Ethnicity Does Not Affect the Homocysteine-Lowering Effect of B-Vitamin Therapy in Singaporean Stroke Patients

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Background and Purpose—Increased total homocysteine (tHcy) is a risk factor for stroke. This study examines whether the efficacy of B-vitamins in reducing tHcy is modified by ethnicity in a Singaporean ischemic stroke population.

Methods—505 patients (419 Chinese, 41 Malays and 45 Indians) with ischemic stroke were randomized to receive placebo or B-vitamins. Fasting blood samples collected at baseline and 1 year were assayed for tHcy. MTHFR polymorphisms were genotyped.

Results—Ethnicity did not independently determine tHcy at baseline. The magnitude of tHcy reduction by B-vitamin treatment was consistent across ethnic groups (Chinese −3.8 ± 4.5, Malay −4.9 ± 4.2, and Indian −3.3 ± 3.6 μmol/L) despite ethnic differences in MTHFR genotype and baseline folate acid (FA) and vitamin B12 (vitB12) concentrations.

Conclusions—Ethnicity does not appear to affect the tHcy-lowering effect of B-vitamins, despite differences in dietary intake and prevalence of MTHFR polymorphisms. This suggests that the effect of B-vitamins in lowering tHcy is generalizable across Asian populations. However, due to relatively small numbers of non-Chinese studied, confirmation in other populations is required. (Stroke. 2009;40:2209-2211.)

Key Words: stroke ■ homocysteine ■ ethnicity

Elevation of total homocysteine (tHcy) has been linked to atherosclerotic vascular morbidity and mortality in a dose-dependent fashion. However, it remains uncertain whether lowering tHcy, by means of B-vitamin therapy, reduces incidence of major vascular events. If ongoing trials confirm the efficacy and safety of B-vitamins in patients with stroke, it will be important to know whether the treatment effect is consistent among patients of different ethnicities, particularly in Asia where the global burden of stroke is greatest and the potential impact of B-vitamin therapy may be greatest.

We had demonstrated that the 5,10-methylenetetrahydrofolate reductase (MTHFR) genotype did not modify the effect of B-vitamin therapy in reducing the mean concentration of tHcy by 3.8 μmol/L compared with placebo after 1 year of treatment. In this study, we aimed to determine whether treatment efficacy is modified by ethnicity, and if so, whether this may be influenced by genetic or dietary factors indirectly measured by serum FA and vitB12.

Subjects and Methods

This study was performed in the Singapore General Hospital (SGH), Singapore as a substudy of the VITATOPS trial. Written informed consent was obtained from all study participants.

Patients’ inclusion and exclusion criteria were as previously described. Patients were randomized to receive B-vitamins (a combination of 2.0 mg FA, 25 mg vitamin B6, and 0.5 mg vitB12) or placebo, both given as a single tablet, once daily. Patients and study personnel were blinded to treatment allocation.

Eligible patients had fasting venous blood specimens collected to measure plasma tHcy, serum FA, and vitB12, and for acquisition of genomic DNA. Repeat blood specimens were collected 1 year after randomization. Samples were processed for tHcy and genomic DNA analysis as previously described. Additionally, serum FA and vitB12 were measured using the chemiluminescent microparticle immunoassay technique (Abbott Diagnostics).

Ethnicity was determined using the Singapore National Registration Identity Card. Eurasians were excluded.

Statistical analyses were carried out using SAS version 8.2 (SAS Institute) by an independent third-party statistician. The primary analysis was a comparison of mean tHcy at 1 year between placebo and B-vitamin treatment arms in the 3 ethnic groups based on the intention-to-treat principle. Our study provided 80% power to detect
The SGH site randomized 733 patients into VITATOPS between July 2000 and March 2006. Baseline tHcy was not measured in 17 patients, 139 did not undergo repeat blood collection due to death, withdrawal from the study, or refusal to have blood taken, and 72 had yet to undergo repeat blood collection by study end. Thus 505 (254 placebo and 251 vitamin treated) patients were eligible for analyses.

The ethnic distribution of study participants was representative of Singapore (Table 1). Baseline demographics and risk factor profiles were similar among ethnic groups apart from a higher prevalence of ischemic heart disease in Indians. At baseline, there was no significant difference in tHcy between the ethnic groups. However, Malays had significantly lower FA and higher vitB12 in comparison to non-Malays. MTHFR C677T allele distribution differed among ethnic groups, with non-Chinese having significantly lower T allele prevalence. MTHFR A1298C allele distribution also differed with non-Chinese having significantly higher C allele prevalence. There were no significant deviations of genotype distributions from expected Hardy-Weinberg equilibrium.

At 1 year, vitB12 remained significantly higher in Malays. There was a similar magnitude of reduction of tHcy associated with B-vitamin treatment across all ethnic groups (Table 2).

Discussion

We did not show any significant differences in baseline tHcy between different Asian ethnic groups despite interethnic differences in FA and vitB12. Our results are consistent with an earlier community-based study in Singapore. It may be hypothesized that in Malays, the effect of lower FA on tHcy

Results

a difference in the change of tHcy levels between baseline and 1 year of 2.0 μmol/L between Chinese and Malays, 1.7 μmol/L between Chinese and Indians, and 2.4 μmol/L between Malays and Indians.
Table 3. Effect of the MTHFR C677T and A1298C Polymorphisms on Plasma tHcy Levels at Baseline and 1 Year

<table>
<thead>
<tr>
<th></th>
<th>Baseline tHcy</th>
<th>1-Year tHcy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Participants Mean (SD)</td>
<td>Placebo Mean (SD)</td>
</tr>
<tr>
<td>MTHFR C677T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>13.5 (4.5)</td>
<td>14.2 (4.7)</td>
</tr>
<tr>
<td>CT</td>
<td>14.0 (4.8)</td>
<td>15.4 (6.8)</td>
</tr>
<tr>
<td>TT</td>
<td>17.1 (7.2)</td>
<td>15.2 (5.6)</td>
</tr>
<tr>
<td>P value (ANOVA)</td>
<td>0.001</td>
<td>0.328</td>
</tr>
<tr>
<td>MTHFR A1298C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>14.6 (5.3)</td>
<td>15.4 (6.2)</td>
</tr>
<tr>
<td>AC</td>
<td>12.9 (4.2)</td>
<td>13.6 (4.8)</td>
</tr>
<tr>
<td>CC</td>
<td>13.2 (4.1)</td>
<td>16.1 (4.5)</td>
</tr>
<tr>
<td>P value (ANOVA)</td>
<td>0.003</td>
<td>0.063</td>
</tr>
</tbody>
</table>

may be offset by higher levels of vitB₁₂. By contrast, a study from the United Kingdom reported that Indian Asians had higher tHcy compared to Europeans, which was attributed to lower vitB₁₂ and FA among Indian Asians.

Our study demonstrated a significantly lower prevalence of T alleles in non-Chinese compared to Chinese, with no TT genotype observed among Indians. A Canadian study showed significant differences in MTHFR C677T allele frequency between Asians and Caucasians, however the prevalence of TT genotype among Chinese was reported to be similar to South Asians. The association of A1298C polymorphism and mean baseline tHcy only in Chinese may be attributable to the low number of non-Chinese subjects. The lack of significant differences in baseline tHcy between ethnic groups despite variation in functional MTHFR polymorphisms suggests that the effect on tHcy of a higher frequency of A1298 C alleles in Indians is possibly offset by the low frequency of C677 T alleles.

The effect of vitamin therapy on tHcy-lowering has not been extensively explored in Asian populations but is critically important because vitamin intake and response to vitamin therapy may vary across different ethnic groups due to differences in food preparation since FA is heat labile and destroyed by prolonged cooking, a feature of Malay cuisine. Moreover, vitB₁₂ may be lower in Indians because of a vegetarian diet.

The strength of our study is the ability to examine the effect of vitamin therapy within the context of a randomized, double-blind, placebo-controlled trial which minimizes systematic bias. Limitations include lack of data on dietary information and socio-economic status together with the relatively small number of non-Chinese in this study, which has limited power.

Our results suggest that the magnitude of reduction in tHcy with B-vitamin therapy does not differ between ethnic groups despite differences in dietary intake and genetic makeup. This indicates that efficacy of B-vitamin therapy in lowering tHcy is likely to be generalizable across Asian populations. However, given the relatively small numbers of non-Chinese in this study, confirmation in other populations is required.

Acknowledgments

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Disclosures

Dr. Chen was a consultant to VITATOPS International Steering Committee. All other authors have nothing to disclose.

References

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