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AN ANTIOXIDATIVE EFFECT OF *PUNICA GRANATUM* (POMEGRANATE) ON BIOCHEMICAL PARAMETERS IN PATIENTS WITH MYOCARDIAL INFARCTION: A DOUBLE BLIND PLACEBO CONTROLLED TRIAL.

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ABSTRACT
Myocardial Infarction (MI) is one of the leading diseases in the world wide. The pathogenesis of MI is Coronary Artery Disease and Oxidative stress. Lots of medicines are being prescribed to cure MI and to keep Coronary artery profile healthy, but these medicines are not safe and have some side effects. WHO recommends to use alternative medicine to cure MI because herbal products are natural and don't have such side effects. One of such herb is pomegranate; usually consumed as fruit. As per Ayurvedic literature, Pomegranate seeds may cure MI and pulps contain lots of Antioxidants. This prompted us to find out; whether the presence strong antioxidants in pomegranate have any prognostic effects in patients with MI? So we prepared a whole Fruit extract of Pomegranate (PEWF) to investigate its effect in patients with MI. 100 patients of either gender with MI were included in this study. Demographic information, Clinical and Biochemical investigations related to Oxidative stress and Coronary Artery Disease (CAD) were done in 4 ml fasting venous blood. All participants were assigned in two groups (50 each). One group were under "Add On" therapy of Active Drug which includes Pomegranate extract of whole fruit (PEWF) (300 mg twice daily for One Month), matching Placebo of same colour, shape and size was used as comparator agent for second group. The Drug was issued to the Patients initially for 15 days after which they were recalled for clinical evaluation, compliance monitoring, adverse effect monitoring if any; and drug refill for next 15 days. At the end of the month, the base line investigations were repeated for all participants. Results were analysed by using, Z test and chi square indicates that significant difference has been obtained in post drug effect. Coefficient of Variations shows that when mean of active and placebo were compared with each other; patients who were under "add-on" therapy of PEWF for one month, shows highly significant. This indicates the prognostic effect of PEWF in MI patients.

KEYWORDS: Pomegranate, Antioxidants, MI, Serum Homocystein, hs-CRP.

INTRODUCTION
Myocardial infarction (MI) is a leading disease in world wide. According to a Spanish study, the incidence of MI rate was 301/100,000 persons/year for men and 48/100,000 person/year for women [1] The incidence of MI in India is 64/1000 person/year in men of aged 29-69 years during year 2010.[2] Cardiovascular disease is the major cause of death and disability in the United States.[3]

The cellular mechanisms involved in the pathogenesis of MI is complex and involve the interaction of number of cell types, including coronary endothelials, circulating blood cells (e.g. leukocytes, platelets), and cardiac myocytes.[4,5,6] Most of which are capable of generating reactive oxygen species (ROS). These ROS have the potential to injure vascular cells and cardiac myocytes directly, and can initiate a series of local chemical reactions; genetic alterations that ultimately result in an amplification of the initial ROS-mediated cardio myocyte dysfunctions or cytotoxicity.

Pomegranate is known to be rich in antioxidants, and levels of antioxidants have been found to be higher than in other natural juices and in red wine.[7] Antioxidants have numerous positive properties, including protection against cholesterol oxidation and anti- aging effects. Polyphenols reduce cholesterol absorption in intestine by decrease in cholesterol absorption across the brush border membrane. [8]

Lots of techniques are being used by the patients to keep their Coronary Profile as healthy by Drugs and Surgical techniques like angioplasty, stent placement and by coronary artery bypass. Even then, these techniques are not safe and have lots of limitations; but if pomegranate extract of whole fruit (PEWF) administration as tablet of 300 mg twice daily is found to be prognostically effective, this may help the patients in keeping coronary profile healthy without having any side effect.

HYPOTHESIS

As PEWF is rich in natural antioxidants and Polyphenols, the consumption of this extract may improve disease condition. Null Hypothesis (H_0) will be implemented during the trial.

MATERIAL AND METHODS

1. Trial Design

A randomized, double-blind, placebo controlled, parallel trial was conducted in Base Hospital, Srikot, Pauri-Grahwal, Uttarakhand, India attached to Veer Chandra Singh Garhwali Government Institute of Medical Sciences & Research, Srikot, Pauri Garhwal, Uttarakhand ,India (VCSGGIMSR) and Netaji Subash Chander Bose Subharti Medical College(SMC) and C.S. Subharti Hospital, Meerut(U.P.) India, in collaboration with Department of Biochemistry, Pharmacology and Medicine.

2. Inclusion and Exclusion criteria

A total 100 patients of both men and women with MI and satisfying inclusion and exclusion criteria were enrolled in the present study by applying the formula.

$$\mathbf{n = [(z\sigma)/E]^2}$$

Where 'Z' is constant value 1.96 for the Confidence level 95%

'σ' is standard deviation for the sample size , which is ±3.

'E' is error which is 0.9

'n' is total number of participants in each group.

Inclusion Criteria

1 Men / Women: aged 20-60 years
2 Myocardial infarction as per signs and symptoms: Chest pain (typically down the left arm or left side of the neck), shortness of breath, nausea, sweating, anxiety, palpitations.
3 Participants who are permanent residents of this study area either by birth or those who are staying since more than 10 years were enrolled in this study.

Confirmatory tests

1 E.C.G. with changes - Q and ST segment elevation of 1mm or more in two neighboring leads.
2 Creatinine phospho kinase MB (CPK-MB): CPK-MB levels more than the reference ranges (0-25 U/L at 37^0c).
3 Troponin 'T' level more than the reference range.

Exclusion Criteria

1 Patients with acute illness, pregnant, lactating, and postoperative patients.
2 Patients with CNS disorders, systemic chronic diseases e.g. renal failure and chronic hepatic disease.
3 Post operative conditions like angiography, angioplasty or any other surgical interventions.

3. Method of Randomization

Selected participants were randomized as per criteria given in Table 1 by generating a list of sequential assignments to a treatment group, using the "random seed" function in the Statistical Package for the Social Sciences (SPSS) software program, version 16.0 or its equivalent.

Table 1: Assignment of Participants

Dose	PEWF(Active) 1 BD x 1 month	Placebo 1 BD x 1 month
Myocardial Infarction	n=50	n= 50

4. Assessment of treatment effect

Fasting 4 ml venous Blood sample were collected in a plane vacutainer. After coagulation, samples were centrifuged at 8000 R.P.M. for 15 minutes and serum was collected in separate test tube. Samples were processed on the same day for Bio chemicals markers for MI are Total Cholesterol, Serum Triglyceride, High Density Lipoproteins (HDL), Non HDL Cholesterol, Low Density Lipoproteins (LDL), Oxidized LDL (OX-LDL), High Sensitive C-Reactive Protein (hs-CRP) and Serum Homocystein (Hys) on fully automated Biochemistry analysers like Cobas 6000 and Vitros 250 (Johnson and Johnson).

5. Trial Medicines

Trial medicines were given as "add-on basis" along with other prescribed medicine.

5.1 Description of the drug: The active drug has pomegranate extract of whole fruit (PEWF). Matching placebo of same color, shape, size and weight was used. The PEWF/Placebo was given orally, as tablets of 300 mg twice daily (BD) for one month.

5.2 Trial procedure

1. Duration of treatment

Participants were treated daily with either active medicine or placebo for one month. Regular follow-up of patients were carried by frequents visits and personal communications.

Visit I (Week 0), screening visit (Pre Dug Analysis)

After obtaining an informed consent, patients with MI were included in this study. 4 ml fasting venous blood sample were collected for Biochemical parameters related to MI. Base line titer has been obtained and recorded in separate sheet.

Visit II (Week 1)
The participants were under the "add-on" therapy of PEWF or Placebo (as per table number 1), the dose was issued for 15 days initially and participants were recalled for next visit.

Visit III (Week 3)
Follow up information was obtained regarding any adverse effects of treatment. The participants were questioned regarding any missed doses of trial medicine and second dose of medicines were issued for next 15 days.

Visit IV (Week 5), Final Visit (Post Drug Analysis)
The participants were questioned regarding any missed doses of the trial medicine, All Biochemical parameters related to T2D and ROS were repeated.

5.3 Assessment of Compliance
The participants; who had 80% consumption of PEWF / Placebo, will be considered as compliant.

RESULTS AND INTERPRETATION
A total 100 participants of either men and women of age between 20- 60 year were participated in this study. In these,12 participants were of age group belongs to 40-45 year, 18 participant were of age group 45-50 Year , 30 participants were of age group between 50-55 year and 40 participants were of age group 55-60 years.. Out of these, 50 participants (44 men and 06 women) consumed PEWF (active) and 50 participants (47 men and 03 women) consumed Placebo medicine.

Table number 2, 3 summarizes the Descriptive Statistics for active and placebo medication in both Pre and Post Drug effects. Mean and Standard Deviation of Pre and Post Drug analysis shows the reduction in level of Bio-chemical markers related to MI and CHD after active medication. This is a good statistical sign of prognosis.

Table number 4, 5 shows the Z test for active and placebo medication of post drug effect in comparison with pre drug analysis. In table 4, 5 pair 1, 2, 3, 4 and 5 shows the Biochemical parameters for Lipid profile, these are risk factors for MI and CHD. Pair 1 and 2 shows the $p<0.05$, this indicates that there is significance difference in mean for Total Cholesterol and Triglyceride in post drug analysis as compare to pre drug analysis after active and placebo medications. Pair 3,4 and 5 shows that $p<0.05$, this indicates that significant difference of mean has been found in HDL, LDL and Non HDL Cholesterol for post drug analysis, after active and placebo medication. These results show significant improvement in lipid profile in post drug analysis after active and placebo medication. Pair 6, 7 and 8 shows the advance Bio chemical parameters related to MI and CHD, these are OX-LDL, hs-CRP and Homocystein, Statistical results shows $p<0.05$. This indicates the reduction of risk factor related to MI and CHD; which proves the prognostic effect after medication. These results indicate the rejection of Null Hypothesis (H_0) and acceptance of Alternative Hypothesis (H1). This proves that significant difference has been found in parameters after post drug analysis. Z test analysis shows statistical significance; in both active and placebo medication because all the patients were of MI and CHD medication as prescribed to them by clinician. PEWF was given on "ADD-ON" basis with other regular medications.

Table number 6, 7 shows, chi square test for active and placebo medications after post drug analysis, independent variables were found statistically significant($p<0.05$) .Which indicates the prognostic effect in patients with both active and placebo medication; thus rejection of Null Hypothesis (H_0).

Table number 8 shows the difference in coefficient of variations (C.V.) in post drug analysis for active and placebo. CV of Total Cholesterol, Serum Triglyceride, HDL, Non HDL cholesterol, LDL and OX-LDL are 0.20, 0.22, 0.11, 0.068, 0.10 and0.25 for active and 0.26, 0.29, 0.19,0.15, 0.13 and 0.50 for placebo, which means CV of active is less then placebo. This shows that active medicine has much higher prognostic effect.

The parameters like hs-CRP and Serum homocystein, the C.V. are 0.26, 0.25 for active and 0.42, 0.41 for Placebo. This indicates that C.V. of active is less then C.V. of placebo, this suggest that Coronary risk factor has been reduced significantly after active medications.

Table Number 2: Descriptive statistics for PEWF (active) medication in Pre and Post Drug Analysis

		Pre Dug analysis		Post Drug Analysis	
Sr.no	**Parameters**	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**
1.	Total Cholesterol (mg/dl)	381.24	81.85	231.10	46.55
2.	Serum Triglyceride (mg/dl)	513.15	110.85	271.04	61.77
3.	HDL (mg/dl)	24.15	4.82	76.07	8.82
4.	Non-HDL cholesterol (mg/dl)	160.8611	10.70955	140.0556	2.82787
5.	LDL (mg/dl)	109.48	13.93	88.07	8.92
6.	OX-LDL (mg/dl)	2.31	0.70	0.84	0.21
7.	hs-CRP (mg/dl)	3.05	0.62	1.35	0.35
8.	Serum Homocystein(mg/dl)	49.35	12.91	21.46	5.47

Table No: 3: Descriptive statistics for Placebo in Pre and Post Drug Analysis

		Pre Dug analysis		Post Drug Analysis	
Sr.no	**Parameters**	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**
1.	Total Cholesterol (mg/dl)	314.55	82.02	296.88	79.74
2.	Serum Triglyceride (mg/dl)	426.10	128.93	396.93	115.64
3.	HDL (mg/dl)	26.16	4.48	30.45	5.98
4.	Non-HD cholesterol (mg/dl)	163.83	15.33	156.55	11.43
5.	LDL (mg/dl)	108.3	11.00	101.02	10.64
6.	OX-LDL (mg/dl)	1.91	0.89	1.54	0.77
7.	hs-CRP (mg/dl)	1.94	0.82	1.60	0.68
8.	Serum Homocystein(mg/dl)	25.63	9.8	31.99	9.04

Table Number: 4: Z Statistics of PEWF (active) for Post Drug in comparison to pre drug analysis.

Paired Samples Test				
Pairs	**Parameters**	**Z Test**	**Degree of Freedom**	**Sign(2 Tailed)**
Pair 1	Total Cholesterol for Pre and Post Drug Analysis	241.371	7254	0.00
Pair 2	Serum Triglyceride for Pre and Post Drug Analysis	223.949	7254	0.00
Pair 3	HDL for Pre and Post Drug Analysis	421.753	7254	0.00
Pair 4	LDL for Pre and PostDrug Analysis	254.070	7254	0.00
Pair 5	Non-HD cholesterol for Pre and Post Drug analysis	173.504	7254	0.00
Pair 6	*OX-LDL for Pre and Post Drug Analysis*	202.831	7254	0.00
Pair 7	hs-CRP for Pre and Post Drug Analysis	81.428	7254	0.00
Pair 8	Serum Homocystein for pre and post drug analysis	252.924	7254	0.00

Table Number: 5 Z Statistics of Placebo for Post Drug in comparison to pre drug analysis.

Paired Samples Test				
Pairs	**Parameters**	**Z Test**	**Degree of Freedom**	**Sign(2 Tailed)**
Pair 1	Total Cholesterol for Pre and Post Drug Analysis	89.952	4528	0.00
Pair 2	Serum Triglyceride for Pre and Post Drug Analysis	71.119	4528	0.00
Pair 3	HDL for Pre and Post Drug Analysis	54.648	4528	0.00
Pair 4	LDL for Pre and PostDrug Analysis	115.280	4528	0.00
Pair 5	Non-HD cholesterol for Pre and Post Drug analysis	143.667	4528	0.00
Pair 6	OX-LDL for Pre and Post Drug Analysis	141.385	4528	0.00
Pair 7	hs-CRP for Pre and Post Drug Analysis	63.803	4528	0.00
Pair 8	Serum Homocystein for pre and post drug analysis	126.541	4528	0.00

Table Number: 6 Chi square test of PEWF (active) for Post Drug in comparison to pre drug analysis

Paired Samples Test				
Pairs	**Parameters**	**Chi square**	**Degree of Freedom**	**Sign(2 Tailed)**
Pair 1	Total Cholesterol for Pre and Post Drug Analysis	190.187	20	0.00
Pair 2	Serum Triglyceride for Pre and Post Drug Analysis	79.700	15	0.00
Pair 3	HDL for Pre and Post Drug Analysis	48.74	139	0.00
Pair 4	LDL for Pre and PostDrug Analysis	2.705	139	0.00
Pair 5	Non-HD cholesterol for pre and post drug analysis	26.817	139	0.00
Pair 6	OX-LDL for Pre and Post Drug Analysis	54.964	2	0.00
Pair 7	hs-CRP for Pre and Post Drug Analysis	99.992	15	0.00
Pair 8	Serum Homocystein for pre and post drug analysis	48.586	6	0.00

Table Number: 7 Chi square test of Placebo for Post Drug in comparison to pre drug analysis

Paired Samples Test				
Pairs	**Parameters**	**Chi square**	**Degree of Freedom**	**Sign(2 Tailed)**
Pair 1	Total Cholesterol for Pre and Post Drug Analysis	191.912	20	0.00
Pair 2	Serum Triglyceride for Pre and Post Drug Analysis	313.259	25	0.00
Pair 3	HDL for Pre and Post Drug Analysis	0.206	1	0.00
Pair 4	LDL for Pre and PostDrug Analysis	48.010	4	0.00
Pair 5	Non-HD cholesterol for pre and post drug analysis	33.217	139	0.00
Pair 6	OX-LDL for Pre and Post Drug Analysis	168.469	12	0.00
Pair 7	hs-CRP for Pre and Post Drug Analysis	351.654	30	0.00
Pair 8	Serum Homocystein for pre and post drug analysis	146.246	9	0.00

Table number: 08 Coefficient of Variations for PEWF (active) & placebo medicine

Descriptive Statistics	**PEWF (ACTIVE)**				**PLACEBO**	
Post Drug Analysis	**Mean**	**Std. Deviation**	**C.V.**	**Mean**	**Std. Deviation**	**C.V.**
Total Cholesterol	231.1	46.55	0.20	296.88	79.74	0.26
Serum Triglyceride	271.0	61.77	0.22	396.93	115.64	0.29
HDL	76.07	8.82	0.11	30.45	5.98	0.19
Non HDL Cholesterol	160.8786	10.97116	0.068	139.9571	3.14602	0.15
LDL	88.07	8.92	0.10	101.16	10.64	0.13
OX-LDL	0.84	0.21	0.25	1.54	0.77	0.50
hs-CRP	1.35	0.35	0.26	1.60	0.68	0.42
Serum Homocystein	21.46	5.47	0.25	21.99	9.04	0.41

DISCUSSION

Literature reviews suggest that antioxidants and polyphenols prevent MI and CHD. The mechanism of this is still unclear; ROS stimulate the generation of OX-LDL, this OX-LDL activates protein kinase C and prevents nitric oxide mediated arterial relaxation. [9] Antioxidants and polyphenols improve nitric oxide action by reducing the oxidation of LDL. This helps in maintaining of normal vascular physiology. [10]

ROS stimulate leukocyte adhesions to smooth vascular cell by activation of vascular cell adhesion molecules (VCAM), this action promote the monocytes adhesion to vascular endothelial cell and promote the entry of monocytes to intima. This mechanism is stimulated by signaling molecules like Selectin, integrins and monocyte chemoattractent protein1 (MCP1). Antioxidant therapy reduces the production of selectins and prevents the entry of monocytes in endothelium to prevent CHD.[11]

A enzyme paraoxonase (PON 1) is present on HDL, [12] which prevents the production of OX-LDL and prevention of Platelet Activation Factor (PAF) [13,14]PAF promote the plaque formation and is the cause of CHD, Antioxidants and Polyphenols protect PON1 from loss of its activity by ROS. [15]

Now day's lots of natural and artificial supplements are available to improve body antioxidants level, among these supplements antioxidant rich beverages including 100% fruit juice, iced tea and red wine are available, apart from these PEWF has the most potent antioxidant capacity. [16]

Results were analyzed and statistically presentation showed that in Z test; the mean level of total cholesterol, triglyceride, HDL, LDL, Non-HDL cholesterol and OX-LDL after post drug analysis of PEWF(active) and placebo shows highly significant ($p<0.05$), this indicate that risk markers for CHD and MI has been reduced significantly. Statistically analysis rejects the Null Hypothesis (H_0) which means that significant difference has been observed in patients with Pre and Post drug effects, which indicates that Alternative Hypothesis (H_1) will be accepted. Mean level of Bio Markers for CHD and MI like hs-CRP and homocystein showed $p<0.05$ after PEWF (active) and placebo medication, Reduction of mean shows the significant prognostic improvement.

In chi square test; when independent variables were tested in both active and placebo medicine, Parameters like Total cholesterol, Serum Triglyceride, HDL, LDL, OX-LDL, hs-CRP and Serum Homocystein shows that $p<0.05$, indicates the prognosis after post drug analysis.

Both Z and Chi square tests highlights that there is significant difference in parameters after post drug analysis and rejection of Null Hypothesis (H_0).

In C.V. when mean of PEWF (active) is compared with placebo for post drug analysis found to be lower than placebo. This indicates that high prognostic effect has been obtained in patients who were in "add-on" therapy of PEWF.

CONCLUSION

Statistically presentation shows that PEWF supplementation as an "ADD-ON" basis with regular medication for MI shows the decrease of cardiac risk factors and improvements of antioxidants status in blood. A significance decrease in biomedical parameters like Serum Homocystein and hs-CRP and OX-LDL are the good sign of prognosis.

In conclusion, The Polyphenols and Antioxidants rich fruit supplements containing PEWF has found to be beneficial in patients with MI & CHD.

ETHICAL CONSIDERATIONS

Ethical clearance has been obtained in written form, Institute Ethics Committee (IEC) of VCSGGIMS&R & SMC. Clearance from Clinical Trial Registry India (CTRI) (A unit of Government of India Undertaking) has been obtained before to conduction of present trial. This trial was conducted according to Good Clinical Practice and the Declaration of Helsinki.

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