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Endothelial Cells Strengthening: Improving Functions in Management of Acute Coronary Syndrome (A Double Blind Randomized Interventional Control Trial)

Tarun Saxena^{1*}, Sanjay Patidar², Shailesh Verma³, Azeema Ozefa Ali⁴ and Manjari Saxena⁵

Affiliation

¹Department of Internal Medicine, Senior Consultant, Mittal Hospital and Research Centre, Ajmer, Rajasthan, India

²Community Medicine and Biostatistics, Honorary consultant, Mittal Hospital and Research Centre, Ajmer, Rajasthan, India

³Cardiology Associate, Mittal Hospital and Research Centre, Ajmer, Rajasthan, India

⁴Resident Doctor, Mittal Hospital and Research Centre, Ajmer, Rajasthan, India

⁵Department Yoga and Physical education, Mittal Hospital and Research Centre, Ajmer, Rajasthan, India

***Corresponding author:** Tarun Saxena, Senior Consultant, Department of Internal Medicine, Mittal Hospital and Research Centre, Ajmer, Rajasthan, India, Tel: +91-982 908 9284, E-mail: yogdiab@gmail.com

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Abstract

Objective: Endothelial dysfunction/injury is the main reason for Acute Coronary Syndrome (ACS). Current therapy includes antiplatelet, lipid lowering and thrombus removal by drugs/ intervention. Endothelial strengthening in management of ACS is less narrated in literature. This study describes endothelial strengthening and clinical outcome in ACS with Triphala powder, a mixture of Amla (*Phyllanthus emblica*), Harad (*Terminalia chebula*), and Behda (*Terminalia bellirica*).

Methods: This is a double blind randomized interventional control trial. 80 cases coming to the emergency department were selected for study, divided into two groups. Group 1 (n=40, control), group 2 (n=40, study). Further subdivided into subgroup 1A and 2A ST-Elevation Myocardial Infarction (STEMI) and subgroup 1B and 2B Unstable Angina (UA). All subgroups were given clopidogrel, aspirin and atorvastatin and subjected to thrombolysis or Coronary Angiography (CAG) according to requirement. In addition study group was given Triphala powder 10 grams in a cup of water. Outcome was observed for relief in chest pain, ECG, Echocardiography changes at 50 minutes; (SSR) Sympathetic Skin Response was done initially. Statistical analysis was done by SPSS 20 software.

Results: In intervention subgroups 2A and 2B there was significant relief in chest pain, settling down of ECG changes, and improvement in regional wall motion in echocardiography (p<0.001). There was increased sympathetic activity in all subgroups (spike response in SSR).

Conclusion: Sudden mismatch in ATP (Adenosine Triphosphate) supply results in UA/STEMI. Triphala increases ATP synthesis by increasing mitochondrial capacity to maximum; strengthens endothelium which behaves like normal endothelium and resolves symptoms and signs of ACS.

Keywords: Endothelial cells dysfunction, Acute coronary syndrome, Adenosine triphosphate, Sympathetic skin response.

Abbreviations: ACS- Acute Coronary Syndrome, SSR- Sympathetic Skin Response, ATP- Adenosine Triphosphate, ICU- Intensive Care Unit, CAG- Coronary Angiography, LV- Left Ventricular, RMS- Recorder and Medicare System, LDL- Low Density Lipoprotein, UA- Unstable Angina, STEMI- ST-Elevation Myocardial Infarction, tPA- Tissue Plasminogen Activator, PTCA- Percutaneous Trans-Luminal Coronary Angioplasty.

Introduction

Endothelial dysfunction/injury is the prime reason for the development of atherosclerosis and its sequel (vulnerable plaque) which likely results into Acute Coronary Syndrome [1-5]. Till date, therapy is directed towards antiplatelet, lipid-lowering and thrombus removal by drugs or intervention in ACS [6,7]. Healthy endothelium has the antiplatelet/antithrombotic and fibrinolytic property [8-11].

Literature is lacking in the strengthening of endothelium and utilizing the above properties in ACS. Therefore this study focuses upon endothelial cells strengthening in ACS and to observe its impact upon the clinical profile of ACS. Triphala a mixture of Amla (*Phyllanthus emblica*), Harad (*Terminalia chebula*), Behda (*Terminalia bellirica*) has strong properties to support endothelium. Previous studies have found the pivotal role of Amla in increasing ATP synthesis and removing oxidative stress at the cellular level [12-14].

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Methods

This is a double-blind randomized interventional control trial. Arbitrarily 80 cases of ACS coming to the emergency department of an institute were selected and randomized for study between 1st April 2017 to 30th September 2018 (recruitment period/randomization period) [15]. The cases were randomly divided into two groups. Group 1 (n=40, control), group 2 (n=40, intervention). This stratification was not based upon severity into cases and controls. Randomization protocol was decided even before the registration of first case through random number generated by computer, alternate patients were given into cases and controls. First case was allotted to group 1 and next case was allotted to group 2. If any case in group 2 was excluded at any time, the next was allotted to group 1. Alternate sequence was followed till the recruitment of last case.

Further stratification into subgroups A and B was based upon the clinical profile into UA (subgroup B) or STEMI (subgroup A). The age group was 35-65 years, all males. Complete history and examination including pulse rate, blood pressure, respiratory rate, and oxygen saturation were recorded. Informed written consent (especially requirement of urgent intervention) and approval of institutional ethical committee was taken. In both groups cases having STEMI were categorized into subgroup A i.e. Subgroup 1A (n=20) and 2A (n=20) respectively. Cases having UA were categorized into subgroup B i.e. Subgroup 1B (n=20) and 2B (n=20) respectively. No follow-up protocol after the discharge from the hospital was planned.

Inclusion Criteria

Cases coming with chest pain typical of coronary artery disease suggestive of Acute Coronary Syndrome along with ECG changes (depression or elevation) were selected for the study.

Exclusion Criteria

Patient coming with severe chest pain requiring morphine, breathlessness, shock, any degree of block or arrhythmia in ECG and any past history of cerebrovascular accident or patients requiring urgent cardiac intervention (thrombolysis/ coronary angiography) were excluded.

Intervention: Intervention was done during shifting to ICU (Intensive Care Unit) from the emergency unit and a close watch was kept on the patients.

Group1: (control) Patients were given clopidogrel 300 mg, aspirin 300 mg, and atorvastatin 80 mg stat with 10 grams of *lactobacillus* powder dissolved in a cup of water with subjected to thrombolysis or CAG if required.

Group 2: (Intervention) Patients were given clopidogrel 300 mg, aspirin 300 mg, and atorvastatin 80 mg stat with 10 grams of Triphala powder dissolved in a cup of water with subjected to thrombolysis or CAG if required. Flavored essence and the artificial color were added to both liquids to make liquids identical.

Outcome Measurement

1. Relief in chest pain (at 50 minutes).
2. ECG changes- initial ST-T changes like elevation or depression was compared with ST-T changes at 50 minutes.
3. Echocardiography changes- regional wall abnormality and LV functions (Left Ventricular) initial were compared with changes at 50 minutes in 2D and M-mode Echocardiography (GE vivid s 6 probe M4s/RS machine).
4. The requirement of pharmaco-invasive therapy-Patients requiring thrombolysis in view of ongoing chest pain/ECG changes and not willing for CAG (during or after 50 minutes).

5. The requirement of urgent coronary angiography- Patients requiring CAG in view of ongoing chest pain/ECG changes (during or after 50 minutes).

Sympathetic Activity Assessment

(Done at the time of admission by 2 methods)

1. Heart rate measurement in ECG (>100/minute, overt increase)
2. SSR (Sympathetic Skin Response)- Recorded without any stimulation only at room temperature of 22-24°C in ICU by applying 2 EMG electrodes over palm and forearm RMS (Recorder and Medicare System) at the time of admission, if spike response is present then it suggests high basal sympathetic discharge [16].

Statistical Analysis

The collected data were entered in a Microsoft Excel sheet. Statistical analysis was carried out by using SPSS 20.0 Statistical software. The appropriate test of significance was applied (Chi-square test).

Results

1. Maximum cases (90%) presented within the first 6 hours of symptoms. These cases were asymptomatic i.e. no chest pain, no discomfort before 24-48 hours.
2. Sympathetic activity assessment- In group 1 and 2 mean pulse rate/minute was 84 and 86 (admission time), 15% cases had an overt increase in sympathetic activity, in SSR spike response was present in almost 90% cases suggestive of increased basal sympathetic discharge.
3. In group 1 and 2 mean blood pressure in mm Hg was 156/84 and 158/82 (admission time) and 152/80 and 148/84 (during last one year) mean HbA1c% (glycosylated hemoglobin) was 8.5 and 8.8 (admission time), and 8.9 and 8.6 (during last one year) mean LDL mg% (Low Density Lipoprotein) was 130 and 138 (admission time) and 141 and 139 respectively (during last one year). History of smoking/tobacco intake was 10%.
4. In intervention group 2 as a whole, there was significant relief in chest pain, settling down of ST-T changes in ECG, and improvement in regional wall motion in echocardiography as compared to group 1 (p<0.001).
5. In intervention subgroups 2A and 2B, there was significant relief in chest pain, settling down of ST-T changes in ECG, and improvement in regional wall motion in echocardiography as compared to group 1A and 1B (2A v/s 1A, 2B v/s 1B, p<0.001) (Figures 1-7) No major side effects like fall in blood pressure, tachycardia were observed only minor side effects like nausea and upper abdominal discomfort was present in 5% of cases.

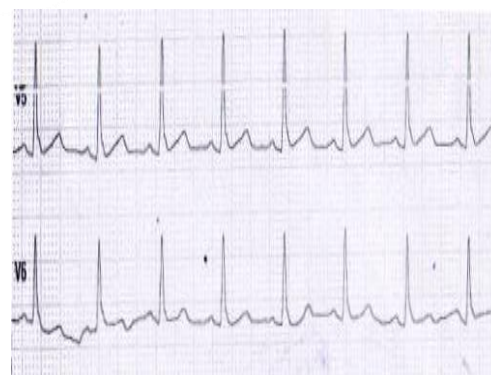


Figure 1: USA- (Pre) lead V5-V6- ST up sloping.

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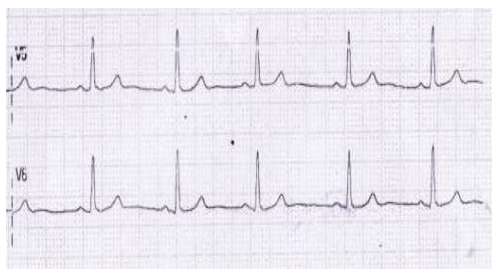


Figure 2: USA (Post) lead V5-V6- ST settling down.

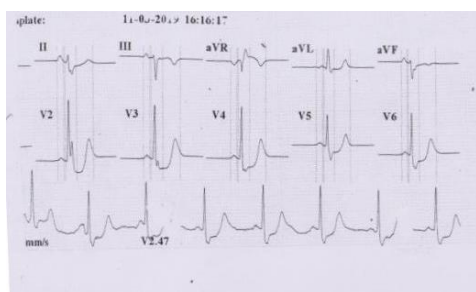


Figure 3: STEMI- Pre-acute infero posterior MI with reciprocal changes in anterior leads (presented after 24 hours, ongoing chest pain).

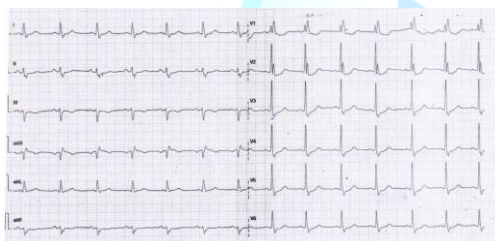


Figure 4: STEMI- Post- ST settling down in inferior leads and reversal of reciprocal changes in anterior leads, relief in chest pain.

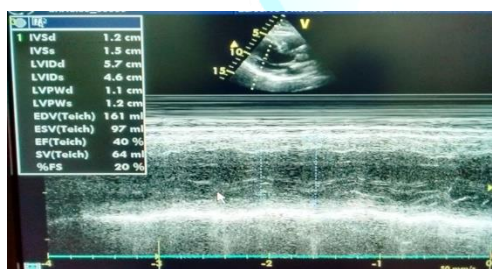


Figure 5: STEMI presented in one hour- Echocardiography showing hypokinetic posterior wall (M-mode).

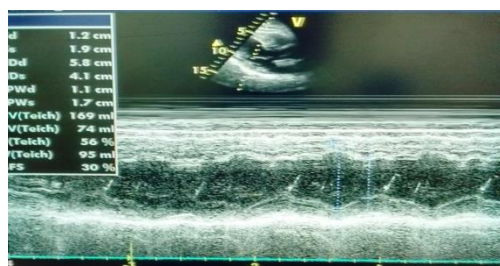


Figure 6: STEMI- Normal wall motion of posterior wall (M-mode).

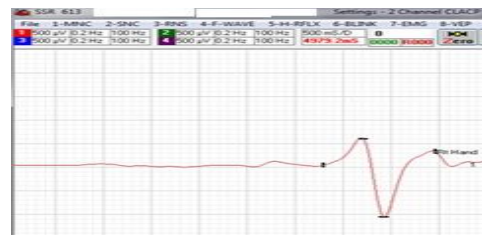


Figure 7: Increased basal sympathetic discharge (spike response in all groups).

Discussion

Endothelial dysfunction/injury is found to be the prime reason for the development of atherosclerosis and its sequel (vulnerable plaque) which likely leads to ACS [1-5]. In this modern time with development in various horizons of medicine, the therapeutics is mostly directed towards antiplatelet, lipid-lowering and thrombus removal by drugs or intervention in ACS [6,7]. Literature related to endothelial strengthening in ACS is lacking, therefore, the study was planned to see the effect of endothelial strengthening on clinical profile in ACS. Triphala powder a mixture of Amla (*Phyllanthus emblica*), Harad (*Terminalia chebula*), Behda (*Terminalia bellirica*) has strong properties to support endothelium [12-14]. This is a double-blind randomized interventional control trial. 80 cases from the emergency department of an institute were randomly selected for the study. Cases having chest pain typical of coronary artery disease, history suggestive of ACS with ECG changes were included for the study. The cases were randomly divided into two groups. Group 1 (n=40, control), group 2 (n=40, study). In both groups cases having UA were categorized into subgroup B i.e., Subgroup 1B and 2B respectively.

Cases having STEMI were categorized into subgroup A i.e. Subgroup 1A and 2A respectively. The age group was 35-65 years, all males in both groups and subgroups. All cases in subgroup 1A, 1B, 2A, 2B were given clopidogrel, aspirin, and atorvastatin. In addition intervention subgroups 2A and 2B were given Triphala powder, whereas control subgroups 2A and 2B were given *Lactobacillus* powder dissolved in a cup of water. The results were observed at 50 minutes for outcome measurement for relief in chest pain, ECG changes, Echocardiography changes, and the requirement of thrombolysis or CAG. After 50 minutes, in subgroups 2B v/s 1B, there was significant relief in chest pain (100% v/s 10%), ST-T changes settling down in ECG (100% v/s 10%) and improvement in ECHO findings (100% v/s 5%) ($p < 0.001$). After 50 minutes, in Group 2A v/s 1A, there was significant relief in chest pain (90% v/s 10%), ST-T changes settling down in ECG (80% v/s 5%) and improvement in ECHO findings (75% v/s 5%) ($p < 0.001$) (Table 1,2).

We revise our findings/interpretations

1. Acute development of symptoms/findings of UA/STEMI in an asymptomatic person in less than 24 hours suggested by history, ECG, ECHO findings.
2. Presence of one or more risk factors for atherosclerosis like hypertension/diabetes/dyslipidemia/smoking etc. in almost 70% in all groups and subgroups for last many years.
3. No significant change in blood pressure/ diabetes status (HbA1c)/ lipid (LDL) values at the time of admission and the mean value for the past 12 months.
4. Increased basal/overt sympathetic discharge in all groups and subgroups at the time of admission. SSR showed spikes in 90% of cases.
5. A significant response to treatment in chest pain, ECG, ECHO findings ($p < 0.001$) in subgroup 2A and 2B, as compared to subgroup 1A and 1B respectively.

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Groups	Age in years (mean)	Sex	Pulse rate/min	BMI Kg/M2	Blood Pressure mm Hg (mean)	Comorbidities in % (D-diabetes/ O-Obesity/H-Hypertension)
Group 1A(n=20)	56	Male	80	24	158/88	D 30
						O 25
						H 40
Group 1B(n=20)	59	Male	82	25	154/82	D 28
						O 27
						H 42
P value 1A v/s 1B	>0.05	-	>0.05	>0.05	>0.05	>0.05
Group 2A(n=20)	58	Male	84	24	156/82	D 32
						O 27
						H 44
Group 2B(n=20)	57	Male	79	25	148/78	D 35
						O 29
						H 40
P value 2A v/s 2B	>0.05	-	>0.05	>0.05	>0.05	>0.05

Table 1: Basic characteristic of the patients.

	GROUP 1		GROUP 2	
Number of cases in each subgroup (results at 50 minutes)	STE MI (1A)	USA (1B)	STE MI (2A)	USA (2B)
	N=20	N=20	N=20	N=20
Types of MI		PW-4, IW-6, AS-8, AL-2		PW-4, IW-6, AS-8, AL-2
Relief in chest pain	N=2 (10%)	N=2 (10%)	N=18 (90%)	N=20 (100%)
p value			(1A v/s 2A) p<0.001	(1B v/s 2B) p<0.001
ECG changes (ST-T settling down)	N=1 (5%)	N=2 (10%)	N=16 (80%)	N=20 (100%)
p value			(1A v/s 2A) p<0.001	(1B v/s 2B) p<0.001
Echocardiography findings (improvement in regional wall motion)	N=1 (5%)	N=1 (5%)	N=15 (75%)	N=20 (100%)
p value			(1A v/s 2A) p<0.001	(1B v/s 2B) p<0.001
LVEF%				
(A)>50%	N=2	N=10	N=2	N=10
(B) 40-50%	N=8	N=8	N=8	N=9
(C) 30-40%	N=10	N=2	N=10	N=1
(D)<30%	N=0	N=0	N=0	N=0
Improvement in LVEF>10-15%	5%	10%	60%	80%
SSR findings- admission time (spike/increased sympathetic activity)	90%	90%	95%	90%
Patients requiring PTCA	90%	85%	15%	NIL
p value			(1A v/s 2A) p<0.001	(1B v/s 2B) p<0.001

*PW- Posterior Wall, IW- Inferior Wall, AS- Antero-Septal, AL- Antero-Lateral, PTCA- Percutaneous Trans-Luminal Coronary Angioplasty.

Table 2: Clinical profile/ECG/Echocardiography findings.

Endothelial dysfunction (A possible mechanism)

In the current study history was classical for ACS and suggestive of acute development of symptoms i.e. person asymptomatic one day back and symptomatic very next day. How healthy endothelium becomes unhealthy? (Healthy endothelium behaves normally to exercise, changes in weather like from winter to summer or summer to winter by increasing or decreasing the ATP level according to the demand. Endothelial dysfunction is the compromise of normal function of endothelial cells leading to the inability of arteries and arterioles to dilate fully in response to an appropriate stimulus which can be further elaborated into atherosclerosis and rupture of vulnerable plaque) [17,18]. In both groups and all subgroups atherosclerosis risk factors remained grossly unchanged during the last 12 months and at admission time, therefore how these factors become critical in less than 24 hours? So their role in the development of ACS remains uncertain. Previous literature hasn't discussed acute blockade in vasa vasorum (blood supply to coronaries) [19,20].

A possible explanation remains in cellular energy metabolism. In the presence of normal blood supply to coronary endothelial cells, ATP production occurs at a normal rate and no endothelial dysfunction occurs (ATP is the final energy source for all cells, synthesized in mitochondria of each cell via aerobic respiration by oxygen and glucose). If there is sudden change in ATP requirement then despite normal availability of oxygen and glucose supply cells are unable to cope up with new rate of ATP synthesis and a mismatch (demand/synthesis of ATP) occurs. Increased sympathetic activity present at the time of admission (basal/overt) increases ATP requirement [21]. Other reasons for ATP mismatch may be exposure to sudden environmental temperature change. In the current study sudden development of ACS, symptoms could be attributed to a mismatch in ATP supply at the cellular level (coronary endothelial cells) which results in endothelial dysfunction. Endothelial dysfunction results in the inability of coronary vessels to dilate in response to various stimuli, symptoms of angina arise, in severe cases breach in endothelial cells

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layer occur, there is entry of platelets, inflammatory cells, cascade of events occur, endothelium is unable to hold the plaque, plaque ruptures into the lumen there is block in lumen of coronary vessels, results in STEMI [22-26].

Endothelial cells strengthening: (A possible mechanism)

Triphala powder contains Amla, which increases spare mitochondrial respiratory capacity to increase the synthesis of ATP, a difference between basal ATP synthesis and maximum ATP synthesis. Sufficient availability of ATP prevents cellular dysfunction/breach in coronary endothelium [27]. Amla also stimulates the antioxidant system, has cytoprotective effect removing oxidative stress. Amla has a cooling property whereas harad and behda have a warm effect to the body. Combination of all three makes suitable for all seasons and protects from a change in ATP requirement due to seasonal change or BMR. The overall effect is stabilization or strengthening of the endothelium. Once the endothelium is stabilized/ strengthened then it behaves like healthy endothelium quickly normalizes the flow in the coronary vasculature, and removes findings of ACS in the following way (Figure 8).

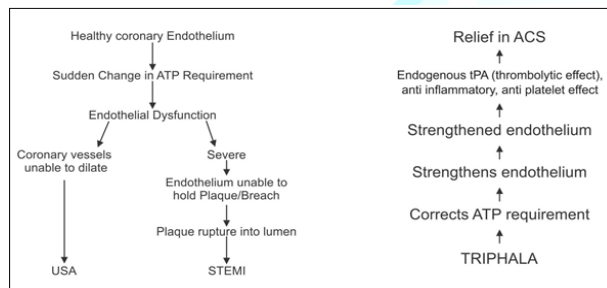


Figure 8: Endothelial Cell Dysfunction/Endothelium Strengthening-Possible Mechanism.

Unstable Angina: After endothelial stabilization, endothelium exerts effects like healthy endothelium in normal circulation i.e., vasodilatory effect which reduces angina pain, removes micro thrombi, removes the possibility of breach in endothelium, inhibits accumulation of platelets, entry of inflammatory cells, lipids, and overall plaque is no more unstable. Clinically effect is observed in the form of symptomatic improvement in chest pain, ECG and echocardiography findings (Subgroup 2B) [18,27-33].

STEMI: Besides all effects observed above additional advantage is observed in the form of thrombolytic effect by the support to the extra release of endogenous tPA (Tissue Plasminogen Activator) normally released from damaged endothelium. Clinically effect is observed in the form of improvement in chest pain, ECG and echocardiography findings (subgroup 2A) [27-33].

Summary

Sudden mismatch or unavailability in ATP supply in endothelial cells resulted in endothelial dysfunction. ATP mismatch occurred primarily due to an increase in sympathetic discharge (overt or basal). Endothelial dysfunction results in the development of ACS. Triphala increases mitochondrial capacity, therefore, increases ATP synthesis corrects ATP mismatch, strengthens endothelium which now behaves like healthy endothelium. Strengthened endothelium, inhibits entry of platelets, inflammatory cells and supports the release of endogenous tissue tPA to lyse thrombus. The overall effect is significant relief in ACS. Study finds a positive role of endothelial strengthening in ACS with Triphala.

Limitations of the study- small sample size

Suggestions: Study with large sample size and use of other plants or drugs [Ginseng a Chinese medicine and Ashwagandha (*Withania Somnifera*)] which have potential to support mitochondrial activity may be used for endothelial strengthening to further consolidate the findings of the study [34,35].

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