Folic Acid Supplementation for Stroke Prevention in Patients With Cardiovascular Disease

Tao Tian, MD, PhD, Kun-Qi Yang, MD, Jin-Gang Cui, MD, PhD, Lan-Lan Zhou, BN and Xian-Liang Zhou, MD, PhD

ABSTRACT

Background: Controversy remains regarding the efficacy of folic acid supplementation in reducing the risk of stroke. This study aimed to evaluate the effect of folic acid supplementation on stroke prevention in patients with cardiovascular disease (CVD).

Materials and Methods: We searched the PubMed, EMBASE and Cochrane Library databases through October 2016 to identify randomized clinical trials of folic acid supplementation to prevent stroke in patients with CVD. Relative risks (RRs) with 95% CIs were used to examine the association between folic acid supplementation and the risk of stroke with a fixed-effect model. Stratified analyses were performed according to modifiers that may affect the efficacy of folic acid supplementation.

Results: Eleven studies with a total of 65,790 participants were included. Folic acid supplementation was associated with a significant benefit in reducing the risk of stroke in patients with CVD (RR = 0.90; 95% CI: 0.84-0.97; $P = 0.005$). In the stratified analysis, greater beneficial effects were observed in participants with a decrease in homocysteine concentrations of 25% or greater (RR = 0.85; 95% CI: 0.74-0.97; $P = 0.03$), those with a daily folate dose of less than 2 mg (RR = 0.78; 95% CI: 0.68-0.89; $P = 0.01$), and populations in regions with no or partly fortified grain (RR = 0.87; 95% CI: 0.81-0.94; $P = 0.04$).

Conclusions: Our meta-analysis demonstrated that folic acid supplementation is effective in stroke prevention in patients with CVD.

Key Indexing Terms: Folic acid; Homocysteine; Stroke; Cardiovascular disease; Meta-analysis. **[Am J Med Sci 2017;354 (4):379–387.]**

INTRODUCTION

Cardiovascular disease (CVD), a severe disease burden in both developed and developing countries, will be one of the most prominent global public health challenges in the 21st century.[1] Stroke is one of the leading causes of death in the world and threatens the lives of those diagnosed with CVD,[2] thus stroke prevention is of great importance, particularly in patients with CVD. Hyperhomocysteinemia has been identified as a modifiable, independent risk factor for CVD,[3-5] and is associated with an increased risk of stroke. Considerable experimental evidence has been accumulated to support the role of homocysteine in promoting atherosclerosis, including inducing oxidative stress,[6] enhancing inflammatory responses,[7,8] and facilitating endothelial dysfunction.[9] Since 1976, a series of case-control studies have provided epidemiologic evidence that elevated homocysteine concentrations are associated with cardiovascular events.[10-13] Folic acid and B vitamins play important roles in regulating homocysteine metabolism, and it is suggested that folic acid and vitamin B6 and B12 supplementation could reduce plasma homocysteine levels.[14,15] A meta-analysis of observational studies showed that, with a 25% lower homocysteine level, the risk of ischemic heart disease and stroke could be reduced by 11% and 19%, respectively.[4]

In the past 2 decades, studies regarding folic acid supplementation for preventing stroke were widely performed. A population-based cohort study showed that, after 2-year implementation for mandatory folic acid fortification of grain products in the United States and Canada, the mortality rate from stroke improved overall and in nearly all population strata, while there was no improvement in mortality from stroke in England and Wales where folic acid fortification was not required during the same period.[16] Moreover, the HOPE2 study and the SU.FOL.OM3 study showed a 24% and a 41% reduction in the risk of stroke by folic acid supplementation, respectively.[17,18]

However, the efficacy of folic acid supplementation in stroke prevention is still a matter of debate. Several randomized controlled trials (RCTs) with folic acid therapy reported null results.[19-22] A recent meta-analysis indicated that B vitamin supplementation was not associated with a lower risk of stroke.[23] Furthermore, another meta-analysis that analyzed individual participant data of 8 randomized trials concluded that dietary supplementation with folic acid had no significant benefits within 5 years on cardiovascular events,

including stroke.[24] Conversely, Wang et al[25] reported that folic acid supplementation was effective in stroke prevention. In addition, in a recent meta-analysis by Ji et al,[26] the significant benefits of B vitamin supplementation on stroke were also observed, especially in subjects with >130 mm Hg systolic blood pressure and with lower antiplatelet use.

It is of note that these studies analyzed data from participants with different pre-existing conditions, including CVD, end-stage renal disease, esophageal dysplasia, and colorectal adenomas, whereas the efficacy of folic acid supplementation for stroke prevention in CVD population has not been sufficiently analyzed. Therefore, with the recent completion of several randomized trials,[18-20] we decided to perform an updated meta-analysis, focusing on stroke as the disease endpoint in patients with CVD in relation to folic acid supplementation.

MATERIALS AND METHODS

Search Strategy

We searched PubMed, the Cochrane Library, and EMBASE databases up to October 2016 for randomized clinical trials that presented the effects of folic acid supplementation on stroke prevention in patients with CVD. The proceedings from the American Heart Association and American College of Cardiology were manually retrieved. In addition, the reference lists of the identified studies and relevant review articles were also searched. No language restrictions were used. The following terms were used in the search: "homocysteine," "folic acid," "folate," "vitamin B12" and "vitamin B6" crossed with the terms "cardiovascular disease," "myocardial infarct," "myocardial ischemia," "coronary heart disease," "angina," "heart attack," "stroke," "cerebrovascular disease," "cerebrovascular attack," "brain attack," "brain infarct," "brain hemorrhage" and "intracranial hemorrhage." The search was limited to studies in human adults.

Inclusion and Exclusion Criteria

Design of the included study had to meet the following criteria: (1) an RCT, with duration of intervention of at least 1 year; (2) the enrolled participants were at risk of or had established CVD; (3) the intervention group received folic acid with or without vitamin B12 or vitamin B6, and the comparison group received placebo, usual care or low-dose B vitamins and (4) the number of events for stroke that occurred during the trial was reported by intervention and control groups. Privacy rights had been observed for patients in these studies. Our study was approved by the Ethics Committee of Fuwai Hospital.

The exclusion criteria were as follows: (1) studies with patients with end-stage renal disease; (2) the control group received another active therapy that the active treatment group did not receive and (3) a lack of adequate details of study methodology or results from the article or study investigators.

Data Extraction and Quality Assessment

Two investigators (T.T. and K.-Q.Y.) independently selected suitable trials and extracted data from and assessed the quality of included trials. Discrepancies were resolved by discussion with a third reviewer (L.-L.Z.) and by referencing the original report. For each study, the following information was extracted: name of the study, first author, year of publication, sample size, mean age, percentage of male participants, homocysteine levels at baseline and at the end of the study, baseline folic acid levels, vitamin B6 and B12 levels, daily folic acid and vitamin B6 and B12 doses, duration of follow-up, whether there was folic acid fortification, regions where the studies conducted and stroke events.

The quality of the studies was assessed according to the criteria proposed by Juni et al.[27] The criteria included generation of a random sequence, concealment of a treatment allocation schedule, whether the groups were similar at baseline, blinding of patients and caregivers, blinding of outcome assessment, percentage of patients lost to follow-up, and whether all patients were treated as assigned.

Statistical Analysis

Statistical analyses were performed with Review Manager (RevMan version 5.0; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata Statistical Software, Release 12 (StataCorp LP, College Station, TX). Relative risks (RRs) with 95% CIs were used to assess the association between folic acid supplementation and the risk of stroke. And we considered the hazard ratio as RR in the studies. Heterogeneity between trials was assessed using the chi-squared test and I^2 statistics. Heterogeneity was considered significant when the P value of chi square statistics was <0.05. We regarded an I^2 of $<40\%$ as minimal heterogeneity, 40%-75% as modest and $>75\%$ as considerable.[28] We planned to pool data across trials according to the fixed-effects model based on Mantel-Haenszel methods if considerable heterogeneity, $P < 0.05$, or $I^2 > 75\%$ was not present.[29,30] We also compared results obtained from a fixed-effects model with those obtained from a random-effects model to evaluate the influence of small-study effects on the results.[28] Planned stratified analyses were performed based on a decrease in homocysteine levels, intervention regimen, daily dose of folic acid and vitamin B12, baseline level of vitamin B12, prior folic acid grain fortification, history of stroke, and duration of intervention. Meta-regression analysis was performed to identify the relation between a reduction in homocysteine concentrations and the RR of stroke. We also conducted sensitivity analysis by excluding studies that provided unclear methodology or failed to adopt a blind method.