Original Paper

EFFECT OF FOLIC ACID SUPPLEMENTATION ON SERUM HOMOCYSTENE AND LIPID PROFILE IN ACUTE MYOCARDIAL INFARCTION

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Abstract

This double blind randomized placebo controlled experimental study was carried out at the department of Biochemistry and Cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh over a period of one year. A total number of sixty (60) hospitalized acute myocardial infarction (AMI) patients of both sexes, age ranging 35 to 65 years, agreed after informed written consent, were included in the study. Cases were selected purposively on the basis of specified inclusion and exclusion criteria from hospitalized diagnosed patients of AMI.

After detail history, clinical examination, physical and anthropometrics measurements study subjects were randomized into two groups and treated with 5 mg folic acid or placebo for 4 weeks. Fasting serum homocysteine (Hcy) and lipid profile of all the study subjects were estimated both before starting the drug and after completion of treatment, Hcy concentration was estimated by fluorescence polarization immunoassay (FPIA) method in 'AxSYM system' (Abbott, USA). Statistical analyses were done by using 'SPSS 12.0, continuous data were expressed as mean ± SEM and categorical data in percentage (%) and frequency. AMI patients Hcy concentration was higher than normal reference value (5 - 15 μmol/L). Folic acid supplementation decreased serum Hcy concentration very significantly ($p<0.001$) in drug group (from 25.92 ± 2.47 to 15.38 ± 0.68 μmol/L) but effect in placebo group was found no significant ($p>0.05$). In this study folic acid supplementation at a dose of 5 mg/day decreased Hcy concentration almost by 27%. Folic acid supplementation significantly ($p<0.05$) increased HDL concentration but shown no significant effect on other parameter of lipid profiles.

Key words: Acute myocardial infarction (AMI), homocystein (Hcy), folic acid (Folate).

Introduction

Acute Myocardial Infarction (AMI) is one of the most common presentations of Coronary Artery Disease (CAD) and CAD is the single most important cause of premature death[1]. In more than 90% cases AMI develops due to atherosclerotic coronary arterial obstruction[2]. Over the past few decades it has been observed that a moderate elevation in plasma concentrations of the amino acid Homocysteine (Hcy) contributes as a risk factor for atherosclerotic vascular disease in the coronary, cerebral and peripheral vessels. Furthermore, this association is graded and independent but may enhance the effect of conventional risk factors also[3].

Hyperhomocysteinemia, a condition that recent epidemiological studies have shown to be associated with an increased risk of atherosclerotic vascular diseases, may be given an equal importance to hypercholesterolemia, hypertension and smoking in the list of etiology of atherosclerosis[4]. In a meta analysis by Boushey et al[3] also suggested that an increase of plasma Hcy by 5 μmol/L could increase coronary risk by a degree similar to an increase by 20 mg/dl of serum cholesterol. Hcy is sulfur containing amino acid, derived from methionine, an essential amino acid and produced in small amounts by the human body. It is metabolized by remethylation (which relies on folic acid and vitamin B_{12}) and transsulfuration (which depends on vitamin B_6)[5]. According to 1999 science advisory from "American Heart Association Nutrition Committee" considered plasma concentrations of fasting Hcy 5 - 15μmol/L as normal[6]. A positive relationship between Hcy and risk of AMI was seen in a large prospective community study from Norway[7]. In the US Physicians Health Study, hyperhomocysteinemia was an independent risk factor for subsequent myocardial infarction (MI) and it was seen that Hcy concentration, more than 16 μmol/L predicted a 3.4 fold increase incidence of MI[8]. Plasma Hcy is determined by both genetic and nutritional factors.

The B-vitamins; folic acid, B_{12} and B_6 all play a key role in Hcy metabolism and in fact it has been proposed that about two-thirds of all cases of hyperhomocysteinemia are due to an inadequate status of one or all of these vitamins. Of the three, folic acid appears to be the most important determinant and has been shown that, it can significantly lower Hcy concentration when administered at doses ranging from 0.2 to 10 mg/day in both healthy

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and hyperhomocysteinemia subjects. It is also found that Hcy levels are inversely related to blood concentrations of folic acid[9].

In a review from series of studies by Lutteri et al[10] suggested that, these vitamins might be given, alone or in combination, for the treatment of hyperhomocysteinemia but folic acid supplementation plays most significant role, though some of these studies showed folic acid in a dose of 0.4 to 5 mg/day can reduce Hcy level by 30% but few others did not find any significant reduction of Hcy. High-dose folic acid (5 mg/day) also improves endothelial function in CAD, though the mechanism is not very clear[11]. Folic acid and vitamin B_{12} are essential coenzymes for the remethylation of Hcy to methionine, and dietary supplementation of these vitamins can lower plasma Hcy by up to 30%[12]. Doshi et al[11] also recommended that only folic acid supplementation at a dose of 5 mg per day can decrease Hcy level by 25%. Moreover folic acid is one of the inexpensive, nontoxic and safely prescribed vitamins. So we have conducted this study to evaluate the effect of oral folic acid supplementation on fasting serum Hcy concentration and lipid profile in AMI patients.

Materials and Methods

This study was a double blind randomized placebo controlled experimental study, carried out at the department of Biochemistry and Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2003 to June 2004. A total number of sixty (60) hospitalized AMI patients of both sexes, age ranging 35 to 65 years, agreed after informed written consent, were included in the study. Patients of less than 7 days onset of AMI, or patients suffering from renal failure or hepatic failure or hypothyroidism or any other case of frank metabolic and/or endocrine disorders or having recent drug history of corticosteroid, methotrexate, carbamazepine or any 'B' group of vitamins were excluded from the study.

After selection of the subjects, the objectives, nature, purpose and potential risk of all procedures used for the study were explained to them. Then detail history, clinical examination, physical and anthropometrics measurements were taken and recorded in a prescribed data collection form. Study subjects were randomized into any of the two groups (Drug / Placebo) and treated with 'yellow capsule' (5mg folic acid or placebo), one capsule daily for 4 weeks. After all aseptic precaution 5 ml fasting blood samples were collected twice (one before starting the drug and another after completion of treatment) from all the study subjects, for estimation of Hcy and lipid profile (TG, TC, HDL-C, LDL-C). Fasting serum total Hcy concentration was estimated by fluorescence polarization immunoassay (FPIA) method in 'AxSYM system' (Abbott, USA) and lipid profiles were measured by auto-analyzer (Bekman Culter, Germany). By using 'SPSS 12.0 for Windows' all the collected raw data was organized into statistical format and appropriate statistical analyses were done. All the continuous data were expressed as mean ± SEM (standard error of mean) and categorical data in percentage (%) and frequency.

Table-I: Socio-demographic characteristics of the study subjects.

Variable	Groups		'p' value
	Drug (n=30)	Placebo (n=30)	
Age in years (mean ± SEM)	50.30 ± 3.52	51.40 ± 2.45	> 0.05
Sex :			
Male	23 (76.7%)	22 (73.3%)	> 0.05
Female	07 (23.3%)	08 (26.7%)	
Life Style:			
Active	12 (40.0%)	10 (33.3%)	> 0.05
Sedentary	18 (60.0%)	20 (66.7%)	
Smoking Status:			
Smoker	20 (66.7%)	22 (73.3%)	> 0.05
Non-smoker	10 (33.3%)	08 (26.7%)	
BMI	28.63 ± 0.59	27.51 ± 0.32	> 0.05
Blood pressure (in mm of Hg)			
Systolic	145.0 ± 6.36	143.0 ± 6.42	> 0.05
Diastolic	089.6 ± 3.73	092.0 ± 4.37	

Note: For Age, BMI & BP 't' test and for Sex, Life style & Smoking status χ^2 test was done.

Results

Socio demographic characteristics like; age, sex, life-style pattern, smoking status, blood pressure (BP) and basal metabolic index (BMI) were found with no significant ($p>0.05$) differences between drug and placebo groups (Table-I). Before supplementation serum homocysteine concentration was 25.92±2.47 (µmol/L) in drug group and 24.80±1.22 (µmol/L) in placebo group. But after supplementation those were 15.38±0.68 (µmol/L) and 23.89±1.31 (µmol/L) respectively. Folic acid supplementation decreased serum homocysteine

Table-II: Effects of Folic-acid supplementation on serum homocysteine

Groups	Hcy concentration (µmol/L)		'p' value
	Before supplementation	After supplementation	
Drug (n=30)	25.92 ± 2.47	15.38 ± 0.68	< .001
Placebo (n=30)	24.87 ± 1.22	23.89 ± 1.31	> 0.05

Note: Paired 't' test between before & after supplementation was done.

Table-III: Effects of Folic-acid supplementation on serum lipid profile.

Groups	Before supplementation	After supplementation	'p' value
TG concentration in mg/dl (mean ± SEM)			
Drug (n=30)	238.7 ± 18.67	217.5 ± 16.15	> 0.05
Placebo (n=30)	223.4 ± 23.08	207.4 ± 22.19	> 0.05
Total Cholesterol concentration in mg/dl (mean ± SEM)			
Drug (n=30)	234.7 ± 09.42	219.0 ± 10.68	> 0.05
Placebo (n=30)	221.6 ± 14.09	212.0 ± 15.39	> 0.05
HDL-Cholesterol concentration in mg/dl (mean ± SEM)			
Drug (n=30)	34.6 ± 1.17	38.9 ± 1.83	< 0.01
Placebo (n=30)	37.1 ± 1.87	38.1 ± 1.02	> 0.05
LDL-Cholesterol concentration in mg/dl (mean ± SEM)			
Drug (n=30)	138.8 ± 16.25	141.1 ± 10.90	> 0.05
Placebo (n=30)	126.5 ± 10.31	120.6 ± 11.26	> 0.05

Note: Paired 't' test between before & after supplementation was done.

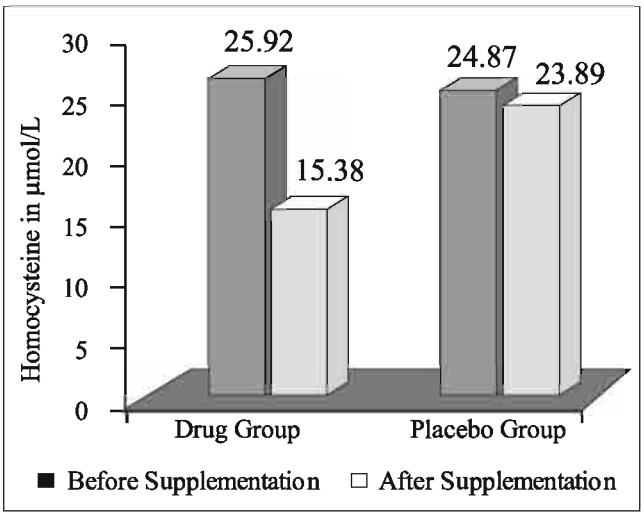

Fig-1: Effects of Folic acid supplementation on serum homocysteine

concentration very significantly ($p < 0.001$) in drug group; but placebo group showed no significant ($p>0.05$) effects (Table-II & Fig-1). Folic acid supplementation also causes significant ($p<0.01$) increase of HDL-cholesterol from 34.6±1.17 to 38.9±1.83 (µmol/L), but no significant ($p > 0.05$) effects were observed on TG, TC and LDL-C of drug group and any lipid profile parameters of placebo groups (Table-III).

Discussion

In this study it was observed that, in AMI patients Hcy concentration was higher than normal reference value. Folic acid supplementation decreased Hcy level very significantly ($p<0.001$), but there was no significant ($p > 0.05$) effect on placebo group. This findings conforms to similar studies [10, 11, 12]. Chambers et al[12] and Lutteri et al[11] found that folic acid supplementation could reduce Hcy level by 30%. On the other hand Doshi et al[10] observed that only folic acid supplementation at a dose of 5 mg/day decreased Hcy level by 25%. In the present study it was found that folic acid supplementation at a dose of 5 mg/day decreased Hcy concentration almost by 27%.

In this study folic acid supplementation increased HDL-C significantly ($p<0.01$). Of course there was no effect on other parameters of lipid profile. Similar type of study done by Chambers et al[12] and Grundy[13] also found folic acid supplementation significantly increased HDL-C concentration, but others did not observed any effect [6, 11].

Conclusion

High level of homocysteine, one of the independent and graded risk factor of subsequent MI, can be minimized almost inexpensively by folic acid supplementation. This study was carried out with small sample size, further studies with large sample size and longer duration and measurement of folic acid level before supplementation can give more conclusive idea and may help to control risk factors of AMI.

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