B-vitamin therapy lowers homocysteine and improves cognitive outcomes in the FAVORIT Ancillary Cognitive Trial


Background and Aim

Results of clinical trials using B-vitamins to reduce the cognitive risks attributed to elevated plasma homocysteine (tHcy) have been inconsistent. A high prevalence of hyperhomocysteinemia and of cognitive impairment in kidney transplant recipients makes them a convenient population in which to evaluate whether B-vitamin therapy to lower tHcy would prevent cognitive decline.

Methods in Brief

Intervention:
• Double-blind randomized placebo-controlled ancillary study of cognition in the FAVORIT Trial – a multisite homocysteine lowering trial to reduce cardiovascular endpoints in stable transplant recipients with hyperhomocysteinemia.
• Participants of the FAVORIT trial aged 35-70.
• Stable kidney allograft for at least 6 months.
• Elevated tHcy ≥ 12 µmol/L for men or ≥11.0 µmol/L for women.
• Not visually or hearing-impaired (capable of cognitive testing).
• Recruited from 18 sites in North America and Canada between 2002 and 2007.

Outcomes: Intention to treat cross-sectional analysis of differences between treatment arms using last available scores and of longitudinal change in cognition.

Results

FAVORIT cohort (n=4,110)

Total cohort in USA & Canada: total subject enrolled for in-person testing (n=584)

Total subjects treated at least 6 months before follow-up testing (n=547)

Subjects with complete data for end of trial cross-sectional ITT analysis (n=524)

Treatments with at least 1 test (n=250)

Controls with at least 1 test (n=274)

Cognitive Domain | Test | Description | Scoring | Placebo | Treatment
--- | --- | --- | --- | --- | ---
Verbal memory | Word List Learning | Learning and delayed recall of a 12 word list; immediate recall: words recalled over 4 trials; delayed recall: words recalled after 12 word recall after 25-35 minute delay | Number of words correctly recalled; immediate recall score range 0 to 12; delayed recall score range 0 to 12 | 546 (512, 583) | 511 (478, 548)
Executive Function & Processing Speed | Trails A&B | "Connect-the-dots" for (A) consecutive number sequence, and (B) alternating between numbers and letters | Number of seconds to completion, test censored at 300 seconds | 15.4 (14.4, 16.7) | 15.9 (14.7, 17.2)
Visuospatial Construction & Fluid Reasoning | Block Design | Reproduction of designs with a set of colored blocks | Number completed, weighted for time of completion, score range: 0 to 68 | 45.8 (39.5, 52) | 43.4 (37.9, 48.9)
Depression | CES-D | Rating of depressive symptoms experience over the past month | Number of symptoms endorsed, weighted by severity, score range: 0 to 60 | 3.4 (3.2, 3.5) | 3.3 (3.1, 3.4)

Change in Cognitive Score Between 1st and Last Test

Mean scores were adjusted for age at baseline, sex, race, education, smoking tHcy, hypertension at baseline, diabetes at baseline, eGFR, time on treatment, number of testing time-points, and FAVORIT site.

Discussion

• High-dose B-vitamin therapy to lower tHcy had a modest, statistically significant beneficial effect on select cognitive outcomes among kidney transplant patients, a population with high tHcy and prevalent cognitive impairment.
• Failure to normalize tHcy in nearly half of the treatment group, and the smaller but significant reduction in tHcy in the placebo group may have weakened any tHcy-related cognitive effects of treatment.
• Because relatively few participants had baseline cognitive testing prior to randomization into the parent trial, analyses focused primarily on cross-sectional instead of trial group comparisons rather than longitudinal cognitive changes for which we were underpowered. While cognitive impairment was common among our participants, progressive decline was unexpectedly infrequent. This too may have limited our ability to fully evaluate the effects of tHcy lowering on cognition.
• Almost none of the participants in this study were insufficient in folate or vitamin B12. It is possible that if this population had had a greater prevalence of folate and vitamin B12 deficiency, we would have observed a stronger response to treatment. Whether B-vitamin repletion in older individuals with inadequate B-vitamin status will have cognitive benefit remains an open question.

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