cme.medscape.com

From Medscape Family Medicine > Best Evidence Review

Folic Acid -- Finally Some Good News: A Best Evidence Review

Charles P. Vega, MD

Published: 01/03/2008

Introduction

Best Evidence Reference

Wang X, Qin X, Demirtas H, Li J, Mao G, Huo Y. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. *Lancet*. 2007;369:1876-1882.

Abstract

Stroke is associated with high rates of morbidity and mortality. Folic acid supplementation is a fairly benign intervention which has been hypothesized to reduce the risk for cardiovascular events, but its efficacy in clinical trials has generally been disappointing. The current review refocuses on these trials and the specific effects of folate supplementation on the risk for stroke.

This study was selected from Medscape Best Evidence, which uses the McMaster Online Rating of Evidence System. Of a possible top score of 7, this study was ranked as 6 for newsworthiness and 6 for relevance by clinicians who used this system.

Commentary

Among the diagnoses that clinicians treat, stroke is one of the most serious in terms of mortality and disability. In a study of 279 adults who suffered stroke, the rate of medical complications in the post-stroke period was 95%.[1] Over a period of 3 months, the mortality rate was 14%.

While stroke is associated with a high rate of mortality, it may be becoming less deadly in the developed world. In comparing the periods 1971-1975 to 1988-1994, the number of patients surviving stroke in the United States actually increased.[2] Nevertheless, many patients with a history of stroke live with significant degrees of disability. In the United Kingdom, for example, neurologic damage, which is primarily related to stroke, accounts for approximately 40% of all cases of severe disability.[3]

Depression is one of the most common complications of stroke. In a study of 164 patients with stroke, the rates of depression were 12% at 3 months after stroke but rose to 20.7% at 15 months post-stroke.[4] Depression among these patients was associated with higher rates of cognitive deficits and reduced functional ability, with subjects who had a second cerebrovascular event having the highest rates of depression.

Cognitive disorders are also common after stroke. A study of 190 patients examined 3 weeks after stroke found rates of cognitive impairment up to 74%.[5] Executive function and visual perception/construction were the domains most frequently affected.

Although the neuropsychiatric and functional complications of stroke are well documented, stroke produces a myriad of more subtle effects which can lead to other negative outcomes. For example, impairment of motor, sensory, or cognitive function can increase the risk for fracture; in a study of veterans, fracture occurred in 4.7% to 6.1% of subjects who had experienced stroke.[6]

Appropriate medical therapy and rehabilitation of patients after stroke is important to prevent and treat complications, but the best strategy for reducing the overall burden of disease associated with stroke is primary prevention. The role of homocysteine in promoting cerebrovascular disease is controversial, as is the issue of whether homocysteine reduction with folate and B vitamins can improve the risk for stroke. A population-based cohort study suggested that folic acid fortification of foods in the United States and Canada improved the mortality

rate after stroke in these countries compared with post-stroke mortality rates in England and Wales, where routine folic acid fortification was uncommon.[7]

However, the performance of folate in improving cardiovascular outcomes in clinical trials has been disappointing. It is unclear whether folate can improve endothelial function, and some research has found no effect of folate on this marker of cardiovascular risk.[8] There is even some evidence that folate may do harm in terms of cardiovascular outcomes. In one study, 636 patients who had undergone successful coronary artery stent procedures were randomly assigned to receive folic acid, vitamin B_6, and vitamin B_{12}, or matching placebo.[9] In this study, rates of restenosis of the coronary arteries were actually higher in the folate/B vitamin group compared with the placebo cohort.

Folate was particularly disappointing in improving cardiovascular outcomes in 2 clinical trials. One trial randomized 3749 patients with recent acute myocardial infarction to receive folic acid, vitamin B_{12}, and vitamin B_6, or matching placebo.[10] While the mean total homocysteine level was reduced by 27% among patients in the active treatment group, there was no difference in the rate of recurrent cardiovascular events between the intervention and placebo groups during a mean of 40 months of follow-up. In fact, there was a trend toward an increased risk for these events among subjects receiving folate and B vitamins.

In another trial of 5522 patients with either known vascular disease or diabetes, treatment with folate and B vitamins reduced mean plasma homocysteine levels by 2.4 mmol/L.[11] However, again, treatment with folate and B vitamins failed to improve the rate of a composite outcome of cardiovascular events or the risk for death from cardiovascular causes when compared with placebo treatment.

Nonetheless, the results of this trial were notable for a 25% relative reduction in the risk for stroke among participants receiving folate and B vitamins vs placebo. The authors of a current meta-analysis under review were interested in the particular effects of folate on the risk for stroke, and they performed a literature search for randomized controlled trials published between 1966 and 2006 which addressed this issue. Studies were included only if they documented more than 10 incident cases of stroke and followed patients for at least 6 months, and researchers included trials that allowed concurrent treatment with B vitamins during folate therapy.

Of 308 abstracts reviewed, the authors focused on 8 trials. The total number of patients in these trials was 16,841. The dosage of folic acid varied significantly in the research, from 0.5 mg per day to 15 mg per day. Generally, the studies included in the meta-analysis had an average patient age of mid-60s. Three trials were completed in areas where grain was enriched with folate, and 4 trials were performed in areas without grain enrichment. Only one trial focused on patients without a preexisting history of cardiovascular disease or end-stage renal disease.

Overall, folate supplementation reduced the risk for stroke by 18%, a significant benefit compared with placebo. There were some interesting caveats to the positive results associated with folate therapy. An analysis of study characteristics suggested that only trials lasting over 36 months demonstrated a significant benefit for folate therapy. In addition, folate was effective only in areas without grain enrichment and among patients without a previous history of stroke.

The relative reduction in homocysteine associated with folate treatment vs placebo varied between 10.9% and 39.4%. In trials in which the mean relative reduction in homocysteine levels associated folate was less than 20%, active treatment was not superior to placebo in preventing stroke. However, the relative risk for stroke among subjects receiving folate vs placebo when homocysteine reduction was 20% or more was 0.77.

Although the overall results of the meta-analysis are positive, the research has some limitations. The optimal dosage of folate could not be derived from available research, and most trials included concurrent treatment with vitamin B_6 and vitamin B_{12}, clouding the issue of which part of therapy was most effective for stroke prevention. Moreover, most trials were focused on combined cardiovascular endpoints as opposed to stroke specifically as the primary outcome. Collectively, this may weaken their methodologic rigor in focusing on the risk for stroke associated with folate vs placebo therapy.

The meta-analysis should help clinicians to reach some (tentative) conclusions. It generally supports the concept of

fortification of grain with folic acid. However, in many Western countries this routine practice obviates the need for additional folate therapy to individual patients to prevent stroke. In countries that do not routinely fortify grain, clinicians need to keep in mind that folate therapy should be initiated prior to the first cerebrovascular event, and it may be effective only when continued over a period of years. Providers may also consider titrating the dose of folic acid to achieve a reduction in homocysteine levels which exceed 20%, if such monitoring is feasible in the practice setting.

Folic acid supplementation is associated with a very low rate of adverse events, which include rash, pruritus, and malaise. It is available naturally mostly in green vegetables but is also present in some animal products. Given the significant mortality and morbidity associated with stroke, it appears reasonable to consider prescribing folate to at-risk patients. However, this benefit may be limited to countries where routine folate fortification has not been implemented.

The current meta-analysis focused on patients at high risk for stroke. While the scope of a trial of folate to prevent stroke among adults at average risk would be daunting, it would also be highly worthwhile in determining whether folate therapy should be applied to a larger proportion of adults.

References

1. Johnston KC, Li JY, Lyden PD, et al. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. Stroke. 1998;29:447-453. Abstract
2. Muntner P, Garrett E, Klag MJ, Coresh J. Trends in stroke prevalence between 1973 and 1991 in the US population 25 to 74 years of age. Stroke. 2002;33:1209-1213. Abstract
3. Ward NS. Mechanisms underlying recovery of motor function after stroke. Postgrad Med J. 2005;81:510-514. Abstract
4. Brodarty H, Withall A, Altendorf A, Sachdev PS. Rates of depression at 3 and 15 months poststroke and their relationship with cognitive decline: the Sydney Stroke Study. Am J Geriatr Psychiatry. 2007;15:477-486. Abstract
5. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, De Haan EH, Kappelle LJ. Cognitive disorders in acute stroke: prevalence and clinical determinants. Cerebrovasc Dis. 2007;23:408-416. Abstract
6. Whitson HE, Pieper CF, Sanders L, Horner RD, Duncan PW, Lyles KW. Adding injury to insult: fracture risk after stroke in veterans. J Am Geriatr Soc. 2006;54:1082-1028. Abstract
7. Yang Q, Botto LD, Erickson JD, et al. Improvement in stroke mortality in Canada and the United States, 1990 to 2002. Circulation. 2006;113:1335-1343. Abstract
8. Hirsch S, Pia De la Maza M, Yanez P, et al. Hyperhomocysteinemia and endothelial function in young subjects: effects of vitamin supplementation. Clin Cardiol. 2002;25:495-501. Abstract
9. Lange H, Suryapranata H, De Luca G, et al. Folate therapy and in-stent restenosis after coronary stenting. N Engl J Med. 2004;350:2673-2681. Abstract
10. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med. 2006;354;1578-1588. Abstract
11. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med. 2006;354:1567-1577. Abstract

Authors and Disclosures

As an organization accredited by the ACCME, Medscape, LLC requires everyone who is in a position to control the content of an education activity to disclose all relevant financial relationships with any commercial interest. The ACCME defines "relevant financial relationships" as financial relationships in any amount, occurring within the past 12 months, including financial relationships of a spouse or life partner, that could create a conflict of interest.

Medscape, LLC encourages Authors to identify investigational products or off-label uses of products regulated by the US Food and Drug Administration, at first mention and where appropriate in the content.

Author(s)

Charles P. Vega, MD

Associate Professor; Residency Director, Department of Family Medicine, University of California, Irvine

Disclosure: Charles P. Vega, MD, has disclosed that he has served as an advisor or consultant to Novartis.

Editor(s)

Carol Peckham

Director, Editorial Development, Medscape, LLC

Disclosure: Carol Peckham has disclosed no relevant financial relationships.

Contents of *Folic Acid -- Finally Some Good News: A Best Evidence Review* [http://cme.medscape.com/viewprogram/8493]

CME/CE Information

CME/CE Released: 01/03/2008; Valid for credit through 01/03/2009

This activity has expired.

The accredited provider can no longer issue certificates for this activity. Medscape cannot attest to the timeliness of expired CME activities.

Target Audience

This activity is intended for family physicians, physician assistants, nurse practitioners, and nurses who treat patients at risk for stroke.

Goal

The goal of this activity is to educate health professionals on the evidence concerning homocysteine, folic acid, and stroke prevention.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Describe rates of mortality and morbidity associated with stroke

2. Describe the role of homocysteine and homocysteine reduction in stroke
3. Identify outcomes of folate supplementation in previous clinical trials
4. Specify factors that might make folate more effective in preventing stroke

Credits Available

Physicians - maximum of 0.25 *AMA PRA Category 1 Credit(s)™*

Nurses - 0.25 *nursing Contact Hour(s)* (0 contact hours are in the area of pharmacology)

All other healthcare professionals completing continuing education credit for this activity will be issued a certificate of participation.

Physicians should only claim credit commensurate with the extent of their participation in the activity.

Accreditation Statements

For Physicians

MedscapeCME Medscape, LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Medscape, LLC designates this educational activity for a maximum of 0.25 ***AMA PRA Category 1 Credit(s)*** . Physicians should only claim credit commensurate with the extent of their participation in the activity.

Contact This Provider

For Nurses

This Activity is sponsored by Medscape Continuing Education Provider Unit.

Medscape is an approved provider of continuing nursing education by the New York State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

Awarded 0.25 contact hour(s) of continuing nursing education for RNs and APNs; none of these credits is in the area of pharmacology.

Provider Number: 6FDKKC-PRV-05

Contact This Provider

For questions regarding the content of this activity, contact the accredited provider for this CME/CE activity noted above. For technical assistance, contact CME@medscape.net

Instructions for Participation and Credit

There are no fees for participating in or receiving credit for this online educational activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within the time designated on the title page; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity online during the valid credit period that is noted on the title page.

Follow these steps to earn CME/CE credit*:

1. Read the target audience, learning objectives, and author disclosures.
2. Study the educational content online or printed out.
3. Online, choose the best answer to each test question. To receive a certificate, you must receive a passing score as designated at the top of the test. Medscape encourages you to complete the Activity Evaluation to provide feedback for future programming.

You may now view or print the certificate from your CME/CE Tracker. You may print the certificate but you cannot alter it. Credits will be tallied in your CME/CE Tracker and archived for 6 years; at any point within this time period you can print out the tally as well as the certificates by accessing "Edit Your Profile" at the top of your Medscape homepage.

*The credit that you receive is based on your user profile.

Hardware/Software Requirements

Medscape requires version 4.x browsers or higher from Microsoft or Netscape. Certain educational activities may require additional software to view multimedia, presentation or printable versions of their content. These activities will be marked as such and will provide links to the required software. That software may be: Macromedia Flash, Apple Quicktime, Adobe Acrobat, Microsoft Powerpoint, Windows Media Player, and Real Networks Real One Player.