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Integrative Ayurvedic Treatment for Vascular Atherosclerotic Disease: Namely, Coronary Disease, Deep Vein Thrombosis and Cerebro Vascular Accident-Embolic Stroke

Dr. Sujata Vaidya[1], Dr Shripad Bhat[2], Dr. Sachin Kshirsagar[3]

[1]Researcher
Corresponding Author Email: *drsujatavaidya[at]gmail.com*
Mobile: 9822311565

[2]HOD, Medicine Dept SKNMC & GH)
Email: *suprabhatdiabetes[at]gmail.com*

[3]BAMS, SKNC & GH

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Abstract: ***Cardiovascular disease is the third highest cause of mortality world over. Atherosclerosis as an underlying vascular disease, leads to heart diseases, cerebral stroke and deep vein thrombosis. Ayurvedic formulations have shown beneficial results on such patients previously. This pragmatic, single centric, double blind, placebo controlled, two arm clinical trial was conducted on randomly assigned 144 patients, suffering from symptoms associated with atherosclerosis at SKNMC &GH, Pune. Pre and post study evaluated the impact of proprietary ayurvedic intervention given in addition to ongoing hospital treatment. Intervention included proprietary ayurvedic multi-herbal formulation brand Suved capsule andcolostrum in brand Reimmugen capsule previously given to such patients. Results indicated intervention was well tolerated with no harms. Pre post three months intervention showed significant positive improvements in symptoms. Significant Clinical improvements in vascular status seen in Intima-Media-Thickness with Carotid Doppler investigation and in Cardiac function seen in Ejection Fraction from2 D Echo investigation.***

Keywords: Ayurveda, atherosclerosis, cardiac function, immune-modulation

1. Introduction

Cardio Vascular diseases (CVD) are leading cause of death globally. Atherosclerosis is considered as an underlying cause, leading to Ischemic heart disease (IHD), CVD, cerebrovascular accident (CVA) or a stroke and deep vein thrombosis (DVT)[(1).] Management focuses on lifelong drugs and invasive interventions such as angioplasty and stent placement, endarterectomy and CABG surgery.

Postoperative complications, ReStenosis and adverse reactions to long term drugs are being reported [2]. India has over 32 million patients (2020), of which only 8 million received formal treatment. The staggering burden from complications of CVDs estimated on India's GDP is to the scale of $4.58 trillion by 2030 [3]. In India 52% of cardiovascular deaths occur below the age of 70, compared with 23% in countries with established market economies. [(4)]Patients forego treatment due to high costs; often leading to expensive emergency visits and complications. Growing awareness and demand for Ayurveda with positive outcomes has encouraged such clinical research [7, 8].

Objective: This study was conducted to evaluate and substantiate the benefits of combination treatment of proprietary ayurvedic formulation SUVED and Colostrum in REIMMUGEN, for its benefit on patients of IHD, CVD, CVA and DVT [(9)].

2. Method

2.1 Trial Design

This was a double-blind, placebo-controlled study conducted on registered patients in SKNMC & GH, Pune under treatment for complaints of chest pain, breathlessness, fatigue associated with vascular disease and poor cardiac health.

No changes in design were made during study period.

2.2 Participants

Patients taking treatment at SKNMC hospital were approached for the study. They essentially lived in sub-urban, rural Pune population, were of either gender, aged between 18 and 70.

Exclusion criteria included pregnant and lactating women, those admitted with acute IPD operative condition and/or with haemorrhagic cerebrovascular stroke.

All participants gave informed consent before starting the study and verified they understood the study instructions and would comply with the study procedures at time of consent.

Ethical approval for the study from the registered Ethics Committee was obtained prior to recruiting and commencement of the study

2.3 Interventions

Ayurvedic proprietary formulation 'SUVED™ (FDA, since 2006)' based on "Bhav Prakash" is multiherbal and most of the herb have been researched with potential disease reversal action. Suved is composed of Arjuna (cardiotonic; cardio protective) [10]. Ashwagandha-Withaniasomnifera (de-stressor, rejuvenator) [11, 12], Draksha-Vitis vinifera-(flavonoids, antioxidant, endothelial function, atherosclerosis) [13], Pomegranate / Dalimb-Punica granatum (polyphenols for endothelial function recovery, reduced macrophage cholesterol) [14]; Haritki-Terminalia chebula-(cardio protective, antioxidant, antibacterial and anti-fungal) [15], Musta Cyperus rotundus-(diuretic, hepatoprotective, cardioprotective, neuroprotective, anti-inflammatory) [16], Ajmoda-Apium graveolens (antibacterial, cardiovascular, antidiabetic, anti-depressant activity) [17], Pimpli-Piper longum-Piperin and piperlonguminine alkaloids, (thermogenic, digestive, respiratory stimulant) [18], Dhamasa-Fagonia Arabica (clot lysis, thrombolysis) [19], Amla-Emblica officinalis (Dyslipidemia, anti-oxidant and rejuvenation) [20], Bibhitak-Terminalia belerica (free radical scavenging, lipid level reduction) [26]. Kamal phool-Nymphaea stellata, anti-aging, rejuvenation)[21], Brahmi-Bacopa Monnieri (cerebral ischemia and infarct)[22].

'REIMMUGEN™ Capsules' (FDA, since 2012) contain Colostrum nutrient used as immunity modulator, antioxidant, rejuvenator. Colostrum contains immunoglobulin, natural Vitamins and Minerals [23].

- Patients enrolled in test arm received 1 capsule of Suved 500 mg BD and 1 capsule of Reimmugen Colostrum 300 mg TDS for 3 months.
- Patients enrolled in control arm received 1 capsule of Placebo filled with jowari BD and ragi flour (Common Millets) TID for 3 months

2.4 Outcomes

Symptomatic screening was done on a modified questionnaire approved by PI (HOD Medicine), based on Symptom Status Questionnaire-Heart Failure (SSQ-HF) for breathlessness, fatigue, poor stamina, giddiness.

Clinical screening included Carotid Dopplar studies to evaluate Intima Media Thickness (IMT) as a marker of Atherosclerosis which is established as a major threat in vascular disease leading to IHD, CVD, CVA, DVT [5, 6]. 2 D Echo investigations for Cardiac health.

2.5 Sample size

There was no prior study for similar pragmatic study for reference Pilot study was conducted with sample size of n=32, (control=16; test=16). Final Study Sample size of 96 subjects with 10% variance /confidence was suggested. 144 participants, 72 in each group were considered for analysis. Recruitment stopped when target sample size was reached.

2.6 Randomization

Simple randomization divided patients into two groups. There were no statistical differences between groups on education, income, marital status, race, and employment status.

2.7 Blinding

Allocation concealment: Trial and control intervention capsules were packed in similar capsules in strips, put in marked bags and given to participants to be taken at home.

i) Subjects were blinded to intervention content of Trial or Control medications.

ii) Clinical Investigators performing (2 D Echo and Doppler studies) were blinded to intervention type.

2.8 Statistical Methods

Paired t Test was used for statistical analysis. Statistical significance was defined as a two-sided P value < 0.05 with confidence interval of 95% for variables Ejection fraction and IMT

1) Paired t-test is applied to compare Pre and Post effect of medicine for IMT:

95% CI for mean difference: (0.0152, 0.1489); P-Value = 0.018. Since P-value = 0.018 <0.05; Significant at 5% l.o.s. Conclusion: Significant difference is observed in IMT thickness (Left)

95% CI for mean difference: (0.0390, 0.1712); P-Value = 0.003. Since P-value = 0.003 <0.05; Highly Significant at 5% l.o.s. Conclusion: Significant difference is observed in IMT thickness (Right)

2) Paired t-test is applied to compare Pre and Post effect of medicine for EF

H1: Mean Ejection fraction of patients differ significantly before and after administration of medicine.95% CI for mean difference: (-5.416,-0.422). P-Value = 0.023

Since P-value = 0.023<0.05; Significant at 5% l.o.s.

Conclusion: Significant difference is observed in EF.

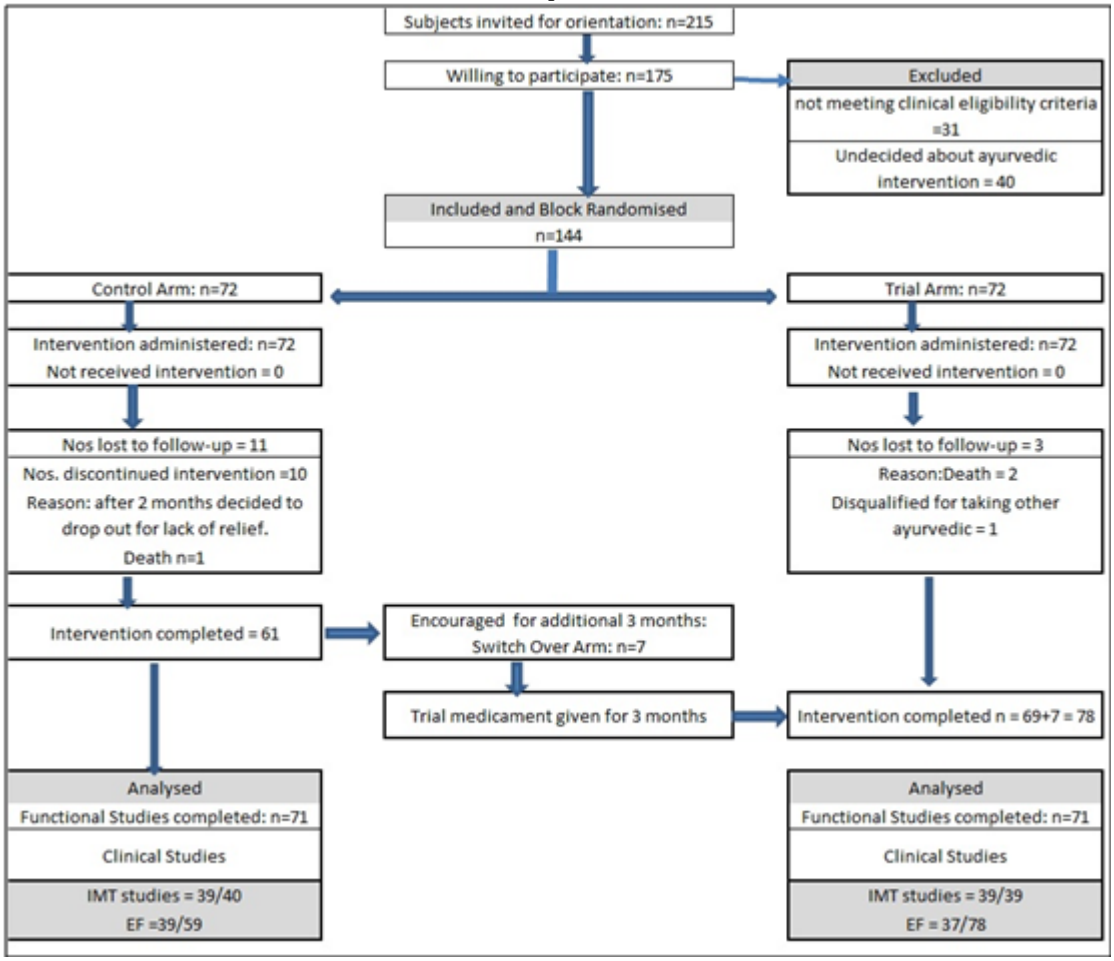
3. Results

3.1 Participants flow

Participants were recruited from Jan 2015 till June 2017. Orientation lectures were given with information on trial expectations from participants. Written Consent was obtained from 175 patients. Primary screening indicated eligibility. 31 participants were removed from study as they did not meet eligibility criteria. 144 participants were randomized into two groups. During the study, 3 patients expired and 1 was removed for protocol violation.

Participants from Control group who completed pre-post evaluation were encouraged to continue. N=7 participants consented and were given Trial medication without informing them of change of medication content.

Table 1: Participants Flow Chart



3.2 Recruitment

Subjects were recruited from 1st January 2016 to 1st August 2017.

3.3 Basic characteristics of the patients:

Participants taking treatment at the hospital of either gender, aged between 18 and 70, irrespective of economic or educational status were recruited. Of 144 participants between age group of 18 to 72 years, there were Males-107 (74%), average age 54.9and Females-37 (26%) average age 59.25.

3.4: Clinical distribution of morbidity: Subjects OPD case history paper which included ECG/2D Echo report was considered for morbidity at baseline.

Table 2: Clinical Distribution of Morbidity

	Control arm (N=72)		Trial arm (N=72)	
	Males	Females	Males	Females
	n=54 (75%)	n=18(25%)	N=55(76.4)	n=18(23.6)
Average Age	55.8	59	54	59.5
DVT; n (%)	6 (11.36%)	0 (0)	7 (11.7%)	2 (11.11%)
IHD; n (%)	22 (40.91%)	6 (29.4%)	25 (40%)	10 (55.56%)
CVA; n (%)	12(22.73%)	4 (23.5%)	12 (18.3%)	2 (11.11%)
Diabetes mellitus n (%)	1 (2.27%)	7 (35.3%)	4 (6.7%)	1 (5.56%)
Diabetes mellitus + IHD n (%)	7 (13.64%)	2 (11.7%)	6 (10%)	3 (16.67%)

3.5 Numbers Analyzed

Participants were analyzed on an intent-to-treat basis. After completion of their 3 months pre-post evaluation, N=7 participants from Control group were added to Trial group.

Final assessment reported Symptom changes in 142 subjects (control n=71 and trial n=71), Clinical changes in IMT in 79 subjects (control n=39 and trial n=39) and LVEF from2D Echo changes in 76 subjects (control n=39 and trial n=37).

3.6 Outcomes and Estimation

Clinical investigations

Carotid dopplar pre and post 3 months intervention indicated changes in IMT. Few Trial arm subjects showed reduction in plaque and IMT from 1.3mm to 0.8mm.

Table 3: IMT studies

	Control group n=39				Trial group n=39			
	left		right		left		right	
	%	n=	%	n=	%	n=	%	n=
Increase in IMT/plaque	23.1	9	25.6	10	23.1	9	10.3	4
No change in IMT	56.4	22	61.5	24	30.8	12	30.8	12
Reduced plaque, improved IMT	20.5	8	12.8	5	46.2	18	59.0	23

More participants from Trial arm (left n=46% and right n=59%) showed reduction in Carotid IMT than seen in Control group (left n=20.5% and right n=12.8%). Over 50% participants from Control arm and 30% from Trial arm showed no changes in IMT.

Cardiac function with 2 D Echo. Ejection Fraction is considered as a parameter of Cardiac function. An increase of 5 to 10% in LVEF in 40% Trial arm subjects verses 18% from Control arm indicated improved cardiac function.

Table 4: Change in Cardiac Function measured with Ejection Fraction from Baseline

LVEF	Control arm n=39		Trial arm n=37	
	n=	%	n=	%
reduced cardiac strength	5	12.8	6	16.22
no change in EF	27	69.2	16	43.24
Improved EF	7	18	15	40.54

Ejection Fraction did not display any changes in 69% Control arm subjects and in 43% Trial arm subjects.

Symptomatic assessment: n=71each from Control and Trial arm completed Symptomatic pre-post 3 months intervention assessment.

In the modified SSQ questioner, pre post evaluation of self-assessed status for breathlessness, fatigue, poor stamina, giddiness was taken. Baseline value was considered at Point '5'. Improvement in symptoms increased count on scale till '10'. Worsening of symptoms reduced count till '0'. For reporting, "N" indicated = Not an issue (remained at 5): M = Moderate changes (up to 7); S = Significant changes (9 or 10); D = detrimental/condition worsened (down to 1).

Table 5: Important Symptoms for consideration Symptomatic changes from Baseline based on Symptom Status Questionnaire

Changes in symptom intensity	breathlessness	walking distance	chest pain	giddiness	swelling	fatigue
TRIAL Group	%	%	%	%	%	%
condition worsened	0	0	0	0	0	0
Not an issue	9	0	32.1	60.7	42.9	0
No change	3.6	3.6	3.6	0	3.6	0
mild change	7.1	7.1	3.6	3.6	10.7	5.4
Moderate improvement	39.3	41	25	16.1	21.4	41
Significant improvement	41	48.2	35.7	19.6	21.4	54
CONTROL Group						
	%	%	%	%	%	%
condition worsened	19	19	24	14	35.7	40.5
Not an issue	7.2	0	33.34	31	40.5	0
No change	47.6	52.4	33.34	28.6	12.0	50
mild change	23.8	21.4	9.5	21.4	9.5	7.1
Moderate improvement	2.4	7.2	0	2.4	2.4	2.4
Significant improvement	0	0	0	2.4	0.0	0

Significant improvements in symptoms with reduced intensity to total relief from symptoms seen in almost all Trial arm subjects.

Table 6: Secondary symptoms for consideration: Symptomatic changes from Baseline based on Symptom Status Questionnaire

Changes in symptom intensity	pain in other part of body	throbbing in head	walking stamina	sleep	self dependency
	%	%	%	%	%
TRIAL Group					
condition worsened	0	0	0	0	0
Not an issue	25	57.2	60.71	80.36	26.8
No change	7.1	0	1.8	1.8	0
mild change	21.4	5.4	7.1	1.8	5.4
Moderate improvement	30.4	23.2	16	5.4	30.4
Significant improvement	16	14.3	14.3	10.7	37.5
CONTROL Group					
	%	%	%	%	%
condition worsened	31	16.7	21.4	21.4	12
Not an issue	24	43	33.34	59.5	40.5
No change	38	21.4	35.7	9.5	28.6
mild change	7.1	14.3	4.8	4.8	12
Moderate improvement	0	4.8	4.8	4.8	7.1
Significant improvement	0	0	0	0	0

3.7 Ancillary analysis

No ad-hoc analysis was performed in this study.

3.8 Harms

No adverse events or interactions were reported in this study due to trial medicines.

4. Discussion

4.1 Limitations

Trial medicines were allowed only as additional intervention with ongoing medication and modifications in dosages were not considered. Additional guidelines to improve lifestyle, diet were not included. Study was limited to three months intervention.

4.2 Generalisability

Improvements in clinical investigations has indicated this to be amongst the most encouraging results for regression of atherosclerosis (Carotid IMT); and revival in cardiac strength (2D Echo) with significant improvements in symptoms.

A prior published study claimed reduction in IMT of 0.09 with 3-year aggressive statin therapy[24].This clinical trial showed significant reduction in IMT as regression of atherosclerosis clinically evaluated in 3 months.

Further research is solicited to find the active ingredients from the specific herbs which play an important role in disease arrest and healing at root level to reverse the burden of such auto-immune diseases.

5. Future Scope

Integrative treatment of Ayurvedic Suved and Reimmugen colostrumis compatible (with conventional drugs) and has achieved significant symptomatic and clinical improvements within 3 months. This can meet the challenges for over 85% global patients as prevention in high-risk persons, to prevent Restenosis and to overcome allopathic drugs side effects.

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Disclaimers on any conflicts of interest: None declared.

Ethical Clearance: The study was approved by the institutional ethical committee.

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Author Profile

Sujata Vaidya is an independent pursuer of Integrative therapies. PhD in Energy Field Studies, using PIP technique for health assessments and Interpretation. Zoroastrian College, Open International University. Jan 2002.

MD (Ayur-European Ayurveda Academy-Mind Body healthcare), Manas Ayurveda (philosophy for Mind Body) for treatment of Cardiac diseases and vascular blockages. European Ayurveda Academy, Italy. Dec 2009;MBA:University of Pune. 1985 B.Sc Fergusson College, University of Pune 1983; Fellowship of Cardiac Rehabilitation: UN designed Post Doctorate Fellowship, Medvarsity, Apollo Hospitals, 2007

National Conferences: Scientific Validation & Technical Evaluation of Ancient Medical Systems (SVTEAMS) 2006 as Coordinator. Paper presented during SVTEAMS: Aura sturdies as Biofield study for Disease assessment

2nd World Ayurveda Congress Nov 2006, Pune; Chief Coordinator: Integrative HealthCare

Invited Speaker during 3 consecutive New Age Doctors Association Seminars in Pune, Hyderabad

SHARP paper presented during numerous Medical practitioner's conferences

Director of Institute of Integrative Healthcare, a Multiversity venture from 2005 to 12. Practiced Integrative therapies from 2002 till date.

Partner Director of Supra Health Solutions LLP (previously Health Solutions)

Author of book: Heart and Health like Never Before. Published by India International Multiversity: Foreword by Padmabhushan Dr B M Hegde; special note by Dr Avinash Inamdar (leading Cardio surgeon of India) and Back Cover by Parmashree Dr Vijay Bhatkar.