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Original Article

A randomized placebo controlled trial of homocysteine lowering to reduce cognitive decline in older demented people☆

T. Kwok [a,*], J. Lee [a], C.B. Law [b], P.C. Pan [c], C.Y. Yung [d], K.C. Choi [e], L.C. Lam [f]

[a] Department of Medicine and Therapeutics, Prince of Wales Hospital and Shatin Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong
[b] Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong
[c] Psychogeriatric Service, United Christian Hospital, Hong Kong
[d] Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong
[e] Centre for Epidemiology and Biostatistics, School of Public Health, The Chinese University of Hong Kong, Hong Kong
[f] Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong

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SUMMARY

Introduction: Whether homocysteine lowering by B vitamins can reduce cognitive decline in Alzheimer disease and vascular dementia patients is unclear.
Methods and materials: 140 subjects with mild to moderate Alzheimer disease or vascular dementia were randomly assigned to take 1 mg of methylcobalamin and 5 mg of folic acid, or placebo once daily for 24 months. The primary outcome was Mattis dementia rating scale (MDRS). Secondary outcomes were MDRS domain scores, neuropsychiatric inventory and Cornell scale for depression in dementia. Measurements were performed at baseline and every six months during the study. Fasting plasma tHCY concentrations were measured at baseline and month 18.
Results: Trial groups were well matched in baseline characteristics. The average plasma tHCY concentration of subjects was 14.1 ± 3.8 μmol/L. 80% of subjects completed the trial. The supplement group had average plasma tHCY reduced to 9.3 ± 2.7 μmol/L. There was no significant group difference in changes in any of the neuropsychological scores, but among those with elevated plasma tHCY (>13 μmol/L), the decline in MDRS (construction domain) was significantly smaller in the supplement group (median 0 versus 2 points in placebo group, $P = 0.003$).
Conclusion: Homocysteine lowering in dementia patients did not significantly reduce global cognitive decline.

1. Introduction

Alzheimer disease (AD) and vascular dementia are associated with elevated plasma total homocysteine (tHCY). For example, plasma tHCY is elevated in patients with AD,[1] stroke and post stroke cognitive impairment.[2] In addition, in population based studies of older people, elevated plasma tHCY is associated with silent brain infarcts, small vessel disease in the brain,[3] and cognitive impairment.[4] In prospective cohort studies of older or middle aged people, elevated plasma tHCY is associated with higher incidence of dementia, Alzheimer disease,[5] silent infarcts[6] and accelerated brain atrophy.[7] In particular, plasma tHCY ≥ 14 μmol/L in older people was associated with a two-fold increase in risk of AD.[5]

Randomized placebo controlled trials (RCT) of homocysteine lowering in cognitively normal older people for up to two years had shown no significant difference in cognitive change[8,9] though significant benefits in memory, information processing speed and sensorimotor speed over three years were found in one randomized trial of folic acid supplement.[10]

In a recent randomized placebo controlled trial of homocysteine lowering by B vitamins in older people with mild cognitive impairment (MCI), a prodromal stage of dementia, the active group had significantly lower rate of brain atrophy as measured by serial volumetric MRI over two years.[11] Consistent with the hypothesis that homocysteine contributes to cognitive decline, those supplemented subjects with elevated plasma tHCY (>13 μmol/L) had greater relative reduction (50%) in rate of brain atrophy, while those with normal plasma tHCY (<9.5 μmol/L) showed no reduction. Interestingly those with history of stroke or transient ischemic attack benefited more from supplementation.

There is a lack of randomized trials of homocysteine lowering in persons with clinical dementia. In one prospective study of mild to moderate dementia outpatients, only those with plasma tHCY > 19.9 μmol/L improved significantly in cognitive function

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* Corresponding author. Tel.: +852 26323594; fax: +852 26373852.
E-mail address: tkwok@cuhk.edu.hk (T. Kwok).

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after two months of oral vitamin B_{12} and folic acid.[12] In a large RCT of homocysteine lowering by B vitamins in mild to moderate AD patients, no benefit in cognition as measured by ADAS Cog was observed over an eighteen month period.[13] However, probably because of the common use of vitamin supplements and the mandatory folic acid fortification of flour in the United States, the average baseline plasma tHCY of the trial participants was only 9.2 μmol/L, which was much lower than the levels previously reported in populations of people with dementia.[5,3] In addition, ADAS Cog may not be sensitive enough to detect small cognitive changes.[14] The exclusion of subjects with co-existing cerebrovascular disease also limited the generalizability of the findings.

We therefore reported a RCT of homocysteine lowering in outpatients with Alzheimer or vascular type dementia in Hong Kong where there was no mandatory or voluntary folic acid fortification policy. The hypothesis was that homocysteine lowering by high dose oral vitamin B_{12} and folic acid would lower the rate of cognitive decline in demented people.

2. Subjects and method

This was a double blind randomized placebo controlled trial of 1 mg of methylcobalamin and 5 mg of folic acid in demented patients over a twenty four month period. According to a meta-analysis, this combination of vitamins can be expected to lower plasma tHCY by an average of 32%.[15] Neuropsychological testing was performed once every six months and plasma tHCY was measured at baseline and month 18. The protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

Mild to moderate dementia Chinese patients aged 60 years or more were recruited from memory, psychogeriatrics or geriatrics clinics of Prince of Wales Hospital, Taipo Nethersole Hospital, Northern District Hospital, Princess Margaret Hospital and United Christian Hospital in Hong Kong. These publicly funded hospitals were located in three major health regions in Hong Kong, with a total catchment population of over three million people. Dementia was diagnosed by psychogeriatricians or geriatricians after a detailed history of dementia and co-existing illnesses and a neurological examination, including mini-mental state examination. The diagnosis and classification of dementia were determined clinically as well as by CT head scan appearance according to NINCDS–ADRDA criteria for AD[16] and NINDS–AIREN criteria for vascular dementia.[17] AD with clinical or radiological evidence of cerebrovascular disease was regarded as mixed dementia. Subjects with other types of dementia were excluded (see Fig. 1).

All potential subjects had blood taken for serum vitamin B_{12}, folate, creatinine, complete blood count, thyroid function test, and Venereal Disease Research Laboratory (VDRL) test for screen for syphilis. Those with serum vitamin $B_{12} < 150$ pmol/L, folate < 9.5 nmol/L, creatinine > 250 μmol/L, hypothyroidism and syphilis were treated medically and excluded from the trial.

After obtaining written consent from the eligible subjects or family caregivers (if the subjects were incapable of giving informed consent), blood samples were taken after an overnight fast. Plasma was separated within 3 h and kept frozen at −80 °C. The frozen samples were later thawed and analyzed for homocysteine by IMX method by a trained laboratory technician.[18] Plasma tHCY >13 μmol/L was considered to be elevated. In order to confirm the long term effectiveness of vitamin supplementation in lowering plasma tHCY in most subjects, fasting blood was taken in the same way at month 18 for plasma tHCY, serum vitamin B_{12} and folate.

Neuropsychological test battery was administered by one designated trained research assistant (RA). It included Cantonese version of mini-mental state examination (MMSE),[19] and Chinese Mattis Dementia Rating Scale (MDRS).[20] The MDRS assesses global cognitive function, consisting of 36 items in five subscales – attention, initiation/perseveration, construction, conceptualization and memory. The maximum total and domain scores are 144, 37, 37, 6, 39 and 25 respectively. The MDRS was selected as the primary outcome because it yields a total score as well as individual domain scores that represent functioning in different cognitive areas. The domain titles are self-explanatory except for initiation/perseveration, which is generally considered to be reflective of executive ability.

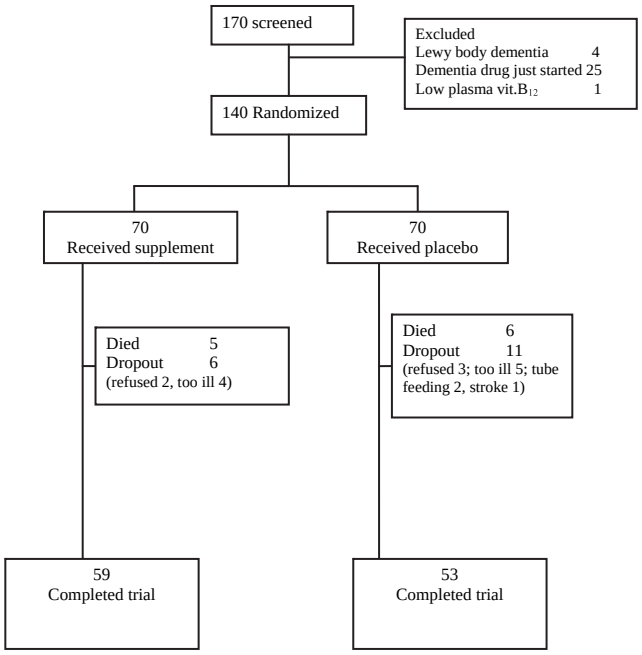

Fig. 1. Recruitment and dropout.

Family caregivers were interviewed by the Chinese version of the Neuropsychiatric Inventory (CNPI) which had been locally validated to quantify neuropsychiatric symptoms associated with dementia. The maximum total score is 144.[21] The clinicians aided by the family caregivers administered the Cornell scale for depression in dementia (CSDD)[22] which has been validated for depression in dementia. It is based on the combination of clinical observation and informant-based questions. A score of 8 or more suggests depression. The inter-rater reliability kappa was 0.67. The group difference in the incidence of depression at any follow-up visit among those who were not depressed at baseline was compared by Chi square test. Depression was defined by scores of 8 or greater in the Cornell Scale for Depression in Dementia, or the documented prescription of anti-depressant.

2.1. Randomization

Double blind randomization was performed. The subjects, RA's and clinicians were kept blinded to the group assignment. The supplement group subjects took one capsule containing methylcobalamin 1000 μg in powder form and one capsule containing folic acid 5 mg in powder form once daily. The placebo group subjects took two capsules containing starch but with appearances identical to those containing methylcobalamin or folic acid. One-month supply of trial capsules was packaged in separate bottles and three-month supply of trial capsules was dispensed to family caregivers at each follow-up visit. Drug administration was supervised or directly performed by family caregivers. A pill count was performed by RA at each follow-up visit. All subjects were allowed to take any other medication, except B vitamins. Cholinesterase inhibitors were allowed if they had been taken for more than three months before