Homocysteine and stroke prevention: Have the trials settled the issue?

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Abstract Recent publicity surrounding disappointing results of clinical trials of homocysteine lowering has led to the claim that 'homocysteine is dead'. However, there is strong evidence that elevated plasma total homocysteine is an important independent risk factor, and the highly plausible biological rationale is the following: total homocysteine increases coagulation, impairs endothelial function, increases oxidative stress and low density lipoprotein oxidation, and treatment with vitamins reverses these effects and hails progression of carotid plaque. Some studies have shown clinical benefit of vitamin therapy in coronary angioplasty and peripheral vascular disease. It has recently become apparent that vitamin B12 absorption is impaired in the elderly, and that metabolic B12 deficiency is much commoner than would be appreciated by statistical definitions of 'normal' serum B12; higher doses of B12 and perhaps other therapies such as betaine and thiols may be needed to achieve adequate reductions of total homocysteine. It remains likely that effective lowering of total homocysteine will reduce stroke and other vascular events.

Key words: Homocysteine, B12, Vitamin, Stroke, Prevention, Cardiovascular

Homocysteine as a risk factor

In 1997 two important prospective studies showed that tHcy was a significant independent risk factor for myocardial infarction and stroke, with a doubling of vascular risk for levels of tHcy above 10 (5), and that the risk increases steeply with tHcy; levels of tHcy above 20 are associated with an eightfold increase in vascular risk (6). Some of the mechanisms by which tHcy harms include increased thrombosis, impaired endothelial function, increased oxidative stress and increased oxidation of LDL (7,8).

Effects of vitamin therapy

Treatment with folic acid, pyridoxine (B6) and cobalamin (B12) reduces levels of tHcy (9) and reverses endothelial dysfunction associated with elevated tHcy (10–12). In patients with renal failure, whose cardiovascular risk is elevated approximately 17-fold (13), vitamin therapy lowers tHcy, fibrinogen and Lp(a) (14). In patients with progression of carotid plaque despite treatment for traditional risk factors, treatment with folate/B6/B12 halted progression of carotid plaque, both in patients with tHcy >14 (15) and in patients with normal levels of tHcy (16). In patients with peripheral vascular disease, vitamin therapy reduced new onset of myocardial ischemia in patients with peripheral vascular disease (17).

In patients undergoing coronary angioplasty, a study with higher doses of B12 showed slowing of restenosis (18) and a reduction of clinical events (19). A study in coronary angioplasty patients with similar doses of folate and B6, but only 40mcg daily of B12, did not show any benefit of vitamin therapy (20). This discrepancy raises a key issue in clinical trials of homocysteine lowering.

Recent large clinical trials of secondary prevention

More recently, three clinical trials have not shown reduction of cardiovascular events with folate, B6 and B12. The Vitamin Intervention for Stroke Prevention (VISP) trial was a second-
ary prevention trial in patients with nondisabling stroke. Patients were randomized to a multiple vitamin, which contained the usual recommended daily intake of other vitamins, with either a low dose or high dose of folate, B6 and B12 (8). The intention-to-treat analysis showed no benefit of high-dose vitamins (21). The Norwegian trial of vitamins in patients with coronary artery disease (NORVIT) found no benefit of folate/B6/B12 (22), and the HOPE-2 trial failed to show a reduction of the primary event (23). However, HOPE-2 did show a significant reduction of stroke and of acute coronary syndrome. There was also an apparent separation of the survival curves in favour of the active vitamin therapy.

Inadequate doses of vitamin B12

A key reason why these studies may not have shown the expected benefits is that the doses of vitamin B12 used in all the studies may have been too low for elderly patients. In addition to achlorhydria and loss of intrinsic factor, there are several other ways in which absorption of B12 can become disordered. Salivary and pancreatic factors are also required for B12 absorption, the distal ileum must function properly, and transport proteins such as transcobalamin may be deficient on a hereditary or acquired basis (24, 25). A statistical definition of ‘normal’ serum B12, i.e. the mean + 2 standard deviations, is an insensitive way to detect true metabolic deficiency of B12, which is defined by elevation of methylmalonic acid and/or homocysteine (26). By definition, only 2-5% of the population would be above and 2.5% below the ‘normal’ range. In folate-replete individuals (which, as folate fortification of grain products in North America means 99% of the population), a methylmalonic acid level above 271 nmol/l or tHcy above 14 mol/l can be taken as evidence of B12 deficiency. Metabolic deficiency of B12 is present in approximately 20% of the elderly (27). Quinlivan found that in folate-replete subjects, B12 assumes a major role in determining levels of tHcy (28). Robertson et al. (29) found that in the era of folate fortification, serum B12 was a key determinant of tHcy, and patients with low serum B12 and high tHcy had significantly more carotid plaque. In their population of patients from vascular prevention clinics, 17% had metabolic B12 deficiency; when their study population was divided into tertiles by age, the prevalence of metabolic B12 deficiency was 12% below age 50, 13% between ages 50 and 71, and 30% above age 71.

A dose–response study in patients over age 65 with serum B12 below 221 showed that a B12 dose of 1000 mcg/day was required to overcome metabolic B12 deficiency (30), but all the major clinical trials have used a B12 dose of half that, or less.

Efficacy analysis of the VISP trial

In the VISP trial, we did not have a placebo control. We used a multiple vitamin with the recommended daily intake of many vitamins, with either a high or low dose of folate, B6 and B12. Folate fortification of grain products in North America coincided with the initiation of VISP, and thus the effect of folate in the high-dose arm was largely negated, as the average folate intake of 400 mcg/day achieved with folate fortification is very similar to the doses of folate that Verhoef et al. (31) found to be the top end of the dose–response curve. In addition to using too low a dose of B12 for elderly subjects in the high-dose arm of the study (400 mcg/day), we gave the recommended daily intake of B12 in the low-dose arm (6 mcg/day). We further negated the effect of B12 in VISP by giving injections of B12 to patients with low B12 levels, thus eliminating the effect of high-dose vitamins in patients who stood to benefit most. Furthermore, patients with renal failure are known to be less responsive to vitamin therapy (32).

We therefore, hypothesized that patients capable of responding to the randomized therapy in VISP would be those who could absorb B12 adequately, did not receive B12 injections, and did not have renal failure. An efficacy analysis of the VISP trial, in that subgroup of patients hypothesized as above to be capable of responding, showed a significant reduction of stroke and coronary events, and of stroke, death and coronary events. By stratifying the patients in that subgroup according to the median serum B12 at entry (313 pmol/l), it became apparent that B12 status at baseline was the key determinant of response to vitamin therapy. Patients with entry levels of B12 above 313 pmol/l assigned to high-dose vitamins had the lowest rate of cardiovascular events; patients with lower B12 levels at entry assigned to low-dose vitamins fared the worst, and the other two groups were in between. In the overall analysis the reduction of stroke/death/coronary events was 20% (p = 0.049), but comparing the two outer groups, the difference in events was 33% (12% in the high-dose vs. 18% in the low-dose arm; p = 0.02).

Better treatment is needed

In addition to higher doses of B12, it may be important to consider other therapies to lower homocysteine (33). Thiol compounds, which pull homocysteine off plasma proteins and thus make it more readily excreted in the urine or dialyzed (34, 35) and betaine (36) (trimethylglycine, a methyl donor) are possibilities under study.

Conclusion

Despite recent claims that ‘homocysteine is dead’, it appears likely that therapy to lower levels of homocysteine may yet prove effective. The evidence that homocysteine is an independent risk factor is strong; the mechanisms are plausible, and some studies show benefits on biomarkers; a hypothesis-driven subgroup analysis of VISP suggests benefit. The Vitamins to Prevent Stroke (VITATOPS) trial (37), and other trials are still under way; their results, and perhaps combined analyses of trials, are eagerly awaited.
References


