PILOT STUDY

Effects of Nitric Oxide on Carotid Intima Media Thickness: A Pilot Study

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ABSTRACT

Cardiovascular disease is among the leading causes of morbidity and mortality worldwide. Preventive treatment of high-risk asymptomatic individuals depends on accurate prediction of a person's risk to develop a cardiovascular event. Currently, cardiovascular risk prediction in asymptomatic individuals is based on the level of cardiovascular risk factors incorporated in scoring equations. Improvement in cardiovascular risk prediction is needed because atherosclerosis underlies the occurrence of cardiovascular events, develops over decades, and has a prolonged asymptomatic phase during which it is possible to modify the course of the disease. The carotid intima media thickness test (CIMT) is a measure used to diagnose the extent of carotid atherosclerotic vascular disease. The test measures the thickness of the inner 2 layers of the carotid artery—the intima and media—and alerts physicians to any thickening when patients are still asymptomatic. Early detection may indicate the need for a more aggressive approach to managing the risk factors associated with heart disease and stroke. The role of nitric oxide (NO) in maintaining the integrity of the cardiovascular system is well established. Utilizing a dietary supplement that restores NO production, the author conducted a pilot study involving 10 patients with stable plague. Six months of treatment with the NO lozenge resulted in a statistically significant 10.9% reduction in CIMT. This pilot study suggests this approach may be a safe and effective strategy for patients with early stages of atherosclerotic vascular disease. (*Altern Ther Health Med.* 2016;22(S2):32-34.)

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A small study of 10 subjects who had no history of cardiovascular disease was performed in one medical office (Orlando, Florida) to determine whether increasing nitric oxide (NO) can reduce plaque. The carotid intima media thickness test (CIMT) was used to measure the amount of plaque. The Esaote Mylab 40 ultrasound machine (Esaote, Genoa, Italy) was used to perform the CIMT and it was done with only 1 licensed sonographer. All measurements and patient visits occurred between March 2013 and July 2014.

All the patients volunteered for the study and all of them were not taking a statin medication for this study. There was no informed consent for the study. Average time between measurements was 6.3 months (range, 4–10 months). The CIMT measures the thickness of the plaque by performing 3 measurements in micrometers and averages the 3 measurements. Follow-up CIMT was performed on the patients during a follow-up visit with the physician. None of the subjects were taking red yeast rice or any prescription lipid-lowering therapy.

Baseline measurements were recorded and then patients were administered Neo40 (Neogenis Labs, Austin, TX, USA), a supplement that increases NO, twice daily. They were then re-evaluated 4 to 10 months later. Neo40 is a biphasic-patented (US patent Nos. 8298589; 8303995; 8435570; 8962038; 9119823; & 9241999), over-the-counter, orally disintegrating tablet technology licensed out of the University of Texas Health Sciences Center at Houston (Houston, TX, USA). Neo40 contains a natural source of nitrite and nitrate from beet root but also utilizes natural product chemistry that involves nitrite reductase activity from hawthorn berry extract to generate authentic NO gas as the lozenge is dissolving in the first phase. The second phase recouples NO synthase enzyme to improve endogenous production of NO. The supplement facts panel is included as Figure 1. No other medications were introduced and patients were advised to continue any medications currently prescribed.

Figure 1. Supplement Facts Panel for Neo40

Supplement Facts

Serving Size: 1 tablet **Servings Per Container: TBD**

Amount per Serving		% DV*
Vitamin C (as magnesium ascorbate and ascorbic acid)	100 mg	167%
Vitamin B12 (as methylcobalamin)	50 mcg	833%
Proprietary Nitric Oxide Blend: Beet Root Powder (root), Hawthorn Berry Extract (berry), L-citrulline, Sodium Nitrite	420 mg	†

* Percent Daily Values (%DV) are based on a 2,000 calorie diet
† Daily value (DV) not established

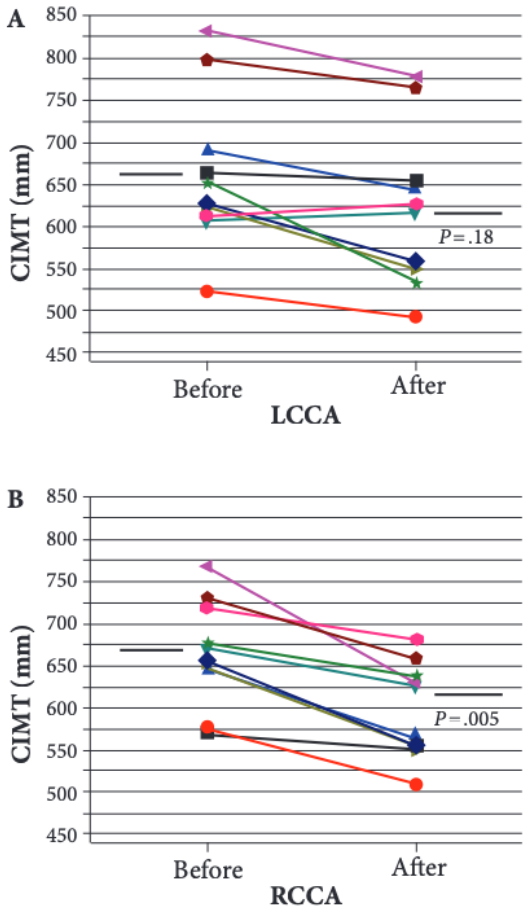
Other Ingredients: dextrose, cellulose, flavors, magnesium vegetable stearate, and silica.

Table 1. List of Medications and Supplements

Medications	No. of patients taking	Supplements	No. of patients taking
Losartan	1	CoQ_{10}	2
Cytomel	2	B-complex	5
Armour	2	Vitamin E	3
Humatrope	1	Magnesium	1
Testosterone	7	Melatonin	5
Progesterone	5	Vitamin D	10
Bupropion	1	Omega 3	4
Arimidex	1	Zinc	2
hGC	1	Vitamin C	4
Metoprolol	1	Probiotic	5
Lisinopril	1	Niacin	1
Vyvanse	1	Glucosamine	1
Liothyronine	1	*N*-acetyl cysteine	1
Adderall	1	SawPalmetto	3
Singular	1		

Abbreviations: CoQ_{10}, coenzyme Q_{10}; hCG, human chorionic gonadotropin.

Figure 2. (A) CIMT Before and After Neo40 Treatment in the LCCA; (B) CIMT Before and After Neo40 Treatment in the RCCA



Note: n = 10 patients on Neo40 for 6 mo; $P = .18$ for LCCA and $P = .005$ for RCCA.

Abbreviations: CIMT, carotid intima media thickness; LCCA, left common carotid artery; RCCA, right common carotid artery.

RESULTS

After obtaining the baseline CIMT, 10 patients were started on a twice daily NO supplement. Patients were on an average of 4.1 prescription medications including hormone replacement therapy and all reported dietary supplement use (Table 1). None of the patients were taking a statin for hyperlipidemia. Both the left and right common carotid arteries were examined for CIMT dimensions. Measurements from the left common carotid artery (LCCA) were slightly more variable. but 8 of 10 patients noted a decrease in the CIMT. Average CIMT at baseline from the LCCA was 662 µm and after approximately 6 months, average CIMT was 622 µm (Figure 2A), or a 6.1% reduction ($P = .18$).

Measurements from the same patients using the right common carotid artery (RCCA) were less variable and experienced a greater reduction in CIMT after treatment with the NO supplement. Average CIMT at baseline from the RCCA was 677 µm and after approximately 6 months, and the average CIMT was 603 µm (Figure 2B), or a 10.9% reduction ($P = .005$). All 10 patients experienced a reduction in the CIMT from the RCCA after treatment. Plaque deposition is a heterogeneous process and does not always

accumulate evenly or consistently in all blood vessels. Similarly, even less is known how plaque within the intima can be reduced. It is therefore not surprising that there were differences between the left and right carotid arteries in terms of total changes. The important issue is that both sides decreased. The right side starting CIMT average was higher than the left and was reduced to a greater extent and, therefore, reached statistical significance.

DISCUSSION

Few treatment regimens have shown plaque regression using CIMT within such short treatment duration. The PEACE (Pitavastatin Evaluation of Atherosclerosis Regression by Intensive Cholesterol-lowering Therapy) study evaluated the effect of intensive statin therapy on regression of CIMT in patients with subclinical carotid atherosclerosis and found no difference between moderate to intensive cholesterol-lowering therapy. However, in the intensive cholesterol-lowering arm (target low-density lipoprotein cholesterol, 80 mg/dL), the change in mean CIMT was -0.024 (95% confidence interval [CI], -0.046 to -0.0014) mm/year ($P < .05$ vs baseline), and -0.0078 (95% CI, -0.028 to 0.012) mm/year ($P = .4406$ vs baseline) in the moderate group.[1]

Meta-analysis of trials using treatment with statins (mean treatment duration, 25.6 months) reveals that a total of 7 trials showed regression and 4 trials showed slowing of progression of CIMT.[2] Pooled analysis of all 11 trials showed that there was a statistically significant benefit with statin therapy in slowing down the progression of CIMT and the common mean difference between statin therapy arm and placebo arm was -0.040 (95% CI, -0.052 to -0.028; $P < .001$). The data show an average of 0.073 mm, or 10.9%, after approximately 6 months using the NO supplement. None of the patients in this case report had evidence of advanced carotid atherosclerosis defined as a thickness between 0.9 and 1.2 mm. All of the patients had thickness less than 0.85 mm (Figure 1).

The NO supplement that has been used in this study has been studied in other clinical trials. In a double-blinded, placebo-controlled clinical trial in patients older than 40 years with known cardiovascular risk factors, patients taking the NO supplement twice per day for 30 days saw a significant increase in NO production, a significant reduction in triglycerides, a modest reduction in blood pressure (BP), and a reduction in C-reactive protein.[3] Additional published trials on NO supplementation resulted in a significant reduction of systemic and diastolic BP in hypertensive patients, dilation of the carotid arteries as measured by ultrasound, significant improvement in vascular compliance, and significant improvement in endothelial function.[4] Further, in patients with pre-hypertensive, Neo40 administration led to a significant reduction in BP by 12 mm Hg systolic and 8 mm Hg diastolic after 30 days treatment.[5]

Study Limitations

This study involved only 10 patients from a single medical practice with stable plague for the previous 3 years. None of the patients had evidence of advanced cardiovascular disease. Patients were also taking a number of other dietary supplements and hormone replacement. However, Neo40 was the only supplement introduced during the treatment period. A randomized, placebo controlled trial involving more patients is needed to corroborate this pilot study.

CONCLUSION

Use of the NO lozenge supplement without the use of a statin shows to reduce plaque as measured by CIMT by 6.1% on the left carotid ($P = .18$) and 10.2% on the right carotid ($P = .005$) in the course of approximately 6 months. Longer term, larger trials are needed to confirm these findings.

AUTHOR DISCLOSURE STATEMENT

Edwin Lee, MD, has no financial interests to disclose.

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