VITATOPS - COGNITIVE SUB-STUDY

A trial of vitamin therapy in the prevention of dementia and cognitive deterioration following stroke

Brief description of proposal

This study will use a comprehensive cognitive assessment battery to assess for the development of dementia or cognitive deterioration following stroke in 1500 patients. It will be a substantive sub-study of VITATOPS which is a randomised, placebo controlled, double blind, multi-centre international study of 8000 patients whose primary objective is to examine the efficacy and safety of vitamin (B12, B6 and folic acid) therapy in patients after a Transient Ischaemic Attack (TIA) or stroke in the prevention of death from all vascular causes, stroke and myocardial infarction. Although one of the secondary objectives of VITATOPS is to determine if vitamin therapy will reduce the incidence of dementia after stroke or TIA, cognitive examination is limited to use of the MMSE and is not mandatory for all centres. Thus, this present study will be unique in that 1) a comprehensive neuropsychological battery will be utilised in all patients and 2) the efficacy of vitamin therapy on the prevention of cognitive deterioration or dementia after stroke will be the primary outcome.

Rationale

Studies have shown that high levels of homocysteine in the blood can lead to atherosclerosis and may be a risk factor for the development of dementia. Homocysteine levels can be effectively lowered using vitamins but as yet, there is no evidence from randomised controlled trials in high risk populations that vitamin treatment can prevent cognitive deterioration or dementia.

Distinguishing features

The main trial centre in Perth is funded by the National Health and Medical Research Council of Australia. Support is requested for a substantial, separate and unique Singaporean study which aims to 1) use an extensive, locally validated cognitive assessment battery to examine the efficacy of vitamin therapy in the prevention of dementia or cognitive deterioration following stroke and 2) identify risk factors (including genetic) for dementia and cognitive deterioration after stroke in Asians.

Relevance to science and medicine*:*

Stroke is the fourth largest cause of death and the most common cause of adult disability in Singapore. Survivors remain at increased risk of having another stroke, myocardial infarction, peripheral vascular disease or developing dementia. It is therefore important to have effective secondary prevention strategies. Furthermore, as cerebrovascular disease is an important cause of dementia in Singapore and Asia, studies are required to identify risk factors and effective therapies.

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DETAILS OF RESEARCH PROPOSAL

Aims of the project

1. To examine the efficacy and safety of multi-vitamin (B12, B6 and folic acid) therapy in patients after a Transient Ischaemic Attack (TIA) or stroke in the prevention of dementia or cognitive deterioration following stroke.
2. To identify risk factors for dementia or cognitive deterioration following stroke.

Background work

The need for better secondary prevention strategies in stroke

Stroke is a major cause of death and long term disability. Despite best medical and surgical therapy (including risk factor modification), stroke survivors are at a significantly increased risk of recurrent vascular events, with an annual risk of stroke, myocardial infarction and death from any vascular cause of about 8% in a recent multi-centre trial of secondary prevention in stroke[1]. Furthermore, dementia is a common sequelae of stroke with a frequency ranging from 16% to 32%[2-4]. Stroke is a strong risk factor for dementia with a relative risk of 5.5 compared to controls[5]. Viable new strategies for secondary prevention and the prevention of dementia after stroke are urgently needed.

Hyperhomocysteinaemia may be a modifiable risk factor for vascular disease and dementia

Systematic reviews of epidemiological studies have shown biologically plausible evidence linking hyperhomocysteinaemia (HHC) in a strong, consistent, independent, dose dependent fashion to atherosclerotic vascular morbidity and mortality[6-7]. HC induces smooth muscle cell proliferation, causes toxicity to endothelial cells by inducing lipid peroxidation and interferes with the vasodilator and anti-thrombotic functions of NO[8]. Plasma levels of HC have been correlated with increasing carotid arterial intimal thickness and extra-cranial carotid artery stenosis[9-10].

HC has been found to be inversely related to cognitive performance in demented patients[11] whilst low blood levels of folate and vitamin B12, and elevated HC levels are associated with Alzheimer's Disease and vascular dementia[12-14]. HHC has been associated with vascular cognitive impairment due to intracranial small vessel disease[15] as well as to silent brain infarcts and white matter lesions[16-17]. Furthermore, a recent prospective study has convincingly shown that in elderly non-demented subjects, there is a strong graded association between HC and the risk of newly diagnosed dementia over an 8 year period of observation[18]. Although patients with mild to moderate dementia and elevated plasma homocysteine levels improved clinically after vitamin supplementation in a small open study[19], it remains to be demonstrated by randomised controlled trials that lowering HC reduces the risk of dementia.

Risk factors for post-stroke dementia

A small number of studies have shown that multiple factors including stroke features (dysphasia, major dominant stroke syndrome), host characteristics (educational level), and prior cerebrovascular disease each independently contribute to the risk of post-stroke dementia[3]. Other factors include stroke subtype (both small subcortical and large cortical

infarcts especially involving the left medial frontal and temporal regions) and additional contributions by demographic and modifiable vascular risk factors[20-21]. Since it is now recognised that the conventional definition of vascular dementia is deficient as stroke may produce a spectrum of cognitive changes but not necessarily prominent memory loss as in Alzheimer's Disease, the concept of "cognitive impairment but not dementia" should also be utilized to better study the full cognitive burden of cerebrovascular illness[22]. There remains a need for well designed studies to identify significant and novel risk factors for post-stroke dementia and cognitive deterioration. This may be particularly relevant for Singapore where dementia is a rapidly growing problem in our fast-ageing population.

Factors influencing homocysteine levels

Plasma homocysteine levels are determined by genetic and nutritional factors. HHC may be caused by deficiency of cystathione beta synthase or methylene tetrahydrofolate reductase (MTHFR). The frequency of mutations in the genes for these enzymes will be a useful field of study in Singaporeans as will be other candidate genes for vascular disease susceptibility. Reduced levels of vitamin co-factors for the re-methylation (folate and B_{12}) and transulphuration (B_6) pathways of HC metabolism may also cause HHC. The prevalence of deficiencies in these vitamins has been little studied in Singaporeans but may be a cause of HHC in stroke.

Homocysteine lowering therapy

An optimal HC lowering regime appears to be a combination of B_{12} 400 micrograms, $B_6$25 milligrams and folate 2 milligrams daily.

Relevant work by the investigators:

- The NMRC has previously funded a study to establish norms for a vascular dementia neuropsychology battery (NMRC/0281/1998). This study has been completed with over 150 normal volunteers recruited for assessment. The data collected has been analysed and a paper submitted for publication (Yeo et al).

- The above vascular dementia neuropsychology battery is being used in ongoing studies and has proved practical to administer with preliminary results indicating that the vascular dementia neuropsychology battery is useful in assessing cognitive performance in stroke patients.

  Briefly, of the 252 patients recruited into a longitudinal study of cognitive performance after stroke, 40% at baseline cognitive assessment were "cognitively impaired, not demented". At 1 year follow-up, 11% of those found to be "cognitive impaired, not demented" at baseline had progressed to dementia whilst 10% of initially "cognitively intact" had progressed to being "cognitively impaired, not demented". This rate of cognitive deterioration is comparable to estimates from the recent analysis of the Canadian Study of Health & Ageing cohort which showed that nearly half of those who had "vascular cognitive impairment without dementia" developed dementia within 5 years[23]. A paper reporting these results has been accepted for publication in the Journal of Neurological Sciences.

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- The SGH Stroke Trials Unit has a proven track record in acute as well as non-acute trials. Its members are represented on the steering committees or advisory boards of major international trials. In the period 1995-2001, over 575 patients have been recruited into acute stroke trials and 610 patients into non-acute stroke trials with excellent (over 95%) follow-up. In the year 2001 alone, 295 patients were recruited into non-acute stroke trials. Since there are approximately 1300 patients with stroke admitted to the SGH Stroke Programme annually, recruitment into this study is not anticipated to be a problem.

- In the first 21 months of participation in VITATOPS at SGH, 221 patients have been recruited. Assessment (including cognitive tests) and follow-up procedures are in place and the recruitment rate can be rapidly increased once funding is available for the additional staff required. 214 patients have undergone baseline cognitive assessments and the rate of 1 year follow-up assessments has been 94%.

- We have already performed homocysteine measurements and analysis of MTHFR polymorphisms in a subset of Singaporean stroke patients. Preliminary results showing that the MTHFR C677 polymorphism associated with HHC is a significant risk factor for young stroke have been accepted for presentation at the Stroke Society of Australasia's Annual Scientific Meeting, Auckland, 2001 and at the European Stroke Conference, Geneva, 2002. A paper is in preparation.

- An interim analysis of the relationship between baseline cognitive assessments and fasting plasma HC in 198 patients for whom data was available shows a significant inverse correlation between baseline HC and MMSE scores ($r=-0.31$, $p<0.01$). Patients with cognitive impairment had significantly higher ($p<0.001$) HC (15.2 ± 5.1 mM) compared to patients without cognitive impairments (13.1 ± 4.1 mM). Further analysis to account for other risk factors is in progress.

Proposed trial design

(the full VITATOPS protocol can be obtained from : http://vitatops.highway1.com.au/

Inclusion criteria

All patients presenting within 7 months of a stroke or TIA are eligible provided they agree to take study medication, be available for follow-up and provide written informed consent.

Exclusion Criteria

- Taking vitamins on medical advice
- Use of vitamin supplements containing B6, B12 or folate (unless patient agrees to take study medication instead of the vitamin supplements)
- Taking methotrexate for any reason
- Pregnancy or women of child bearing potential who are at risk of pregnancy
- Limited life expectancy
- Dysphasia or other significant impediment to cognitive assessment.

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Study Design

Single-centre, randomised, double blind, placebo controlled trial. Eligible patients will be randomised by means of a central 24 hour telephone service or by the Internet after obtaining written informed consent. Patients will be assigned numbered treatment packs with the appropriate medications.

Baseline assessments

All Singaporean patients will be investigated according to the SGH stroke care pathway; this includes a thorough series of investigations for vascular risk factors, demographic information as well as neurovascular-imaging. They will also have a neuropsychological assessment and have blood drawn for neurochemical studies (including homocysteine levels) and DNA banking.

Follow-up visits

A follow-up at 3 and 6 months followed by 6 monthly visits for 1-4 years are required. At each visit data will be collected on outcome events, secondary stroke prevention measures, cardiovascular surgery, occurrence of major events, adverse events, use of vitamins and compliance with trial medication. Patient will have repeat neuropsychological assessments annually as well as a blood sample for neurochemical assays. The dementia syndrome will be diagnosed using DSM-IV criteria by experienced clinicians blinded to neurochemical and genetic data. Patients who do not meet the DSM-IV criteria but are impaired in one or more cognitive domains will be classified as 'cognitively impaired but not demented'. Those who are unimpaired in all cognitive domains will be classified as 'cognitively intact'. Cognitive deterioration will be defined as consistent progression from 'cognitively intact' to 'cognitively impaired but not demented'.

Safety considerations

The vitamins given in this study are a combination of B_{12} 400 micrograms, $B_6$25 milligrams and folate 2 milligrams daily. Whilst B_6 may cause a neuropathy, this side-effect is almost always associated with long term daily doses exceeding 1000 milligrams and is reversible. The addition of B_{12} minimises concerns that folate may mask the clinical onset of B_{12} deficiency.

Neurochemical assays

Samples will be analysed by ELISA for homocysteine. Other markers for atherosclerosis and dementia (CRP for example) will also be assayed.

DNA Bank

Samples will be frozen and stored in the SGH Stroke Gene Bank (EC approval obtained). DNA will be extracted and stored in a DNA Bank and testing for MTHFR, TS polymorphisms and other genetic factors performed according to published methods.

Statistical analysis

The sample size required to detect a 30% reduction in the expected 10% annual incidence of dementia or cognitive deterioration , based on a 3 year follow-up period for 80% power is 1,150. In order to accomodate for drop-outs, a target of 1500 patients has been selected.

Given that over 1,300 patients are admitted annually to the SGH Stroke Programme and

the widely applicable set of entry criteria, it is likely that the sample size is feasible : our target recruitment rate would be 600 per year. In the first 21 months of participation in VITATOPS at SGH, 221 patients have been recruited – the major limitation being lack of funding for staff. If funding is approved, we anticipate that close to 300 patients would already have been recruited.
The final analysis will compare the incidence of the combined primary outcome event (development of dementia or cognitive deterioration) between treated and untreated groups using intention-to-treat and on-treatment analysis. Kaplan-Meier curves will be compared using the Mantel-Haenstel test and Cox-proportional hazards models will be used to adjust for baseline prognostic variables. There will be planned sub-group analysis for age, sex, pathology, pathogenesis, homocysteine mutations and stroke severity.

Univariate and multi-variate analysis will be utilised to assess risk factors for dementia.

Clinicians' involvement
The investigators are members of the SGH Stroke Programme, which cares for the majority of stroke patients in SGH. They will take responsibility for the clinical care and neurological assessment of all patients recruited into the study. The bulk of the funding will be for staff essential for a study of this size and scope : a psychologist to perform the cognitive assessments, a trials coordinator and a scientist.

Expected contribution to this field
In view of the increasing evidence linking homocysteine to dementia and stroke, there is a need for trials in high risk elderly populations on whether vitamin supplements can reduce the risk of dementia. Of the 2 vitamin trials in stroke patients, who are at higher risk of cognitive impairment and dementia than other groups of patients being studied, the recently completed Vitamins in Stroke Prevention study conducted in the United States did not address dementia or cognition. The ongoing VITATOPS study does not employ a comprehensive neuropsychological battery to assess cognition and morever, the only specified cognitive screening instrument (MMSE) will not be performed on all patients. Thus, this study may provide evidence for the use of a widely available and practicable treatment in an important public health issue.

In addition to assessing whether multi-vitamin (B_{12}, B_6 and folic acid) therapy is effective in the prevention of dementia or cognitive deterioration after stroke, this study will also study other risk factors (including genetic ones) for post-stroke dementia or cognitive deterioration in a cohort of Asian stroke patients. Such data is currently incomplete.

Morever, the long term aims of the investigators are to establish :

- evidence-based medicine practice for the care of stroke and dementia. Participation in studies such as this is vital for the achievement of this goal.
- an Asian DNA bank for the identification of genetic risk factors for stroke and vascular dementia
- a large scale stroke trials centre in Singapore so that we can take a regional and international leadership role in the development of new treatments, novel clinical and basic science research.

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References

1. Caprie Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. Lancet 1996 ; 348 : 1329-39.
2. Tatemichi TK, Foulkes MA, Mohr JP, et al. Dementia in stroke survivors in the Stroke Data Bank cohort. Prevalence, incidence, risk factors, and computed tomographic findings. Stroke 1990 ; 21(6):858-66
3. Pohjasvaara T, Erkinjuntti T, Ylikoski R, et al. Clinical determinants of poststroke dementia. Stroke 1998 ;29 :75-81
4. Inzitari D, Di Carlo A, Pracucci G, et al. Incidence and determinants of poststroke dementia as defined by an informant interview method in a hospital-based stroke registry. Stroke 1998;29 :2087-93
5. Tatemichi TK, Paik M, Bagiella E, et al. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. Neurology 1994 ;44:1885-91
6. Eikelboom JW, Lonn E, Genest J Jr et al. Homocysteine and cardiovascular disease : a critical review of the epidemiologic evidence. Ann Int Med 1999; 131 : 363-375.
7. Christen WG, Ajani UA, Glynn RJ, Hennekens CH. Blood levels of homocysteine and increased risks of cardiovascular disease : causal or casual? Arch Intern Med 2000; 160 : 422-434.
8. D'Angelo A Selhub J. Homocysteine and thrombotic disease. Blood 1997; 90: 1-11
9. Malinow MR, Nieto FJ, Szklo M. Carotid artery intimal medial wall thickening and plasma homocysteine in asymptomatic adults. Circulation 1993; 87 : 1107-13.
10. Selhub, Jacques PF, Bostom AG. Association between plasma homocysteine concentrations and extracranial carotid artery stenosis. NEJM 1995; 332 : 286-91.
11. Lehmann M, Gottfries CG, Regland B Identification of cognitive impairment in the elderly: homocysteine is an early marker. Dement Geriatr Cogn Disord 1999;10:12-20
12. Clarke R, Smith AD, Jobst KA, et al. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 1998 ;55:1449-55
13. McCaddon A, Davies G, Hudson P, Tandy S, Cattell H. Total serum homocysteine in senile dementia of Alzheimer type. Int J Geriatr Psychiatry 1998;13:235-9
14. Leblhuber F, Walli J, Artner-Dworzak E, Vrecko K, Widner B, Reibnegger G, Fuchs D. Hyperhomocysteinemia in dementia. J Neural Transm 2000;107:1469-74
15. Faβbender K, Mielke O, Bertsch T, Nafe B et al. Homocysteine in cerebral macroangiopathy and microangiopathy. Lancet 1999; 353 : 1586-87.
16. Matsui T, Arai H, Yuzuriha T et al. Elevated plasma homocysteine levels and the risk of silent brain infarction in elderly people. Stroke 2001; 32:1116-1119
17. Vermeer SE, van Dijk EJ, Koudstaal PJ et al. Homocysteine, silent brain infarcts and white matter lesions : the Rotterdam Scan Study. Ann Neurol 2002; 51:285-289.
18. Seshadari S, Beiser A, Selhub J et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's Disease. N Engl J Med 2002; 346:476-83.
19. Nilsson K, Gustafson L, Hultberg B. Improvement of cognitive functions after cobalamin/folate supplementation in elderly patients with dementia and elevated plasma homocysteine. Int J Geriatr Psychiatry 2001 Jun;16(6):609-14
20. Tatemichi TK, Desmond DW, Paik M, et al Clinical determinants of dementia related to stroke. Ann Neurol 1993;33:568-75

21. Gorelick PB, Brody J, Cohen D, et al. Risk factors for dementia associated with multiple cerebral infarcts. A case-control analysis in predominantly African-American hospital-based patients. Arch Neurol 1993 ;50:714-20
22. Rockwood K, Wentzel C, Hachinski V, et al. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology 2000 25;54(2):447-51
23. Wentzel C, Rockwood K, MacKnight C, et al. Progression of impairment in patients with vascular cognitive impairment without dementia. Neurology 2001 28;57(4):714-6