week 5	3.6
Week 6	4

Score: 4 is excellent and 1 is poor. The product is well tolerated from beginning till end of the study.

Table 4: Global Improvement Scales

Visit/Week #	Baseline Visit	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Investigator Global Improvement Scale	1.8	2.7	3.2	3.6	3.9	3.9	4
Patient Global Improvement Scale	2	2.8	3.4	3.6	3.8	4	4

Score: 4 is excellent and 1 is poor.

4. CONCLUSION

Vasoclear syrup is found to be a trusted alternate to the allopathic drugs with very good patient compliance. This study has proved time and again the beneficial effects of Vasoclear in decreasing the elevated cholesterol and blood pressure, clinically proving it as a remedy for cardio vascular problems by natural means.

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Authors' contributions:

BG Reddy: contributed to the study concept, initiation, design and funding. Arunjothi: critical revision of the manuscript for important intellectual content. Jagadish: contributed to the study concept, analysis and interpretation of data, supervision, drafting of the manuscript. All authors approved the final version of the manuscript.

CTRI Number: Trial registered in Clinical Trial Registry India prospectively with registration number CTRI/2017/06/008818, prior to the first patient enrollment into the study.

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B. G Reddy is the Founder and Managing Director of Rathna Bioteck Private Limited; the remaining authors either full time employees of Rathna Bioteck Private Limited.