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INSIDE

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Exercise for Chronic Heart Failure: A Call to ACTION?

By Susan T. Marcolina, MD, FACP

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HEART FAILURE (HF), THE END RESULT OF MANY CARDIOVASCULAR disorders and a common disabling clinical syndrome, affects almost 6 million people in the United States.[1] This growing public health problem and economic burden accounts for 12-15 million office visits and 6.5 million hospital days yearly.[2] Such patients, in addition to being at increased risk for death, have important quality-of-life issues including diminished social and physical functioning due to dyspnea and fatigue. Although evidence-based pharmacologic treatments[3] and device interventions[4] reduce mortality, they have provided only modest improvements in quality of life *(see Table 1, page 63)*.

Exercise in conjunction with diet and pharmacologic therapy has been an important therapeutic lifestyle intervention to reduce cardiovascular risk factors. Traditionally, physicians have recommended that HF patients limit their physical activity. This position has changed over the past 20 years, however, with the recognition that the ensuing physical deconditioning increases disability and poor outcomes despite optimal medical therapy. Inactivity also increases the risk for thromobembolic events, pulmonary infections, and depression, which increase mortality for HF and all forms of heart disease.[5]

Risk Factors for Heart Failure

Risk factors for developing heart failure are listed in Table 2 *(see page 64)*. Regular aerobic exercise is an important lifestyle intervention for the primary prevention of HF for the initial four risk factors listed. Due to the physiologic adaptations that occur secondary to heart failure, aerobic exercise training could be an important adjunctive treatment for stable heart failure patients.

Quantification of Functional Limitations in Heart Failure

There are a number of ways to quantify the functional limitations caused by HF. The NYHA functional scale—rated from I (asymptomatic) to IV (dyspneic with any exertion)—is in widespread use,

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though is subject to significant differences in inter-observer interpretation.[6] The 6-minute walk distance[7] is useful prognostically, but serial changes in walking distance do not necessarily parallel clinical status changes. Maximal exercise testing with peak oxygen uptake has been used to identify patients for cardiac transplantation, to establish disability determination, and to assist in designing a prescription for exercise training.[8]

Risks of Exercise Testing

Exercise training was contraindicated in patients with moderate-to-severe left ventricular failure because, in the short term, initiation of exercise in formerly sedentary patients increased the risks for myocardial infarction and sudden death. This continues to be a concern; therefore, all patients considered for exercise training should undergo cardiopulmonary exercise (CPE) testing with a modified Naughton protocol (a type of graded exercise test better suited for diseased populations with a more gradual increase in intensity of 1 metabolic equivalent per stage) to rule out abnormal blood pressure responses, significant arrthymias, or ischemic changes that would preclude participation in exercise training and prompt further evaluation and therapeutic interventions. The purpose of the CPE is to establish the target heart rate for exercise. Safety guidelines target heart rate to 60% of the heart rate reserve (HRR, the difference between the peak heart rate, derived from a patient's recent exercise test, and the resting heart rate).[9] The American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines recommend that stable patients with chronic HF participate initially in exercise training as part of a supervised protocol in conjunction with evidence-based pharmacologic and device therapy. Subsequently, they can be transitioned to a home program with periodic follow-up.[10]

Obstacles to Exercise Training

Older patients with lower ejection fractions (less than 20%) tend to have higher attrition rates for exercise training. Other factors that impact compliance include lack of family support, transportation issues, multiple co-existent medical problems such as arthritis and movement disorders, and living alone. Patients with low exercise capacity need increased motivation, individual attention, and positive, ongoing feedback regarding progress.[11]

Pathophysiology of Heart Failure

HF results in neurohumoral excitation with elevations in levels of catecholamines, renin, vasopressin, and atrial naturietics as the body compensates for reduced cardiac output and tissue perfusion.[12] Persistence of this excitation, however, results in deterioration of cardiac function with inflammation, end organ damage, and remodeling, which further compromises cardiac output. Additionally, patients with heart failure have reduced parasympathetic activity with decreased heart rate variability and baroreflex sensitivity with increased risk of malignant arrythmias.[13]

In addition to the cardiac adaptations, diminished flow states and proinflammatory cytokines such as tumor necrosis factor and interleukin (IL)-6 cause skeletal muscle and respiratory muscle myopathy with decreased capillary density, as well as shift from high aerobic capacity to low aerobic capacity muscle fibers with decreased mitochondrial density and structure with decreased oxidative enzymes. As a result, there is increased muscle fatigue and accumulation of metabolic byproducts, which contributes to dyspnea and reduced exercise tolerance.[14]

Although not listed in Table 1 because their effects on morbidity and mortality are unknown,[10] loop diuretics are important in the treatment of HF because they can relieve symptoms of pulmonary and peripheral edema within hours, which is much quicker than the onset of effects for any other HF drug. Diuretics have also been shown to improve exercise tolerance in patients with HF.[15] Close attention to changes in body weight and daily sodium intake restriction to 1,500 mg are important lifestyle and dietary measures essential to the success of exercise training in HF.[16]

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Table 1

Interventions for heart failure

Intervention	Type	Physiologic Benefit	Comments
Beta-blockers	Pharmacologic	Decrease sympathetic tone	Survival benefit post-MI[26]
Angiotensin-converting-enzyme inhibitors (ACEIs)	Pharmacologic	Decrease afterload; improve endothelial function; modulate cardiac remodeling[27]	Avoid use in: Angioedema, cough, pregnancy, creatinine ≥ 3.0 or serum K ≥ 5.5 mmol/L or SBP ≤ 80 mmHG
Angiotensin-receptor blockers (ARBs)	Pharmacologic	Decrease angio II-induced vasoconstriction	Use if intolerant to ACEIs[28]
Implantable cardioverter-defibrillators	Device	Decrease sudden death	Level A evidence with cardiac arrest, destabilizing ventricular arrythmia 40 days post-MI with LVEF ≤ 30% and NYHA II-III with 1-year survival
Biventricular pacemakers	Device	Cardiac dyssynchrony causes decreased LV fill, increased mitral regurgitation, increased mortality[29]	Level A: LVEF ≤ 35%, sinus rhythm, QRS = 120 msec, NYHA III or ambulatory IV on meds
Aldosterone antagonists	Pharmacologic	May increase diuretic effects	Avoid in CR ≥ 2.5; use with loop diuretics
Exercise training (aerobic)	Lifestyle	Decreases sympathetic and increases parasympathetic tone; improves endothelial function; decreases inflammatory cytokine concern	For patients with stable disease[30]
BiDil (fixed isosorbide dinitrate/hydralazine combo)	Pharmacologic	Increases nitric oxide availability	Mortality benefits limited to NYHA III-IV black patients on meds[31]

Adapted from: Hunt SA; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic hear failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;46:e1-e82.

Cardiovascular Adaptations to Exercise Training

In theory, the limited ability of heart failure patients to increase stroke volume and, therefore, cardiac output with exercise training would preclude improvements in exercise capacity. However, patients with heart failure do respond positively to exercise training with increases in maximal peak oxygen uptake ($V0_2$) ranging from 8% to 30%.[8,17] This is because although the degree of cardiac adaptation is limited, HF patients are able to rely on improvements in pulmonary-mediated oxygen uptake and enhanced oxygen extraction and utilization via the peripheral musculature. Exercise training can enhance pulmonary functioning by increasing strength and endurance of pulmonary musculature. Exercise training also decreases neurohumoral tone by decreasing sympathetic activation and increasing parasympathetic activation, which increases cellular oxidative enzyme activity and reduces plasma levels of inflammatory cytokines such as TNF-alpha, IL-6, and IL-1 beta, improving endothelial vasodilatation.[18]

Clinical Studies of Exercise Training for Heart Failure

Keteyian et al trained HF patients for 24 weeks and found that approximately 85% of the total increase in peak oxygen uptake occurred after 12 weeks.[8] Unsustained exercise training (less than 12 weeks) does not result in the same salutary effects as exercise of longer duration.[19]

Nilsson et al conducted a randomized controlled trial

Table 2

Risk factors for the development of heart failure

- Hypertension
- Diabetes
- Obesity
- Metabolic syndrome
- Atherosclerotic disease
- Family history of cardiomyopathy
- Cardiotoxin exposure: alcohol,[32] chemotherapeutics such as anthracyclines,[33] high-dose cyclophosphamide[34] and trastuzumab[35]
- Mediastinal irradiation, especially with cardiotoxic chemotherapy[36]

(RCT) of 80 patients (22% female; average age, 70.1 years) with stable CHF (LVEF of 30%) on optimal medical therapy. Forty patients were assigned to 16-week, group-based, aerobic high-intensity interval training twice weekly for 60-80 minutes/d and were compared to a standard-care control group. After 16 weeks, functional capacity (as assessed with a 6-minute walk test and cycle ergometer test) significantly improved in the exercise group, which gained an average of 58 meters improvement in the 6-minute walk, vs the control group, which lost an average of 15 meters ($P < 0.001$). Quality-of-life scores, measured with the Minnesota Living with Heart Failure Questionnaire, significantly improved in the exercise group compared with the control group and there was a significant inverse correlation between quality-of-life score and functional capacity.[20]

The HF-ACTION multicenter RCT followed more than 2,000 patients (median age 59 years; 27% female) with NYHA class II-IV HF and LVEF of 35% or less randomized to evidence-based medical therapy (EBMT) plus 36 sessions of supervised aerobic (walking, treadmill, or stationary cycling) exercise training (ET) at 60-70% of HRR three times weekly followed by home-based training at the same intensity five times weekly vs EBMT alone. Quality-of-life scores as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score improved by 54% in the patients treated with EBMT plus ET compared with 29% of patients in the EBMT-only group from baseline to three months. This improvement persisted throughout the median 2.5-year follow-up but reached a plateau after the three-month follow-up, probably secondary to the impact of the social support during the supervised exercise training sessions.

Exercise training effects included significant improvements in the 6-minute walk test and peak oxygen consumption of 20 vs 5 meters and 0.6 vs 0.2 mL/min/kg in the EBMT plus ET vs the EBMT-only group, respectively. The time to all-cause mortality or hospitalization was modestly decreased in the EBMT plus ET group vs the EBMT-only group and exercise training was well tolerated and safe, with 3.2% of patients in the exercise group experiencing an exercise-related hospitalization and 0.4% experiencing death after exercise compared to 1.9% and 0.4%, respectively, in the EBMT-only group.[9,21] Notably, in contrast to earlier studies, exercise-related benefits were consistent across sex, race, and age.[22]

Contribution of Depression to HF Symptoms

At baseline, 99% of patients entered into the HF-ACTION trial completed the Beck Depression Inventory (BDI), and it was notable that in this ambulatory, outpatient, relatively young population, depression (defined as a BDI score greater than 10) was common at 43%. This BDI-identified depression was highly correlated with KCCQ score and NYHA class, measurements highly influenced by perception, though the depression score was not associated with objective parameters of function such as the left ventricular ejection fraction. Gottlieb et al found that patients with increased BDI scores had more subjective heart failure symptoms of dyspnea and functional limitations, despite the fact that there were no differences in the more objective measures of disease severity such as left ventricular ejection fraction (25.1% vs 25.3% in depressed and nondepressed patients, respectively). These findings suggest that depression influences the perception of disease severity to a greater extent than severe HF causes depression. Thus, diagnosis and treatment of depression in HF patients has the potential to markedly improve symptoms.[23] Since exercise training has salutary effects on clinical depression,[24] this would be another reason to recommend this lifestyle intervention to stable HF patients.

Exercise Recommendations

According to the ACC/AHA guidelines, patients with HF are advised to perform 30 minutes of moderate-intensity activity, and if unable to continue for 30 minutes to move for as long as possible (an effort level which does not cause the individual to sweat or become short of breath), five days per week. Safety guidelines target exercise heart rate to 60% of the HRR.[10] An effective training session would consist of a warm-up period with stretching and range of motion exercises, followed by light aerobics with a gradual increase in activity to target HR or a Borg perceived exertion of 11-14 on the Borg rating of perceived exertion scale (runs from 6

[easy] to 20 [very intense])[25] for 15-30 minutes, followed by a 10-minute cool-down.[8]

Conclusion

Exercise training has cardiovascular benefits and is associated with pulmonary and skeletal muscle metabolic adaptations that benefit patients with heart failure. CPE should be performed to rule out contraindications to exercise and to establish the target heart rate training zone. Supervised exercise training programs modeled upon cardiac rehabilitation should be considered for patients with stable heart failure who are receiving optimal heart failure therapy (unless a contraindication or intolerance exists) according to the guidelines established by the American College of Cardiology/American Heart Association.[10] These patients should be subsequently transitioned to a home program and encouraged to perform 30 minutes or as long as tolerated of moderate-intensity aerobic activity (walking, treadmill, or bicycle) daily as recommended by ACC/AHA guidelines. Regular exercise may also improve depression syndromes, which can negatively impact HF symptoms.

Recommendation

Stable HF patients may benefit from supervised exercise training programs tailored to a target heart rate of 60% of the HRR for 30 minutes daily or as long as tolerated in conjunction with optimal heart failure pharmacologic and device therapy. Patients should be referred to a cardiac rehabilitation program for initiation of exercise training. HF patients should be screened for depression and treated as this may negatively impact the clinical course of their HF. Physicians should encourage patients to carefully follow daily weights and monitor dietary sodium intake. ❖

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For What 'Ales' You: Ginger, N/V, and Pregnancy

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *A brief intervention of an extract of ginger administered four times daily was effective in ameliorating nausea and vomiting of pregnancy in this small single-blind trial.*

Source: Ozgoli G, et al. Effects of ginger capsules on pregnancy, nausea, and vomiting. *J Altern Complement Med* 2009;15:243-246.

In an attempt to determine the efficacy of an extract of ginger on nausea and vomiting of pregnancy (NVP), researchers from Iran employed a single-blind clinical trial design to study subjects (n = 67 pregnant women) with mild-to-moderate nausea with or without vomiting. Prior to randomization, participants were asked to complete a visual analog scale (VAS, scale 0-10) to document severity of nausea and vomiting over the previous 24 hours. They were then randomized in blinded fashion to either an experimental group taking ginger 1,000 mg/d (250 mg capsules taken in the morning, at noon, in the afternoon, and at nighttime with water) or a placebo group taking capsules containing lactose at the same time periods for four days. They were asked not to use prescription aids during the trial and were counseled to avoid fatty foods, as well as to eat less food at each meal, but were also advised to increase the number of meals consumed each day. The effects of the interventions on nausea severity were to be evaluated twice (noon and bedtime) for four days using a treatment questionnaire and the VAS. After four days the questionnaires were given to a researcher who, based on their responses to questions about intensity of nausea and vomiting, interviewed each of the participants with a special emphasis on adherence to the dietary recommendations.

Mean gestational age and parity of the participants was 13 ± 3 weeks and 1.6, respectively. At baseline, nausea severity was rated as moderate in 54% and 56% of the control and experimental samples, respectively, mild in 25.7% and 18.7%, and severe in 7% and 8%. Subjects who received ginger experienced greater relief from nausea than did those in the placebo group (84% vs 56%) and had fewer vomiting episodes (50% decrease vs 9%). After treatment, 26% of ginger users no longer had nausea, whereas only 10% of the control group experienced complete relief. There were no changes in nausea intensity for 22% of the women in the control group and 9% in experimental group. Roughly 54% in the control group and 44% in the experimental group did not pay strict attention to dietary recommendations. The authors conclude that a standardized extract of ginger in a divided dose of 1,000 mg/d is effective in the treatment of NVP.

■ **COMMENTARY**

Up to 90% of pregnant women experience NVP, a condition that typically resolves spontaneously by the 20th week of gestation. While discomfiting and having a negative impact on quality of life, NVP is generally mild. At the other end of the spectrum, however, is hyperemesis gravidarum, where nausea and vomiting are severe and can result in significant metabolic derangements that endanger both mother and unborn child. The focus of the paper at hand was on the mild form of NVP.

A small number of studies have previously been published that support a possible role for ginger in the treatment of NVP, but dosage and duration of treatment have remained unsettled issues. This trial employed a commonly used divided dosage of 1,000 mg daily and showed significant clinical benefit, but the intervention was offered for only four days. Being that NVP can develop early in pregnancy and continue through the first part of the second trimester, a four-day intervention may not be clinically relevant, although more than one-quarter of women in the active group had complete resolution of their symptoms by trial's end. More research is needed to better determine safety parameters around duration of administration. As a side note—ginger ale is not therapeutic in this regard because it is such a dilute preparation, and often contains a large amount of sugar.

Issues with the current study include the possibility of bias, being that the researcher who interviewed subjects after four days of therapy was not blind to treatment assignment, and unequal numbers of assessments in the two study arms. It is worthwhile to note there was a significant response in the placebo group (56%). These considerations stated, ginger has a long and rich tradition of use across cultures and appears to be safe; still, the discussion centers around the health of mother and baby, and further studies fully evaluating safety for both can only be welcomed. While ginger may be a reasonable option for some women with NVP, other tried-and-true interventions include vitamin B_6, dietary manipulation, and acupressure. ❖

Drug Blues: Antidepressants, Efficacy, and Effectiveness

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *Upon evaluating data from the STAR*D project, researchers concluded that phase III clinical trials often do not recruit representative populations of depressed outpatients, making the recommendations drawn from the studies' conclusions of limited applicability to general clinical practice.*

Source: Wisniewski SR, et al. Can Phase III trial results of antidepressant medications be generalized to clinical practice? A STAR*D report. *Am J Psychiatry* 2009;166:599-607.

DATA FROM THE STAR*D PROJECT, A LARGE MULTISITE, prospective, sequentially randomized clinical trial of outpatients aged 18-75 years with nonpsychotic major depressive disorder (MDD), were assessed by researchers interested in the generalizability of findings of studies on treatment of MDD. STAR*D was initially designed to help define which therapeutic interventions might be most effective for outpatients with nonpsychotic MDD with a history of suboptimal clinical outcome to initial therapy. Standard demographic and self-reported psychiatric history were collected at baseline, together with data from a number of validated tools to assess severity of depression, including the HAM-D, 16-item Quick Inventory of Depressive Symptomatology–Clinician Related, the Quick Inventory of Depressive Symptomatology–Self-Report, and the Psychiatric Diagnostic Screening Questionnaire. Measures obtained were used to estimate the presence of atypical, anxious, and melancholic symptoms. A representative SSRI was chosen (citalopram) and administered at an initial dose of 20 mg/d, which was increased to 40 mg/d by week 4 and then again to 60 mg/d by week 6. Study protocol

instructed patients to make clinic visits at weeks 2, 4, 6, 9, and 12 (with an optional visit at week 14), and for practitioners to make management decisions at weeks 4, 6, 9, and 12 after enrollment. Primary outcome measure was based on the self-rated Quick Inventory of Depressive Symptomatology, with remission defined as a score of 5 or less (equivalent to a score of 7 or less on the 17-item HAM-D) at week 9. The secondary outcome was response, defined as a reduction of 50% or more from baseline score on the self-rated Quick Inventory of Depressive Symptomatology at the last assessment.

A total of 22.2% of the enrolled subjects met typical entry criteria for phase III clinical trials (efficacy sample) and 77.8% did not (non-efficacy sample). The efficacy sample had a shorter average duration of illness as well as lower rates of family history of substance abuse, prior suicide attempts, and anxious and atypical symptom features, yet more of the subjects in this group were seen in psychiatric speciality care clinics. Efficacy participants also tolerated citalopram better, though there was no significant difference between the two groups with respect to dosage used. In addition, they had higher response (51.6% vs 39.1%) and remission (34.4% vs 24.7%) rates. Participants in the efficacy sample were also likely to be younger, more educated, white, non-Hispanic, employed, married, and privately insured, and to have a higher income. The researchers concluded that phase III clinical trials may not recruit representative depressed patients, and the findings of these studies may not reflect characteristics or treatment responses of the general population. The outcomes of phase III trials for the treatment of MDD may thus be more optimistic than results commonly seen in clinical practice.

■ COMMENTARY

There has long been a debate within medical circles regarding efficacy (high on internal validity at the expense of generalizability and favored by researchers) and effectiveness (high on external validity at the expense of careful controls, and preferred by most practitioners).[1] The findings of well-controlled trials may not easily translate into clinical outcomes in "real world" patients who frequently present with comorbidities and other confounding factors. And yet, approval of a new antidepressant drug requires at least two phase III clinical trials to demonstrate safety and (apparently) presumed effectiveness. Such trials employ strict inclusion and exclusion criteria that typically exclude a substantial portion of the broader population of depressed patients. In the setting of depression, where placebo response is recognized to be high, how is a clinician to interpret the results of phase III trials when facing a patient in need of help? This question has no easy answer; in fact, the authors posit that the research methodology employed in phase III trials, at least in addressing MDD, may need to be revisited.

Is it not surprising, then, that at a time when questions arise about the clinical relevance of phase III trials, when questions abound regarding appropriate research methodology in integrative health care (quantitative vs qualitative, for example), and when debate rages on the topic of what constitutes an evidence basis supporting a given therapy, that some of our patients question our recommendations? As practitioners we are sometimes left to ponder how we know what we know, as well as what do we really know? What's new is never really new: "Teach thy tongue to say I know not and thou wilt progress" (Maimonides). ❖

Reference

1. Stricker G: The relationship between efficacy and effectiveness. *Prevent Treatment* 2000;3: article 10.

Warm Baths for Sore Backs

ABSTRACT & COMMENTARY

By Dónal P. O'Mathúna, PhD

Dr. O'Mathúna is Senior Lecturer in Ethics, Decision-Making & Evidence, School of Nursing, Dublin City University, Ireland; he reports no financial relationship to this field of study.

Synopsis: *A study of thermal spa baths for chronic low back pain revealed some benefits over warm tap water baths. However, multiple hypothesis testing takes away from the confidence clinicians can have regarding the true effect. Nonetheless, all patients improved during and after the treatment period of daily baths.*

Source: Kulisch A, et al. Effect of thermal water and adjunctive electrotherapy on chronic low back pain: A double-blind, randomized, follow-up study. *J Rehabil Med* 2009;41:73-79.

THIS RANDOMIZED, DOUBLE-BLIND, CONTROLLED TRIAL compared the effectiveness of thermal mineral water with tap water in the treatment of chronic low back pain. The study was conducted at the spa of Celldömölk in Hungary, which opened in 2005. Seventy-one patients with chronic lumbar pain (more than 12 weeks duration) received 20-minute treatment sessions daily for three weeks. Participants were randomized into two groups,

which used baths filled either with medicinal spa water or with tap water, both at 34° C. Everyone also received standard electrotherapy at the same time, a treatment popular in continental Europe and similar to electrical stimulation that uses long pulse durations. In this study, electrodes were applied to people's waists, but few other details of the therapy were given.

Outcome measures were four visual analogue scales (VAS) for various back symptoms, range of mobility using Schober's test and the Domján's R and L tests, lumbar spine function using the Oswestry index, and quality of life using the Short Form-36 health survey. The tests were administered at baseline, immediately after the three weeks of treatment, and 15 weeks later.

After the three-week treatment period, the thermal water group showed significant improvements in all parameters compared to baseline. These improvements were maintained after 15 weeks of follow-up. All parameters also improved significantly in the control group compared to baseline, but to a smaller extent than in the thermal water group. Between-group comparisons revealed some statistically significant differences. Immediately after the treatment period, the thermal water group had significantly better scores on one VAS score. After follow-up, significant between-group scores existed on one of the other VAS scores and the Schober's index. These results were analyzed according to the intention-to-treat principle. When only those patients who completed the study were analyzed, other study parameters showed significant differences favoring the thermal water bath. The authors' conclusion was: "In the group treated with thermal water, improvement occurred earlier, lasted longer, and was statistically significant."

■ COMMENTARY

This study was well-designed and clearly reported. The inclusion and exclusion criteria for patients were clearly described, with anyone receiving physiotherapy at the same time excluded to avoid confounding effects. The randomization was conducted using a random-number table. An extract of green walnut husks was added to the control baths to make them resemble the thermal water, and all the baths were located in the same hall to provide the same odor and environment.

However, the study's results are limited by a number of factors not discussed by the investigators. The authors noted that the improvements reported were smaller than expected, but they did not report what those expected values were or the results of a power calculation. The 71 participants may have been an insufficient number to detect true differences. In addition, 20 participants did not complete the study, giving a relatively high drop-out rate of 28%. The impact of this can be seen in the subgroup analyses carried out by the investigators. To their credit, their primary analysis was carried out according to the intention-to-treat principle and revealed significant differences in three outcome parameters. When the data for only those who completed the full protocol were analyzed, an additional six parameters were significantly different. While the investigators found this gave credence to the value of the thermal baths, such an analysis inflates the true effect of an intervention and is why the intention-to-treat analysis is used.[1]

An even bigger problem with this study is the large number of outcomes measured. Multiple hypothesis testing is one of the most common problems in clinical research.[2] When two or more hypotheses are tested, the probability of finding a positive result by chance alone is increased. For example, if five tests are used, there is almost a one in four chance that a positive result will be found by random chance. This study used nine tests, each implemented on two occasions, making it highly probable that some positive findings would result. None of the tests was selected as the primary outcome. Testing several hypotheses may be legitimate, but in such cases additional statistical analyses should be used to correct for potential problems.[3] These were not reported in this study.

This interesting and well-designed study demonstrates the benefit of warm baths for chronic low back pain. Both the control group and the thermal water group showed improvements during the three weeks of treatment that were sustained for 15 weeks. However, even this conclusion must be held tentatively as a no-intervention control group was not included in this study. The small number of subjects, high drop-out rate, and numerous hypotheses tested mean that little confidence can be placed in the investigators' conclusion that thermal baths are more beneficial than warm baths with tap water. Given that many more of the parameters tested showed no differences between the two groups, patients can be reassured that they probably do not need to travel far from home to get the benefits of a warm bath. ❖

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'Nutrients Direct': Myers' Cocktail and FMS

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *This small pilot study represents the first controlled assessment of intravenous micronutrient therapy for fibromyalgia. No statistically significant benefit over placebo was identified, though clinical benefit was apparent, and feasibility was established. Regardless of one's bias regarding this type of care, further study is needed.*

Source: Ali A, et al. Intravenous micronutrient therapy (Myers' Cocktail) for fibromyalgia: A placebo-controlled pilot study. *J Altern Complement Med* 2009;15:247-257.

THE AUTHORS OF THIS DOUBLE-BLIND, PLACEBO-CONtrolled, randomized study set out to assess the feasibility, efficacy, and safety of intravenous micronutrient therapy, specifically using the Myers' cocktail, for the treatment of fibromyalgia. By trial's end, data were evaluable on 31 adults (30 women; mean age, approximately 51 years) with American College of Rheumatology (ACR)-defined fibromyalgia syndrome (FMS). Subjects were recruited through advertisements and presentations to FMS support groups, and initial screening took place by phone. Eligible subjects went through a two-week run-in period to assess stability of FMS medication use and then were randomly selected to receive once-a-week infusions for a total of eight weeks of Myers' cocktail (IVMC) or lactated Ringer's solution (placebo) via antecubital fossa slow IV push using a 25 g butterfly needle. Blinding was maintained with the use of an opaque sheet that was placed over the syringe and cannula. Rescue treatment with NSAIDs was permitted as necessary within strict guidelines, and subjects had to agree to stop all vitamin/mineral supplements, as well as other CAM therapies, during the trial. The primary outcome measure was change in the Tender Point Index at the end of the eight-week intervention and after a further four-week wash-out period (12 weeks after the start of infusion therapy) as assessed by a single rheumatologist who was blind to treatment assignment. Secondary measures included global pain assessment as determined by visual analog scale (VAS), and validated measures of physical function (Fibromyalgia Impact Questionnaire), mood (Beck Depression Index), and quality of life (Health Status Questionnaire).

Results of the IVMC intervention were equivocal. While the IVMC group experienced improvements so

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

21. Which of the following is a risk factor for heart failure?
a. Hypertension
b. Obesity
c. Metabolic syndrome
d. Past history of treatment with cyclophosphamide chemotherapy
e. All of above

22. Patients with HF have chronically elevated levels of proinflammatory cytokines.
a. True
b. False

23. Which of the following are cardiotoxins?
a. Cyclophosphamide
b. Alcohol
c. Trastuzumab
d. All of the above
e. None of the above

Answers: 21. e, 22. a, 23. d.

did the placebo group, such that between-group comparisons showed improvements that were clinically, but not statistically, significant. At eight weeks the IVMC group had improvements in tender points, pain, depression, and quality of life, while the placebo group experienced improvements only in tender points. This latter treatment effect persisted in the placebo group when assessments were repeated four weeks later; treatment effects in the IVMC group persisted four weeks later only for tender points, pain, and quality of life. The consistency and magnitude of treatment effects were greater in the IVMT group than in the placebo group. The authors conclude that IVMC therapy for the treatment of FMS is feasible but its effectiveness remains unclear.

■ COMMENTARY

The Myers' cocktail derives from the work of John Myers, MD, and later modification by Alan Gaby, MD. The rationale for this type of clinical intervention stems from the observation that enhanced levels of micronutrients can be achieved using intravenous administrations as compared with oral dosing, thereby making treatment of deficiency states more efficient, and that some of these same nutrients can exert pharmacologic effects.[1] The constituents of the Myers' cocktail as used in this study were:

- 5 mL magnesium chloride hexahydrate (20%)
- 3 mL calcium gluconate (10%)
- 1 mL hydroxycobalamin (1,000 µg/mL)
- 1 mL pyridoxine hydrochloride (100 mg/mL)
- 1 mL dexpanthenol (250 mg/mL)
- 1 mL B-100 B complex containing a combination of 100 mg thiamine HCl, 2 mg riboflavin, 2 mg pyridoxine HCl, 2 mg panthenol, and 100 mg niacinamide
- 2% benzyl alcohol
- 5 mL vitamin C (500 mg/mL)
- 20 mL sterile water

Proponents of this form of therapy report clinical experience with benefit in the setting of at least FMS, migraine headaches, and asthma, but readily acknowledge the lack of scientific study of IVMC.

About 3-4% of U.S. women suffer from FMS, approximately 10 times the prevalence in men, and people experiencing FMS often seek complementary and alternative medical (CAM) therapies for relief of their symptoms at least in part due to the paucity of effective conventional medical options. The etiology of FMS has yet to be fully characterized but the clinical picture is notable for a predominance of widespread pain and muscle tenderness often accompanied by chronic fatigue, sleep disturbances, and a depressed mood. The ACR's criteria for a diagnosis of FMS include: 1) continuous presence of widespread (all four quadrants of the body, including axial) musculoskeletal pain of undetermined etiology for three months or more; and 2) pain in 11 of 18 tender point sites on digital palpation. Some practitioners believe that IVMC may benefit people with FMS due to a combination of modest volume expansion and provision of intravenous magnesium. In general, IVMC appears to be quite safe in experienced hands. Patients should be made aware of the potential for a sensation of heat during administration, and among general precautions espoused,[1] extreme caution needs to be taken with people who may be hypokalemic or who are taking digoxin.

The current pilot trial is the first controlled study of IVMC for FMS and succeeds in establishing feasibility for this type of intervention. The small sample size precludes sweeping conclusions, even in the absence of statistically significant benefit, but the foundation has been laid for further investigation. Many practitioners, especially those conventionally trained, may harbor negative perceptions regarding this form of care, but one cannot argue that a growing number of infusion therapy medical centers are appearing across the country. This reviewer does not presently recommend IVMC but desires additional data to help better classify intravenous micronutrient therapy as an underutilized therapeutic strategy or a treatment no better than placebo. ❖

Reference

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News Briefs

Translating CAM Research Results into Clinical Practice

In an initial investigation of the potential for information from CAM research to influence clinical practice, a 2007 national survey asked acupuncturists, naturopaths, internists, and rheumatologists about their awareness of CAM clinical trials, ability to interpret research results, and use of research evidence in decision making. The survey was conducted by researchers affiliated with the National Institutes of Health, the Mayo Clinic, the University of Chicago, Harvard Medical School, and the University of Massachusetts. The

survey focused on awareness of two major NCCAM-funded clinical trials that studied acupuncture or glucosamine/chondroitin for osteoarthritis of the knee.

- More than half (59%) of the 1,561 respondents were aware of at least one of the two clinical trials, but only 23% were aware of both trials. The acupuncture trial was most familiar to acupuncturists and rheumatologists, the glucosamine/chondroitin trial to internists and rheumatologists. Overall, awareness was greatest among rheumatologists and those practicing in institutional or academic settings.
- A majority of respondents said they were "moderately confident" in their ability to interpret research literature; few—20% of acupuncturists, 25% of naturopaths, 17% of internists, and 33% of rheumatologists—said they were "very confident."
- All groups regarded clinical experience as "very important" in their decision making, although CAM providers were more likely to rate it "most important." Physicians were much more likely than CAM providers to consider research results very important or "very useful" in their clinical decision making. CAM providers were more likely than physicians to say that patient preferences were very important. CAM providers were much more likely than physicians to rank research results as "least important," whereas physicians were much more likely to rate patient preferences as least important.
- Awareness of CAM clinical trials was greatest among respondents with research experience, confidence in their ability to interpret results, and favorable opinions about the role of research in their practice.

The survey team concluded that CAM research has the potential to make a difference in both conventional and alternative medicine clinical practice. They recommend concerted efforts to better train all clinicians in interpretation and use of evidence from research studies, and to improve the dissemination of research results. ❖

Grape Seed Extract May Help Neurodegenerative Diseases

TAUOPATHIES—A GROUP OF NEURODEGENERATIVE CONditions such as Alzheimer's disease—have been linked to the build-up of "misfolded" tau proteins in the brain. (Tau proteins are associated with microtubules, which help to regulate important cellular processes.) In light of previous studies indicating that grape-derived polyphenols may inhibit protein misfolding, an NCCAM-funded research center at the Mount Sinai School of Medicine recently examined the potential role of a particular grape seed polyphenol extract (GSPE) in preventing and treating tau-associated neurodegenerative disorders.[1]

The results of their in vitro study showed that GSPE is capable of interfering with the generation of tau protein aggregates and also disassociating preformed aggregates, suggesting that GSPE may affect processes critical to the onset and progression of neurodegeneration and cognitive dysfunctions in tauopathies.

An earlier study by the Mount Sinai researchers found that this GSPE reduced Alzheimer's-type neuropathology and cognitive decline in a mouse model of Alzheimer's disease and inhibited an Alzheimer's-linked process called cerebral amyloid deposition.[2] In another recent study, the researchers used a variety of analytical techniques to further clarify how the GSPE affects Alzheimer's-related processes; an important finding was the extract's protective effects against cellular toxicity.[3]

The researchers concluded that their laboratory findings, together with indications that this GSPE is likely to be safe and well-tolerated in people, support its development and testing as a therapy for Alzheimer's disease. ❖

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1. If you are claiming physician credits, please indicate the appropriate credential: ○ MD ○ DO ○ Other _____

	Strongly Disagree	Disagree	Slightly Disagree	Slightly Agree	Agree	Strongly Agree
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3. Describe controversies, advantages, and disadvantages of those advances.	○	○	○	○	○	○
4. Make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice.	○	○	○	○	○	○
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