International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 08, 2020
ISSN: 1475-7192

Effect of *Terminalia arjuna* (add-on medication) on Cardiac Function In Patients of Coronary Artery Disease – A Randomized Controlled Clinical Study

[1]Vaishali Kuchewar*, [2]Sourya Acharya

Abstract--- *Background - Coronary artery disease (CAD) is a major cause of death all over globe. Its incidence is rapidly increasing in developing countries also. Despite significant diagnostic and interventional advancement in cardiovascular area, still it is the most common cause of morbidity and mortality. So there is need of integrated approach & to search a medicine which is cardio protective & Rejuvenating. Terminalia arjuna is described as Hridya(Cardio protective). Objective -This study is planned with the objective to evaluate the effect of Terminalia arjuna on Cardiac function in CAD patients. This drug will be given with the drugs prescribed by the cardiologist as add-on medication. Methodology - It is parallel group, exploratory hospital based study. The patients of Coronary artery disease of age group 40 to 70 years will be screened as per inclusion/exclusion criteria and randomly divided into two groups. One group will be received standard conventional treatment and the other group will be on standard conventional treatment with stem bark of Terminalia arjuna(capsule form). The treatment period will be of 90 days. Patients will be closely followed up throughout the trial period every week for first four weeks and then fortnightly for another eight weeks. Primary outcomes include evaluation of effect of Terminalia arjuna on cardiac function with the help of ejection fraction and 6MWT. Secondary outcomes involve evaluation of vascular inflammatory marker (hsCRP) and lipid profile. Ethics approval was obtained from IEC,DMIMS (DMIMS(DU)/IEC/Aug-2019/8309). The conclusion will be drawn from the results and will be published in peer reviewed journal.*

Keywords--- *Coronary artery disease, Terminalia arjuna, Hridya, Ejection fraction, 6MWT, hsCRP*

I INTRODUCTION:

Coronary artery disease (CAD) is also known as coronary heart disease(CHD) or Ischemic heart disease(IHD). It is found to be a leading cause of death worldwide.[1,2] CAD is caused by accumulation of plaque in the coronary arteries. "According to a report of World Health Organization (WHO) in 2005, CVD caused 17.5 million (30%) of the 58 million deaths that occurred worldwide".[3] There is a significant increase in the prevalence of CHD over the past two decades in India. The epidemiologic studies conducted in various parts of the country indicated a prevalence of CHD is between 7% - 13% in urban[4-6] and 2% - 7% in rural populations.[7,8] According to the Global

1, Professor, Department of Kayachikitsa, MGAC, DMIMSU, vkuchewar@gmail.com, Mob. No. 9420998747
2, Professor, Department of Medicine, JNMC, DMIMSU, souryaacharya74@gmail.com, Mob. No. 9511840372
Corresponding author: Dr. Vaishali Kuchewar, Shrikrishna colony, Wardha, email id: vkuchewar@gmail.com, Contact number: 9420998747

Received: 19 Feb 2020 | Revised: 28 Mar 2020 | Accepted: 25 Apr 2020

Burden of Diseases Study, the projected figures of CHD for 2020 were 14.4 million and 7.7 million in men and women respectively.[9]

The important goal of treating patients with stable ischemic heart disease(SIHD) is to minimize the mortality and maintain a quality life with minimizing costs of health care.

In Consideration with above said goals, a search is continuing for preferably non-invasive add-on therapies with Standard conventional treatment. *Terminalia arjuna* is mentioned in many ancient Indian medicinal texts including *Charak Samhita*, *Sushrut Samhita*, and *Ashtang Hridaya*. For the first time, Vagbhat has promoted the use of its stem bark powder in heart disorders.[10] In various studies, Its stem bark is found to be anti-ischemic, antioxidant, blood pressure lowering, antiplatelet, hypolipidemic, antiatherogenic properties.[11] Some studies are conducted to assess the efficscy of *Terminalia arjuna* in different cardio-vascular ailments.[12-17]

In toxicity & safety study, it did not show any type of toxic effect in animal [18]

II RATIONALE OF STUDY –

Coronary artery disease is the prominent cause of death all over globe, and its incidence is rapidly increasing. Despite an advancement of interventions in cardiovascular area, still CAD is the leading cause of morbidity and mortality. The current prescribed lifelong medicines include blood pressure lowering, antiplatelet and hypolipidemic, but none of it acts as a cardio-protective. Thus there is need of integrated treatment.. *Terminalia arjuna* is specifically described as *Hridya*(Cardio protective). Hence this study is intended to evaluate the add on effect of *Terminalia arjuna* on Cardiac function in CAD patients. This medicine will be given as add-on with the medications prescribed by the cardiologist.

It is parallel group, exploratory study in which patient's allocation ratio will be 1:1. The comparator group will be treated with standard treatment protocol and the trial group will be treated with standard treatment protocol and extract of *Terminalia arjuna.*

The objective of the study is to evaluate the effect of *Terminalia arjuna* on cardiac function by measurement of ejection fraction and 6MWT (Six minute walk test).

III METHODOLOGY:

It is an academic hospital based study. It will be conducted in MGAH and AVBRH of Salod and Sawangi respectively.

Inclusion Criteria: Participants will be between 40-70 years of age group, irrespective of sex. The stable patient of CAD diagnosed by any of the following investigations will be registered.

- ECG (ST elevation/depression, T-wave inversion)
- Transthoracic echocardiography(Regional wall motion abnormalities(RWMA))
- Treadmill exercise test(TMT)

Participants will be enrolled after 15 days of its onset and after one month in cases of coronary bypass surgery, or coronary stenting.

Exclusion Criteria: Participants who having following ailments will be excluded from this trial

- Patients of coronary bypass surgery, or coronary stenting of the period < 1 months
- Patients of Arrhythmia
- Patients of severe heart failure
- Patients with any type of serious infection.
- Patients with Renal failure or CKD
- Patients with Portal hypertension
- Critically ill patient
- Patient with Type I DM or uncontrolled Type II DM.
- Patients with severe musculoskeletal disorders
- Patients with COPD

Withdrawal Criteria - Participants who fulfil the following criteria will be withdrawn from the study:

- Want to withdraw from the study
- incidence of a serious adverse event
- Occurance of moderate chest pain or breathlessness
- Not fulfilling study schedule

The patients with adverse event will be treated under observation and free of cost. The patient of moderate chest pain or breathlessness will be referred to AVBRH for further treatment. The reason of withdrawal will be recorded.

Sample size: In previous studies, the sample size ranges from 10 to 50.[19,20]

For this study, the power is set at 0.80 and it is considered as superiority design .So the sample size is calculated by using following formula.[21]

$$N = \frac{1}{2} \times \left(\frac{z\frac{\alpha}{2} + z_{\beta}}{arcsin\sqrt{p} - arcsin\sqrt{P_0}} \right)^2$$

$$N_{Statistical\ superiority} = 2 \times \left(\frac{1.96 + 0.845}{4} \right)^2 \times 6^2 = 36$$

In consideration of 10% dropout,. 40 participants will be assigned in each group.

Randomization – All the participants will be assigned randomly by sequentially numbered system. The allocation will be isolated for both the centres and will be done by assigned research officer.

Blinding - The participants and the clinicians will not be blinded during the clinical trial. but, outcome assessors will be blinded.

Interventions - The control group will be provided Standard conventional treatment prescribed by cardiologist and the interventional group will receive *Ghana*(Aqueous extract) of bark of *Terminalia arjuna* with Standard conventional treatment. The 500 mg capsule will be given 8 hourly with water. The total treatment period will be of 90 days.The dose will be modified in response to effect of the drug. One hour difference in consumption of Standard treatment & trial drug will be advised. The pocket diary will be provided to patient to tick on dose schedule after medicine consumption & to mention any untoward features. The contact number of investigator & Co-investigator will be provided for any emergency. Patient will be given 15 days medicines and asked to bring the container of medicine to monitor drug adherence.

Relevant concomitant care – The patients of both the groups will be advised to follow general diet plan(low salt, low fat & high fibre diet) and daily morning walk of half an hour. It will be mentioned in case proforma to avoid confounding factor.

IV OUTCOME MEASURES –

Primary outcomes include evaluation of effect of *Terminalia arjuna* on cardiac function by calculating ejection fraction with the help of Transthoracic echocardiography at the end of 90 days treatment and 6MWT after every 30 days of treatment.

Secondary outcomes involve evaluation of vascular inflammatory marker (hsCRP) and lipid profile. Atherogenic index will be calculated as follows:

- 'Atherosclerosis Index (A.I) = LDL-C / HDL-C' 22
- 'Cardiac Risk Ratio (C.R.R)=TC/HDL-C' 23
- 'Atherogenic Coefficient (A.C) = TC-HDL-C/HDL-C' 24

Clinical outcomes – The frequency and intensity of chest pain will be measured by the Seattle Angina Questionnaire-7. [25]

The time points of evaluation is showed in table 1

Assessment of adverse event adverse events – According to previous studies, no adverse event was observed. Any troublesome clinical feature observed during study will be recorded in CRF and treated

Schematic diagram of Study methodology

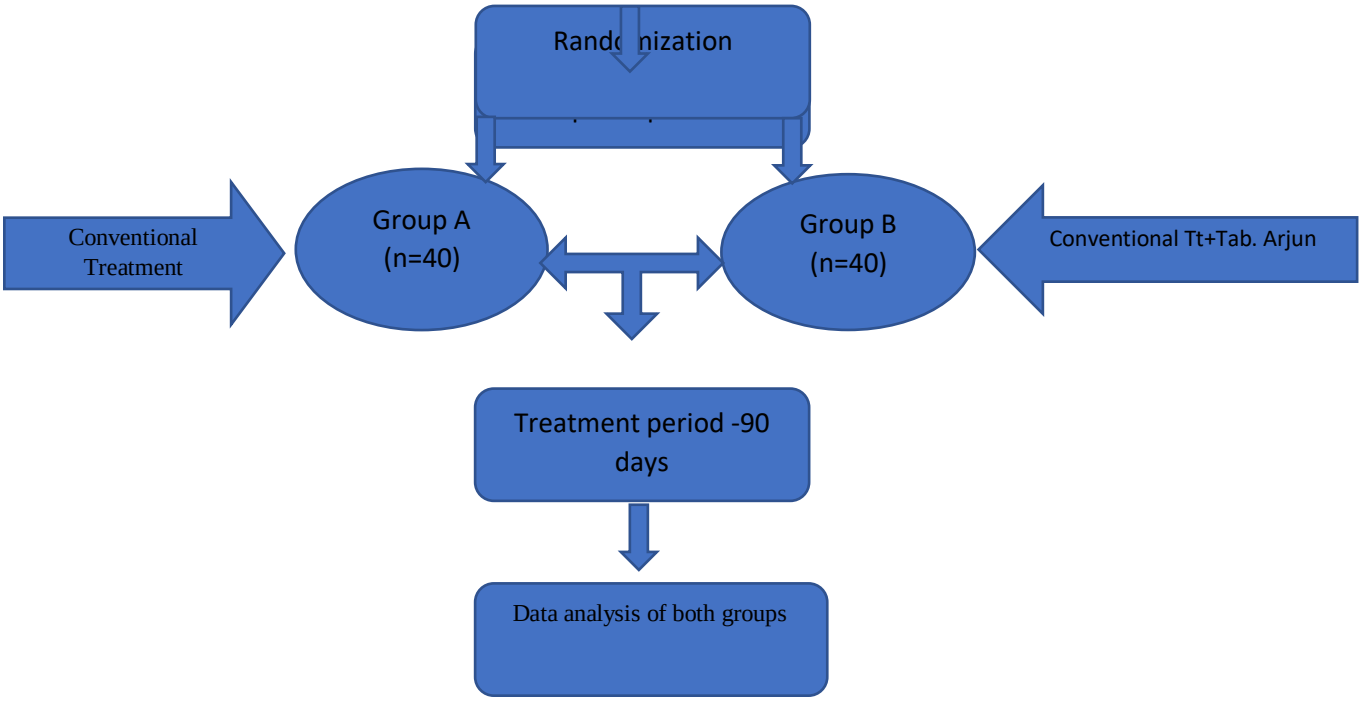

Table1. – Study schedule

Day	0	15	30	45	60	75	90
Time point	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Allocation & Informed consent	*						
Medication to group A	*	*	*	*	*	*	*
Medication to group B	*	*	*	*	*	*	*
Transthoracic echocardiography	*						*
6MWT	*		*		*		*
hsCRP	*						*
Lipid profile	*						*

Data management and monitoring - The demographic data (age, sex, nationality), any previous major or minor illness will be recorded when they are enrolled. The baseline investigations and the investigations after completion of the treatment i.e. at the end of 90 days will be obtained. Adverse events and withdrawals for any reason will be recorded in the CRF by the data administrator.

The follow-up during treatment will be of every 2 weeks. During this period, their diary will be checked for medication adherence and adverse event if any. Participants will be contacted by mobile phone daily for first week and weekly for remaining weeks as a reminder of medication.

Statistical analysis - Statistical analyses will be performed using SPSS software version 22. Paired t-test (Wilcoxon sign rank) and unpaired t- test (Wilcoxon Rank-sum) will be applied to analyze the data.

Ethics and dissemination- This study is approved by the Institutional Ethics Committee of DMIMS (DMIMS (DU/IEC/Aug-2019/8309) All participants will asked to read and sign the informed consent. The study results will be disseminated to study participants and published in peer-reviewed publications.

V EXPECTED OUTCOMES/RESULTS:

This study is planned to investigate the improvement in cardiac function with the help of echocardiography and 6MWT and arteritis and Dyslipidemia are the major components in the pathogenesis of CAD, hence it will also be assessed by hsCRP and lipid profile.

The aqueous extract of *Terminalia arjuna* can be helpful in improving cardiac function because In one animal study, the use of aqueous extract showed increase in the coronary flow.[26] Another experimental study in frog showed the increased force of contraction of cardiac muscle.[27]

One study said 'The bark increased the endogenous antioxidant compounds in rat heart and thus prevent oxidative stress concomitant with ischemic–reperfusion injury'. [28]

VI CONCLUSION: CONCLUSION WILL BE DRAWN FROM THE STATISTICAL ANALYSIS.

REFERENCES –

[1] Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. The Lancet. 1997;349(9063):1436–1442.
[2] Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. The Lancet. 1997;349(9061):1269–1276.
[3] World Health Organization; Geneva: 2005. Preventing Chronic Diseases: A Vital Investment.
[4] Mohan V., Deepa R., Rani S.S. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India. J Am Coll Cardiol. 2001;38:682–687.
[5] Gupta R., Gupta V.P., Sarna M. Prevalence of coronary heart disease and risk factors in an urban Indian population: Jaipur Heart Watch-2. Indian Heart J. 2002; 54:59–66.
[6] Kamili M.A., Dar I.H., Ali G. Prevalence of coronary heart disease in Kashmiris. Indian Heart J. 2007; 61:44–49.
[7] Gupta A.K., Bharadwaj A., Ashotra S. Feasibility and training of multipurpose workers in detection, prevention and control of coronary artery disease in apple-belt of Shimla hills. South Asian J Prev Cardiol. 2002; 6:17–22.
[8] Kumar R., Singh M.C., Ahlawat S.K. Urbanization and coronary heart disease: a study of urban–rural differences in northern India. Indian Heart J. 2006; 58:126–130.
[9] Ezzati M., Lopez A.D., Rodgers A. World Health Organization; Geneva: 2004. Comparative quantification of health risks. global and regional burden of disease attributable to major risk factors.
[10] Tyler VM, Premila MS. Ayurvedic Herbs: A Clinical Guide to the Healing Plants of Traditional Indian Medicine.

[11] Maulik SK, Talwar KK. Therapeutic potential of Terminalia arjuna in cardiovascular disorders. Am J Cardiovasc Drugs. 2012;12:157–63.
[12] Bhatia J, Bhattacharya SK, Mahajan P, Dwivedi S. Effect of Terminalia arjuna on coronary flow–an experimental study (Abstract) Indian J Pharmacol. 1998;30:118.
[13] Jain V, Poonia A, Agarwal RP, Panwar RB, Kochar DK, Mishra SN. Effect of Terminalia arjuna in patients of angina pectoris (A clinical trial) Indian Med Gaz. 1992; 36: 56–9.
[14] Dwivedi S, Agarwal MP. Antianginal and cardioprotective effects of Terminaliaarjuna, an indigenous drug, in coronary artery disease. J Assoc Physicians India. 1994;42:287–9.
[15] Dwivedi S, Jauhari R. Beneficial effects of Terminalia arjuna in coronary artery disease. Indian Heart J. 1997;49: 507–10.
[16] Kumar PU, Adhikari P, Pereira P, Bhat P. Safety and efficacy of Hartone in stable angina pectoris–an open comparative trial. J Assoc Physicians India. 1999;47:685–9.
[17] Bharani A, Ganguli A, Mathur LK, Jamra Y, Raman PG. Efficacy of Terminaliaarjuna in chronic stable angina: A double-blind, placebo-controlled, crossover study comparing Terminalia arjuna with isosorbidemononitrate. Indian Heart J. 2002;54:170–5.
[18] Patil RH, Prakash K, Maheshwari VL. Hypolipidemic effect of Terminalia arjuna (L.) in experimentally induced hypercholesteremic rats. Acta Biol Szeged. 2011;55:289–93.
[19] A.BharaniA.GangulyK.D.Bhargava, Salutary effect of Terminalia Arjuna in patients with severe refractory heart failure. **International Journal of Cardiology.1995;49(3):** 191-199
[20] S. Dwivedi ,**A. Aggarwal**,**M.P. Agarwal**,**S. Rajpal**.Role of ***Terminalia arjuna*** in ischaemic mitral regurgitati0n, International journal of Cardiology,100(3): 507-508
[21] Baoliang Zhong, How to Calculate Sample Size in Randomized Controlled Trial? Journal of Thoracic Disease. 2009; 1(1)
[22] Mertz DP "Atherosclerosis-index" (LDL/HDL): risk indicator in lipid metabolism disorders. Med. Klin 1980;75: 159–61.
[23] Malaspina JP, Bussière H, Le Calve G The total cholesterol/HDL cholesterol ratio: a suitable atherogenesis index. Atherosclerosis 1981;40: 373–75.
[24] Kayamori F, Igarashi K Effects of dietary nasunin on the serum cholesterol level in rats. Biosci Biotechnol Biochem 1994;58: 570– 71.
[25] Chan et al,Development of short seattle angina questionnaire. Circulation: Cardiovascular Quality and Outcomes.2014;7(5):640-647
[26] Bhatia J, Bhattacharya SK, Mahajan P, Dwivedi S. Effect of Terminalia arjuna on coronary flow–an experimental study (Abstract) Indian J Pharmacol. 1998;30:118.
[27] Verma P, Muneesh, Rani S, Bhutani G. Experimental Evaluation of Terminalia arjuna (Aqueous Extract) on cardiovascular system in comparison to digoxin. J Dent Med Sci. 2013;7:48–51.
[28] Gauthaman K, Maulik M, Kumari R, Manchanda SC, Dinda AK, Maulik SK. Effect of chronic treatment with bark of Terminalia arjuna: A study on the isolated ischemic-reperfused rat heart. J Ethnopharmacol. 2001;75:197–201
[29] Kumar, G. K., & Prasad, R. S. (2019). A non-linear kernel feature subset selection based semi-supervised framework for medical disease prediction. International Journal of Advanced Science and Technology, 28(17), 517-526. Retrieved from www.scopus.com
[30] Kumar, R., Pruthi, M., & Taneja, G. (2019). Inventory model for deteriorating products with life time and demand depending on price. International Journal of Advanced Science and Technology, 27(1), 48-52. Retrieved from www.scopus.com
[31] Kumar, S., & Bathla, R. K. (2019). Multimodal approach with face and iris to enhance the efficiency of biometric system using soft biometrics. International Journal of Advanced Science and Technology, 28(16), 1572-1581. Retrieved from www.scopus.com
[32] Lakshmi, P., Bharadwaj, A., & Kumar Srivastava, R. (2019). Microbial profile of bacteriuria in pregnant women and their antibiogram. International Journal of Advanced Science and Technology, 28(14), 337-344. Retrieved from www.scopus.com
[33] Lee, S. -., Choi, A. -., Kim, S. -., Won, J. -., & Lee, K. -. (2019). Comparison of EMG activity using spectrum indices from biceps femoris muscle during treadmill walking. International Journal of Advanced Science and Technology, 28(3), 33-39. Retrieved from www.scopus.com

Received: 19 Feb 2020 | Revised: 28 Mar 2020 | Accepted: 25 Apr 2020