Research Article

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RANDOMIZED, SINGLE-BLIND, DOUBLE-ARM COMPARATIVE STUDY ON THE EFFECT OF ARJUNA (*TERMINALIA ARJUNA* ROXB) AND VITAMIN THERAPY (FOLIC ACID, B6, B12 IN COMBINATION) ON HOMOCYSTEINE

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ABSTRACT

Higher levels of homocysteine are strong indicators of susceptibility to CAD, PAD, myocardial infarction, stroke, metabolic disorders, nutritional deficiency, renal dysfunction and venous thromboembolism. All these disease conditions are studied under santarpana janya vyadhis in Ayurveda. Arjuna (*Terminalia arjuna* Roxb) has been indicated in text books of Ayurveda for Raktapitta, Arshas, Kushta, Prameha, Mutraghata and Vrana. It is also indicated in obesity, diseases of the urinary tract, cardiac disease and Kushta. Aim: Comparative study on the effect of Arjuna (*Terminalia arjuna*) and Vitamin therapy (Folic acid, B6, B12 in combination) in subjects with Homocysteine level >15 as a nutritional supplement. Methods: Randomized, single-blind, double-arm comparative study on Homocysteine levels more than 15 mm/lt are selected for IPD and OPD of SKAMCH&RC were administered 1 gm Arjuna tablets and vitamin tablets for three months, and Homocysteine levels were assessed before and after treatment. Results were evaluated by taking the difference between the baseline data and homocysteine level assessment data and analysed using the Students' paired t-test. Results indicate that Arjuna reduces homocysteine levels significantly and is comparable with Vitamin therapy.

Keywords: Homocysteine, Nutritional supplement, Santarpanajanya vyadhi

INTRODUCTION

Study reveals major incidence of mortality and morbidity throughout the world is due to coronary artery disease (CAD) and peripheral arterial diseases (PADs)[1]. It is observed that elevated Plasma homocysteine levels are a strong indicator of mortality in patients with CAD and PAD[2,3]. In elderly patients, elevated plasma homocysteine is correlated with an increased risk of myocardial infarction, stroke, metabolic disorders, nutritional deficiency, renal dysfunction and venous thromboembolism. All these disease conditions are studied under santarpana janya vyadhis[7] in Ayurveda. Homocysteine level is one of the independent risk factors for the severity of CAD and can have a higher impact on coronary artery bypass grafting (CABG), peripheral vascular surgery, and poor postoperative outcome[4].

Terminalia arjuna (Roxb), belonging to the family Combretaceae, is indicated in Bruhatrayees for Raktapitta, Arshas (Piles), Kushta (Skin diseases), Prameha, (Diabetes) Mutraghata and Vrana (wounds). It is also indicated in Obesity, urinary tract diseases, cardiac disease and skin diseases[5,6,8-11]. The primary objective of Ayurveda is the maintenance of health in healthy and the treatment of diseases. Hence, an alternate approach to use an Ayurvedic drug Arjuna (*Terminalia arjuna*) as a nutritional supplement in hrusiyasi matra (small dosage) [24], i.e., 1 gm /day as adjuvant therapy in subjects with Homocysteine level >15 for maintenance of health and prevention of disease.

Homocysteine, a sulfur-containing amino acid, is a key intermediate in methionine metabolism. It is produced as a byproduct of methyl transfer reactions, essential for synthesising nucleic acids, methylated proteins, neurotransmitters and phospholipids. Retrospective clinical trials (case-control and observational) and prospective studies done over 15 years indicate that elevated homocysteine level is pathophysiologically identified as an independent risk factor for myocardial infarction, stroke, renal diseases, nutritional deficiency, venous thromboembolism, skin diseases, Alzheimer's and Parkinson's[1-4].

The B complex vitamins are essential for Homocysteine metabolism as they are involved in both the transformation and excretion pathways of homocysteine[25]. Supplementation of B complex vitamins reduce total homocysteine levels. The modern medicine system advocates treating hyperhomocysteinemia with folic acid, vitamin B6 and vitamin B12[8].

Homocysteine is used in the body in one of two ways, as homocysteine is a crucial determinant of the methylation cycle [2]. In the case of methionine deficiency, homocysteine is remethylated to form methionine, and in the presence of sufficient methionine, homocysteine is used to produce cysteine [3]. Hyperhomocysteinemia is a medical condition characterized by abnormally high levels (above 15 micro /litre) of homocysteine in the blood [4]. The total concentration of homocysteine level in the plasma of healthy humans (fasting) is low, and its level is between 5.0 and 15 micromole/L when assessed with the use of HPLC / 5-12 micromole/litre when immune assay methods are used [5]. When the level is between 16-30 micromole/litre is classified as moderate, 31-100 micromole/litre is considered intermediate, and a value above 100 micromol/litre is classified as hyperhomocysteinemia [6]. There are two types of hyperhomocysteinemia. They are severing forms due to genetic mutation of the enzymes implicated in Homocysteine metabolism and moderately elevated homocysteine levels related to pathogenesis, such as genetic and environmental factors [1]. The

most common form of the genetic cause of severe hyperhomocysteinemia is classic homocystinuria (congenital homocystinuria), which is believed to be homozygous deficiency of cystathionine-beta-synthase which increases by up to 40-fold in fasting total homocysteine. Other rare causes of hyperhomocysteinemia are considered to be homozygous deficiency of MTHFR, deficiency of methionine synthase and impaired activity of methionine synthase due to genetic disorders of vitamin B12 metabolism [6]. Pathology of hyperhomocysteinemia arises from nutritional deficiency of folate, vitamin B6 and vitamin B12 [6,7]. In ageing-related disorders, elevated homocysteine level exerts a wide range of pathophysiological effects on multiple organs and are associated with several diseases, including cardiovascular disease, dementia, neural tubal defects and cancer through different mechanisms such as vascular dysfunction and increased vulnerability to metabolic syndrome [8]. According to the literature data, including systemic review and meta-analysis, patients with psoriasis have a significantly higher serum homocysteine level, promoting the immune-inflammatory process in the pathogenesis of psoriasis and contributing to psoriatic lesions. [9]

The concept of Agni and ama is as old as the fundamental principles of Ayurveda. Digestion and metabolism play a vital role in forming Rasadi sapta dhatus. Understanding the concept of Agni, a physiological process, and ama, a pathological process, plays a vital role in health and diseased conditions. Agni is basically having Tejo mahabhoota predominance and brings transformation of consumed ahara and aushadhi dravyas by helping in paka / chemical and energy transformation in the body. Agni is responsible for synthesising anabolic and catabolic activity in the body.

Arjuna is Hridaya (good for the heart) as its prabhava, indicated in visha (toxicity), kshtakshaya, urinary tract diseases, obesity, cardiac diseases and wound healing [5,6]. Hence, Arjuna is used in hrusiyasi (small) matra (dose)[24] as a nutritional supplement to evaluate the efficacy of Arjuna in increased levels of homocysteine in comparison with a combination of folic acid, vitamin B6 and vitamin B12 as a daily health supplement. Arjuna (*Terminalia arjuna*) is a drug of choice in treating cardiac ailments, as it has Hridaya property. Bark of Arjuna is used in this study[5,8-11].

Action and uses of Arjuna: The barks are astringent cooling, aphrodisiac, demulcent, cardiotonic, styptic, antidysenteric, urinary astringent, expectorant, lithotripsic and tonic. It is useful in fractures, ulcers, urethrorrhagia, spermatorrhea, leucorrhoea, diabetes, anaemia, cardiac disorders, excessive perspiration, fatigue, asthma, bronchitis, cough, consumption, intrinsic haemorrhages, tumour, otalgia, diarrhoea associated with blood, cirrhosis of liver and hypertension. The fruit is tonic and de-obstruent.

MATERIAL AND METHODS

Drug source

Hydroalcoholic extract of Arjuna (*Terminalia arjuna* Roxb) was purchased from the AYUSH-approved extract supplier in the ratio of 1 part of the extract to 10 parts of the crude drug. The standard drug for comparison as a daily health supplement was a vitamin tablet, a combination of 2.5 mg of folic acid, 50 mg of vitamin B6 and 1 mg of vitamin B12 as daily health supplement[12.]

Method of Preparation of Drug

Vitamin tablets, as standard drug for comparison, were procured from GMP certified manufacturing company with a combination of 2.5 mg of folic acid, 50 mg of vitamin B6 and 1 mg of vitamin B12 [12] coded as CT -VT (Group 1) and one tablet a day was given as daily nutritional supplement as standard for comparative study.

Hydroalcoholic extract of Arjuna was purchased from an approved AYUSH extract manufacturer and supplier, with an analytical study for its physical, chemical analysis, pesticidal residue, metallic contamination and microbial counts. Tablets are prepared from extracts equivalent to 1 gram of crude drug Arjuna and coded as CT – TA (Group 2); 1 tablet per day was administered to the patient for three months as a nutritional supplement as an adjuvant.

Screening method

A total number of 98 subjects who fulfilled the inclusion criteria were screened for the study. 59 subjects having homocysteine levels of more than 15 mml/l are selected for the study from the OPD and IPD of any department of teaching hospital Sri Kalabyraveshwara Swamy Ayurvedic Medical College Hospital and Research Centre, Bangalore, Karnataka, India. Out of 98 subjects screened, 39 were excluded as homocysteine level was below 17 mmol, and 9 subjects were dropouts from the study. The present study is based on data analysis of 50 subjects.

CTRI no: Ref/2019/10/028791. The study is carried out as per ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

Inclusion Criteria

a) Patients who are more than 21 years of either sex.
b) Patients with plasma homocysteine concentration above 15 mmol/L.
c) Patients with a known history of CAD, PAD, renal disease, skin diseases and any metabolic disorder.

Exclusion Criteria

a) Healthy volunteers
b) Terminally ill patients, pregnancy, metastatic cancer, end-stage liver disease.
c) Patients who are on methotrexate, folates, B1, B12, antifolate medications, anticonvulsants, unreliable or likely noncompliant participation

Objective Parameters

All subjects' Homocysteine levels were analysed at the time of enrolment to the study and at the end of three months, i.e., completion of the study. The blood sample was sent to an approved laboratory, and homocysteine levels of >15 mmol/L were taken as hyperhomocysteinemia.

Study design

Randomized single-blind double-arm clinical study
Out of 59 subjects enrolled, subjects were randomly assigned to CT-VT (Group 1) and CT-TA (Group 2) based on the lottery method. Subjects were explained regarding the study in English and Kannada, and the patients' informed consents were obtained before issuing the trial drug. Patients were asked to visit monthly to collect the medicine for three months.

Duration of study

Three months

Dose of the drug

1. CT-VT (Group1): 1 tablet per day was administered as a nutritional supplement to the patient for three months as an adjuvant at a specified time every day.
2. CT-TA (Group 2): 1 tablet per day was administered as a nutritional supplement to the patient for three months as an adjuvant at a specified time every day.

Statistics

The drug's efficacy was assessed by taking the difference between the baseline data and homocysteine level assessment data and analysed using the Students' paired t-test.

RESULTS

Randomized study subjects were administered a vitamin tablet (CT-VT) to Group 1 and *Terminalia arjuna* tablet (CT-TA) to Group 2 for 90 days, and blood samples were studied for homocysteine levels before and after the treatment. Student T test was done to assess the statistical value. The difference in the mean values was considered highly significant at $p<0.001$ and $p<0.01$, significant at $p<0.05$ and non-significant at $p>0.05$. (Table 1)

Reduction in homocysteine level before treatment to after the intervention is statistically not significant in the group treated with vitamin tablets ($p=0.078$). (Tables 2 and 3)

Homocysteine reduction before and after intervention is statistically significant in Group 2 ($P=0.005$). The randomized, single-blind, double-arm clinical study conducted on 50 patients indicates that the group treated with the Arjuna tablet had a significant reduction after treatment compared to before treatment. (Tables 4 and 5)

Comparison of Results between Group 1 and Group 2

Data from 50 patients between the groups shows no significant difference in homocysteine levels between the groups treated with vitamin tablets and Arjuna tablets before treatment; hence, randomization is correct. Analysis of homocysteine levels within the group after the treatment shows that there is statistically no significant difference in the group treated with vitamin tablets (Group 1). There is a substantial reduction in homocysteine levels before and after intervention in Group 2 ($P=0.005$), Indicating the efficacy of *Terminalia arjuna* tablets in reducing the homocysteine level. The reduction in homocysteine level when compared between the Group (Group 1 and Group 2) after intervention shows that the results are comparable. (Table 6)

Comparison of homocysteine levels between the groups before treatment is insignificant, with a p-value of 0.390, indicating proper randomization of the groups.

In comparing the results between the groups, homocysteine levels after treatment were insignificant, with a p-value of 0.095, indicating *Terminalia arjuna* is equally beneficial compared to the vitamin group.

BMI: Comparison of the BMI of the subjects between the groups is insignificant (P value 0.917), indicating that there were insignificant changes in the BMI of subjects treated with *Terminalia arjuna* and vitamin tablet, suggesting randomization of subjects for both groups. (Graph 5)

Table 1: Descriptive Statistics of Group 1 (treated with Vitamin tablets)

Mean	46.160
Std. Error of Mean	3.147
Std. Deviation	15.737
Range	56.000
Minimum	19.000
Maximum	75.000

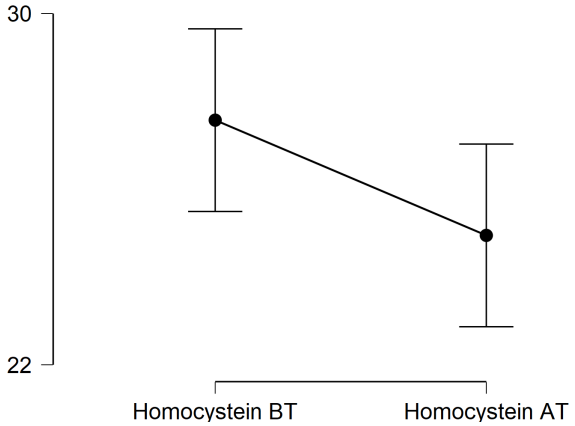
Table 2: Effect of treatment in Group 1 (treated with Vitamin tablet)

Paired sample t-test

Measure 1	Measure 2	t	df	p
Homocysteine BT	Homocysteine AT	1.841	24	0.078

Table 3: Mean Value within Group 1

Descriptive	N	Mean	SD	SE
Homocysteine BT	25	25.572	14.045	2.809
Homocysteine AT	25	24.947	13.353	2.671



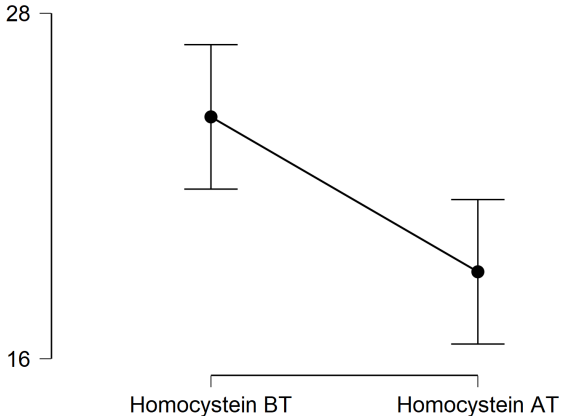
Graph 1: Effect of treatment on Homocysteine within Group 1(CT-VT)

Table 4: Effect of treatment on Homocysteine within Group 2 treated with Arjuna tablet (CT-TA)

Measure 1	Measure 2	t	df	P
Homocysteine BT	Homocysteine AT	3.130	24	0.005

Table 5: Mean value of treatment on Homocysteine within Group 2 (CT-TA)

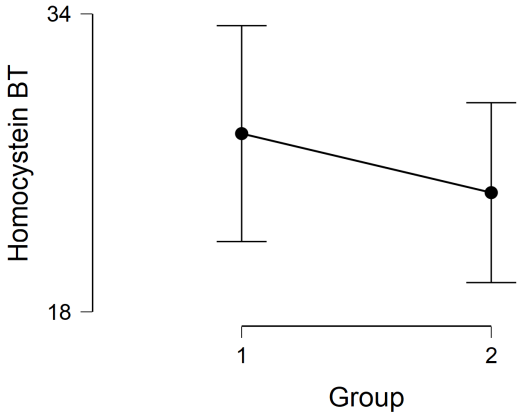
Descriptives	No	Mean	SD	SE
Homocysteine BT	25	24.401	11.701	2.340
Homocysteine AT	25	19.020	11.182	2.236



Graph 2: Effect of treatment in Group 2 (CT-TA)

Table 6: Effect of treatment on Homocysteine between the groups (Group 1 and Group 2)

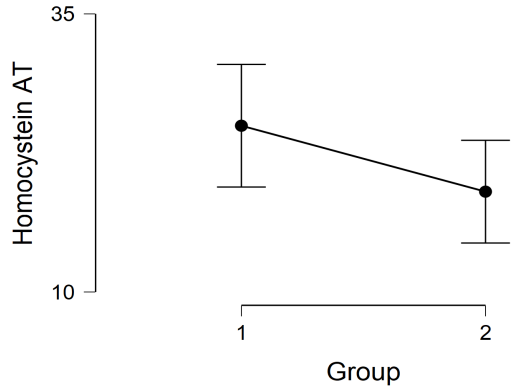
Group descriptive	Group	No	Mean	SD	SE
Homocysteine BT	1	25	25.572	14.045	2.809
	2	25	24.401	11.701	2.340
Homocysteine AT	1	25	24.947	13.353	2.671
	2	25	19.020	11.182	2.236
BMI	1	25	28.218	7.254	1.451
	2	25	28.026	5.688	1.138



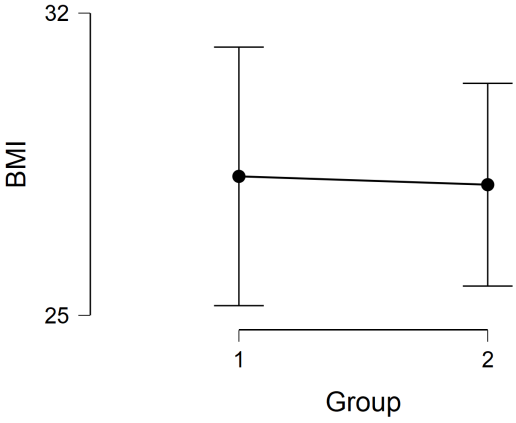
Graph 3: Comparison of Homocysteine level before treatment between the Groups

Table 7: P values between Group 1 and Group 2

Group Descriptive	t value	df	P
Homocysteine BT	0.867	48	0.390
Homocysteine AT	1.701	48	0.095
BMI	0.105	48	0.917



Graph 4: Comparison of Homocysteine level after treatment between the groups



Graph 5: Comparison of BMI level between the Groups' BMI

DISCUSSION

The randomized, single-blind, double-arm clinical study conducted on 50 patients indicates that the group treated with the Arjuna tablet had a significant reduction after treatment compared to before treatment. The decrease in homocysteine levels after intervention between groups (Group 1 and Group 2) shows that the results are comparable. The level of higher homocysteine level is predictive of future coronary artery diseases. There is also evidence that the elevated level of homocysteine has a significant association with atherosclerosis and the formation of atherothrombotic plaque responsible for ischemic heart disease. It is also reported that plasma homocysteine rises with age in both men and women, and its concentration is higher in men than women. This may be due to the difference in muscle mass and renal function, and sex hormones may also influence homocysteine concentration in plasma[13]. Hyperhomocysteinemia can also arise from nutritional deficiency of folate, vitamin B6, and vitamin B12, and to a lesser extent, vitamin B6 is inversely related to total homocysteine. Therefore, a person with a nutritional deficiency that leads to low blood concentrations of the aforementioned is at increased risk of hyperhomocysteinemia[14]. Hyperhomocysteinemia has been recognized as an independent risk factor for cardiovascular disorders[15].

Understanding the homocysteine under the spectrum of ama and management by altering the lifestyles with pathya ahara vihara and correction of Agni through deepana pachana dravyas supported with herbal nutritional supplements plays a significant role in preventing systemic illness because Ayurveda believes in the process of reducing saamatva to niraamatva for successful treatment of vyadhi.

Study on the action of Arjuna as a Hridaya, its broad spectrum of activity in hypercholesteremia, wound healing, ulceration, UTI, regulating hormonal cycle, benefits in bleeding disorders, and lung diseases[17-22] has been well documented. A study on *Terminalia arjuna's* phytoconstituents shows triterpenoids, saponins, flavonoids, phenolic, and nutrients such as zinc, copper and calcium[23]. Arjuna (*Terminalia arjuna*) has no harmful adverse effects on hepatic, renal and haematological parameters[23]. The present observation in the study on homocysteine can be understood based on saamata of ahara rasa circulating throughout the body, which can be rectified by following healthy practices in diet and exercise as given in swasthavritta or it can be corrected by a drug like Arjuna given as adjuvant in a small dosage as a nutritional supplement. Arjuna tab can be used as vitamin therapy with folic acid, B6, and B12, in combination with it, as it is natural and is better absorbed and acclimatized.

CONCLUSION

The present study indicates Arjuna tablet as an adjuvant in managing increased homocysteine had a significant reduction after treatment, indicating the potential scope of using Arjuna as a nutritional supplement in hyperhomocysteinemia. Arjuna tab can be used as a combination of vitamin therapy (with folic acid, B6, and B12). As it is natural, it is better absorbed and acclimatized for the benefit of the patients. Arjuna (*Terminalia arjuna*) effectively manages homocysteine levels at 1 gm as a nutritional supplement and adjuvant. However, to prove the homocysteine-lowering effect of Arjuna, a study on a large sample size over some time is required for the benefit of the subject.

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