Effect of Supplementation of Folic Acid and Mecobalamine in Ischemic Stroke Patients With Hyperhomocysteinemia.

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Summary

In vascular diseases like ischemic stroke hyperhomocysteinemia is considered as one of the risk factor. It was found that plasma homocysteine level can be reduced by supplementation of folic acid and was more beneficial when combined with vitamin B^{12}. Ischemic stroke patient were divided into three groups .Group A consisting of 65 patients who received B_{12} (1500ug/day) ,group B with 67 patient received folic acid (5mg/day) and group C with 67 patients received both B_{12} and folic acid for a period of 9 weeks. Plasma level of homocysteine and these vitamins were followed. A significant fall in plasma homocysteine level was seen in all these three groups, with more fall in group C receiving combination therapy. Vitamin B_{12} synergizes with folic acid in reducing plasma homocysteine in patient with ischemic stroke and combine therapy may be effective in the secondary prevention.

Keywords: Mecobalamine , Folic acid, Homocysteine.

Introduction

Homocysteine is metabolized by two pathways which involve remethylation and trans-sulfuration[1].In the remethylation cycle, homocysteine is salvaged for methionine synthesis by addition of methyl group by methionine synthase [2].Vitamine B $_{12}$ is an essential cofactor for methionine synthase and N^5-methyl-tetrahydrofolate serves as methyl donor. Homocysteine enters the trans-sulfuration pathway when an excess methionine is present or cysteine synthesis is required . In this pathway, homocysteine condenses with serine to form cystathionine, which is catalyzed by vitamin B^6 – dependent enzyme cystathionine β-synthase[2].Hence, there close relations between plasma homocysteine and cobalamine, folic acid and vitamin B_6 .[3-7]

   High plasma homocysteine is considered as a risk factor for vascular diseases and plasma homocysteine is increased in ischemic stroke patient [6-9], peripheral occlusive arterial disease [6], and coronary heart disease [10-12]. Daily folic acid supplementation is found to reduce plasma homocysteine in patients with coronary heart disease, and the

combined administration of folic acid with mecobalamine is highly effective in lowering homocysteine levels in all people[13-14.] Reduction in plasma homocysteine, in stroke patients, may be beneficial for secondary prevention, and the aim of present study was to evaluate the homocysteine lowering effect of folic acid and mecobalamine in patients with ischemic stroke.

Methods

The study was conducted in a Private hospital in Bhubaneswar. One hundred and ninety-nine participants were informed on the nature and consent was obtained from each individual. The hospital is a primary clinic, and the stroke patients in the present study included all cases, from those, self-ambulatory at first visit to emergency patients transported by an ambulance. All of them had first ever non cardio embolic ischemic stroke more than one year before and were in convalescent stage. Patient were excluded if they had renal insufficiency (serum creatinine >1.5mg/dl). The diagnosis of ischemic stroke was based on clinical evaluation, MRI brain scans and MRI angiography.Baseline demographic data, history of vascular risk factors were obtained. The stroke cases were divided into two major etiologic subtypes [15];atherothrombotic and lacunar infarction.The former subtype includes ischemic stroke with (a) extra cranial or intracranial occlusive large artery (MRI angiography) (b) no major cardio embolic source and (c)clinical decision that the most likely cause of brain infarction was atherothrombosis involving aortic arch, carotid arteries and their major branches, or vertebral, basilar and posterior cerebral arteries.Lacunar infarction defines ischemic stroke with (a) maintained consciousness and higher cerebral function (b) one of classical lacunar syndrome (pure motor hemiparesis, pure hemisensory loss, pure hemisensorimotor loss ,ataxic hemiparesis) or (c)MRI brain scan showing a small deep infract in the basal ganglia, internal capsule, or brain stem. Patients were divided randomly into three groups. Group A (n=65) received 1500ug/day of mecobalamine orally, group B (n=67) received folic acid 5mg/day and group C (n=67) received both mecobalamine and folic acid for 9 weeks. The control group consisted of 78 ages and gender matched healthy person who did not have history of stroke and vascular disease or vascular risk factors eg. diabetes mellitus, hypertension, hyperlipidemia, smoking, and alcoholism.

Venous blood was collected in fasting state, and total homocysteine in plasma was determined with HPLC. Serum cobalamine and folic acid were determined using a competing protein binding assay kit.

Values are given in terms of mean$\pm$ SD.Unpaired t-test was used to compare laboratory values between patients and control subjects.The changes in laboratory values after 9 weeks were analysed using paired t- test with the baseline values of their respective groups. Probability values less than 5% were considered significant.

Results

Plasma homocysteine was high and serum cobalamine and folic acid was low in all the three groups of patients in comparison to controls. There was a significant difference in the values of plasma homocysteine, cobalamine and folic acid when compared with the control. During the 9 week period plasma homocysteine got reduced in all the three treatment groups. The reduction of plasma homocysteine when compared with their respective baseline values were found to be statistically significant (p<0.01). There has been an increase in folate and cobalamine levels. Serum cobalamine levels in groups A and C were significantly higher and serum folate level in group B and C were significantly higher as compared to their baseline values, these data suggest the possibility of deficiency of these vitamins in patient with stroke.

Table 1: Demographic and baseline clinical characteristics of the stroke patients at study entry

Variables	Control (n = 78)	Group A (n = 65)	Group B (n = 67)	Group C (n = 67)
Age, years	63.7±8.2	63.2±9.5	62.4+10.7	63.9±11.6
Gender, M/F	43/35	38/27	37/30	40/27
Mean duration of illness (days)	-	736±452	752±389	693±285
Lacunar infarction/ Atherothrombotic infarction	-	35/30	39/28	36/31
Hypertension	-	46(71)	42 (63)	41 (61)
Diabetes mellitus	-	20 (31)	23 (34)	21 (31)
Hypercholesteromia	-	21 (32)	18 (27)	19 (28)
Current smoker	-	32 (49)	37 (55)	34 (51)
Previous vascular event		11 (17)	15 (22)	12 (18)
Plasma homocysteine (nmo1/1)	8.6±2.9	11.5±4.2*	11.3±4.0*	11.7±4.5*
Serum folate (nmo1/1)	6.8±2.5	5.5±1.9*	5.7±1.4*	5.8±1.5*
Serum cobalmine (pmo1/1)	881±403	470±213**	439±262**	432±207**

Group A received 1500 µg mecobalmin/day, group B received 5 mg folic acid/day, and group C received 5 mg.Folic acid and 1500 ug mecobalamin/day.

Values are mean ± SD. Values in parantheses are percentage. * *P* <0.01 vs. control.

** *P* <0.0.001 vs. control.

Table 2: Changes after 9 weeks in the 199 subjects who completed the study

Follow up (value at 9 weeks)			
Variables	Group A (n=65)	Group B (n=67)	Group C (n=67)
Homocysteine (nmol/l)	9.8±3.8*	8.6±3.1**	6.9±2.1**
Folate (nmol/l)	6.1±1.8	228±130**	210±105**
Cobalamine (p ml/l)	1112±329**	485±293	936±334**

P<0.01*   Paired t-test with respective baseline value.

P<0.001** paired t-test with baseline value.

Discussion

A close relation between plasma homocysteine level and ischemic stroke was observed as reported [7,9,16,17,] and plasma homocysteine levels are shown to be high in stroke patient both in acute [18,19,] and convalescent stages [8,20-22]. A high homocysteine accelerates the process of atherosclerosis, hence, its reduction may act as secondary prevention in stroke patient.

Data from the Northern Manhattan Stroke study indicate that advance age, male, heavy alcohol consumption, smoking, low serum vitamin B_{12} or folate levels, high plasma methymalonic acid, and low physical activity are factors related to hyperhomocysteinemia [23].The present study shows increase in plasma homocysteine and decrease in folate and cobalamine level in patient with stroke. Supplementation with vitamins like vitamin B_{12} and folic acid decreases plasma homocysteine level in stroke patients in 9 weeks time. . Hyperhomocysteinemia is suggested to be due to impaired transmethylation of homocysteine to methionine . Present study shows combination of folic acid with vitamin B_{12} reduces plasma homocysteine level and suggests its role in remethylation process thus, reducing homocysteine level in stroke patient.

Hence, it is concluded that hyperhomocysteinemia is prevalent in patient with ischemic stroke and supplementation with folic acid and vitamin B_{12} is effective in reducing plasma homocysteine level. Such a therapy may be expected to be beneficial for secondary prevention.

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