

Evidence Based Medicine

What is the Role of B-vitamins in stroke prevention in Pakistan?

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The VITAMins TO Prevent Stroke-VITATOPS trial and VITAOPS-DEP trial

Why is this study important?

A person who has had a stroke or transient ischaemic attack has a higher risk of experiencing similar major vascular events in the future. This risk remains high despite aggressive medical and surgical management. An elevated homocysteine level in plasma is a known risk factor for major vascular events and it is well established that daily long-term supplementation with Vitamin B12 and Folic acid lowers these levels by a significant proportion. The VITATOPS trial was undertaken to test whether this reduction in homocysteine with vitamin supplementation translates into actual reduction in recurrent vascular events in patients with recent stroke (ischaemic or haemorrhagic) or TIA.

A second add-on substudy (VITATOPS-DEP) was undertaken on participants from VITATOPS who consented to additional assessment to analyze the effect of B vitamin supplementation on depression which is again a very frequent finding in stroke survivors.

Who were the participants?

A total of 8164 individuals from 123 medical centers from 20 countries spread across 4 continents participated in this double-blind, placebo-controlled trial and were followed for a median duration of 3.4 years. Half of the included participants were either Southeast or South Asians. The recruited participants had a documented stroke or transient ischaemic attack within 7 months prior to recruitment. Individuals already on Vitamin B or Folic acid supplementation were excluded. The mean age of the participants was 62.6 years with a slight male preponderance.

A total of 563 patients consented to additional assessment and were included in the VITATOPS-DEP trial, 284 were in the intervention arm and 279 in the placebo arm. During the follow-up period ranging from 1-10.5 years, 157 people died and 133 were lost to follow-up. Therefore for the substudy final analysis was done on 136 patients in the active arm and 137 in the placebo arm.

What was the intervention?

In the main VITATOPS trial 4089 patients were randomly assigned to the intervention (2 mg folic acid, 25 mg vitamin B6 and 0.5 mg vitamin B12) and 4075 to control (placebo pill with same colour and shape) group. Both groups were comparable in terms of age, gender, ethnicity, stroke subtypes and comorbidities. VITATOPS-DEP had the same active drug given to 284 and placebo given to 279 individuals.

What was the outcome?

In VITATOPS, the composite primary outcome of non-fatal stroke, non-fatal myocardial infarction or vascular death occurred in 15% of the participants in the intervention group and in 17% of the patients in the control group (RR 0.91, $p=0.05$, absolute risk reduction 1.56%). When evaluated separately, in comparison to placebo, treatment with daily vitamin B supplement was not associated with a significant reduction in the relative risk for stroke ($p=0.25$), myocardial infarction ($p=0.86$) or death from any other cause ($p=0.49$). A subgroup analysis however, revealed that daily vitamin B supplementation might actually have a role in reducing the risk of vascular events in patients with cerebral small-vessel disease. It was also associated with a significant reduction in vascular deaths ($p=0.04$) when compared to placebo. No adverse effects were encountered in either group.

In the VITATOPS-DEP, primary outcome which was a major depressive episode occurred in 18.4% of patients in the intervention arm and 23.3% patients in the placebo arm. This was a significant difference, translating to a Hazard Ratio of 0.48 for B vitamins. There was also a non significant trend towards reduction in the prevalence of major or minor depression.

What were the conclusions?

The authors concluded that although it is not associated with any adverse event itself, daily vitamin B supplementation in stroke/transient ischaemic attack patients rendered as much future vascular event prevention as did a placebo. There may be a greater benefit for patients with small vessel disease. For prevention of a major depressive episode following stroke, B vitamins now do have a proven role.

What impact does this study hold for the Pakistani patients and practitioners?

Pakistan has a huge number of stroke patients. The economic burden the management of their disease poses is tremendous. Current data suggests that patients with a transient ischaemic attack have a 17% risk of experiencing a stroke within 6 months. Vigorous therapies which promise to reduce or delay this risk are indeed welcome. Although current evidence suggests little role of B vitamins in prevention of recurrent events except in those with small vessel disease, they have shown benefit in prevention of major depression. Thus it is a huge benefit considering that depression does affect functional and cognitive outcomes post stroke. Therefore the use of B vitamins particularly in patients with small vessel lacunar strokes and those with post stroke depression may be a reasonable, useful and harmless

therapeutic option.

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Recommended Reading

1. VITATOPS Trial Study Group. B vitamins in patients with recent transient ischaemic attack or stroke in the VITamins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. *Lancet Neurol* 2010; 9: 855-65.
2. Almeida OP, Marsh K, Alfonso H, Flicker L, Davis TM, Hankey GJ. B-vitamins reduce the long-term risk of depression after stroke: The VITATOPS-DEP trial. *Ann Neurol* 2010; 68: 503-10.