葉酸は安全ではあるが心保護作用はないことが示された（LBCT, abstract＃165）

SEARCHトライアル：高用量の葉酸は安全ではあるが心血管保護作用は有さない

SEARCH Trial: Large doses of folic acid are safe but lack preventive cardiovascular benefits

葉酸は安全であるーしかし心血管系に対する効果はないーとの結果が、2008年American Heart Association学会で発表された。12,064人を対象とした無作為化トライアルである、コレステロールとホモシステインをより低下させることによる有益性に関するスタディ（Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine ：SEARCH）の結果が、Late-Breaking Clinical Trialとして発表された。スタディの参加者は、1日に葉酸（2mg）とビタミンB12（1mg）を内服する群またはプラセボ群に割り付けられた。葉酸群はホモシステインレベルが1年後に3.9μmol/L低下し、トライアル全体の期間（平均6.7年）に3.6μmol/L低下した。研究者らは、葉酸群においてプラセボと比較し、一次エンドポイントである主要な血管イベント（MVEs：非致死性心臓発作、冠動脈死、脳卒中または動脈の血行再建術と定義）の減少は認められなかったと報告した。MVEsは葉酸群患者のうち1,537人（25.5%）に、プラセボ群患者のうち1,492人（24.7%）において認められ、そのリスク比は1.04（95%CI0.97-1.12）であった。これらのビタミンはまた、心筋梗塞の既往のある患者におけるスタディ期間中の非血管性死亡率またはがん発症率を上昇させることはなかった。同じスタディの別の比較において、より強力なコレステロール低下による有益性が支持された。

Full Text

Folic acid is safe - but it lacks any cardiovascular benefits - according to researchers presenting at the American Heart Association's Scientific Sessions 2008. The results from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), a 12,064-person, randomized study, were presented as a late-breaking clinical trial.

Study participants were assigned to folic acid (2mg) plus vitamin B12 (1mg) daily versus matching placebo. The folic acid group yielded reductions in homocysteine levels of 3.9ƒÊmol/L at 1 year and of 3.6ƒÊmol/L over the whole trial period (mean 6.7 years).

Researchers reported that the folic acid group failed to show any reduction in the primary outcome of major vascular events (MVEs, defined as non-fatal heart attack, coronary death, stroke or arterial revascularization) compared to placebo. MVEs were found among 1537 (25.5%) patients in the folic acid group versus 1492 (24.7%) on placebo corresponding to a risk ratio of 1.04 (95%CI 0.97-1.12). The vitamins also did not increase non-vascular death rates or cancer rates during an average follow-up of 6.7 years among patients who had previously had a heart attack, said Professor Jane M. Armitage, co-principal investigator of the study and professor of clinical trials and epidemiology at the University of Oxford, England.

"There was no difference between the treatment groups in terms of vascular events, but importantly, we also didn't see any kind of safety concerns with folic acid," she said. "SEARCH throws cold water on a once-promising hypothesis, based on a well-known association between higher blood levels of the amino acid homocystine and higher cardiovascular disease (CVD) risk, that using B vitamins to reduce blood levels of homocystine would prevent CVD."

The study's finding of no excess risk of cancer or other adverse events from higher than average doses of folic acid provides reassurance for the United States, Canada and several other countries that require folic acid fortification of flour, bread and many cereals to protect newborns from neural tube defects, Armitage said.

At the same late breaking clinical trials session, Armitage's co-principal investigator, Professor Rory Collins, professor of medicine and epidemiology at the University of Oxford, presented a second randomized comparison from the SEARCH trial of 80mg versus 20mg per day of simvastatin - the largest direct comparison of more versus less intensive lowering of low-density lipoprotein cholesterol (LDL-C).

Previous studies have found that statin therapy reduces the relative risk of MVE by about 20 percent per 40 milligram per deciliter (mg/dL) reduction in LDL-C. Compared with the patients assigned 20mg per day of simvastatin in SEARCH, LDL-C was reduced by an average of 14mg/dL more among the patients assigned 80mg per day of simvastatin.

Collins presented the results of SEARCH in the context of an update of a meta-analysis of individual patient data from previous studies of statin therapy published in The Lancet in 2005 (Lancet 2005 Oct 8: 366:1267-78.) Based on that meta-analysis, a 14 mg/dL greater reduction in LDL-C would be expected to produce a 6 percent to7 percent relative reduction in MVE, which is what researchers observed in the SEARCH trial.

Daily doses of 80mg simvastatin were associated with more myopathy cases than 20mg simvastatin, although the SEARCH trial had identified a genetic variant that accounted for much of the excess myopathy risk with the higher-dose simvastatin regimen.

Co-authors are the SEARCH Collaborative Group.

The University of Oxford's Clinical Trial Service Unit designed, conducted, analyzed and interpreted the SEARCH study, which was funded by a research grant from Merck & Co.

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