ALTERNATIVE MEDICINE ALERT®

The Clinician's Evidence-Based Guide to Integrative Medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosure
Russell H. Greenfield, MD (executive editor), David Kiefer, MD (peer reviewer), and Paula Cousins (senior managing editor) have no financial relationships with companies having ties to the material presented in this continuing education program.

Alternative Medicine Alert is available on-line. For more information, go to www.ahcmedia.com/online.html or call (800) 688-2421.

Nasal Saline Irrigation for Upper Respiratory Tract Infection and Seasonal Allergies

By Ted Wissink, MD, Megan Britton, MBBS, and Craig Schneider, MD

Dr. Wissink is Faculty in the Integrative Family Medicine Program at Maine Medical Center. Dr. Britton is a Fellow at the Integrative Family Medicine Program at Maine Medical Center and recently completed a Fellowship at the University of Arizona Center for Integrative Medicine. Dr. Schneider is Director of Integrative Medicine, Department of Family Medicine, Maine Medical Center in Portland; they report no financial relationships to this field of study.

RECENTLY IT SEEMS THAT EVERYONE FROM YOUR AUNT MILDRED TO Oprah is spouting the merits of nasal irrigation. In this review, we attempt to sniff out fact from fiction.

Background

Nasal irrigation, also known as "jala neti" or flushing of nasal cavities with hypertonic saline solution, has been practiced for at least hundreds of years by yoga practitioners in Southern Asia and more recently has become popular around the world as an adjunctive therapy for treating nasal and sinus symptoms. It likely originated in the Ayurvedic medical tradition and descriptions and instructions for use first appeared in Western medical literature in the early 20th century.[1] Saline is inserted into one nostril and allowed to drain out of the other nostril, and may be performed using low positive pressure (spray bottle) or with gravity-based pressure (neti pot with a nasal spout). The precise mechanism of action remains unknown, but several theories have been proposed including mechanical evacuation[2] and improved mucociliary clearance,[3] leading to reduced concentrations of inflammatory mediators such as histamine and leukotriene C4, thus reducing mucosal edema.[4]

Clinical Studies

This review includes studies published since 2000.

Chronic Rhinosinusitis

Several studies demonstrate significant benefit of nasal irrigation with hypertonic saline for patients with frequent sinusitis. In 2002,

Rabago et al randomized 76 patients from primary care (n = 70) and otolaryngology (n = 6) clinics with histories of frequent sinusitis, defined as either two episodes of acute sinusitis or one episode of chronic sinusitis per year for two consecutive years, into intervention or control groups.[5] The intervention group used daily saline irrigation for 6 months while the control group continued treatment of sinus disease in their usual manner. Participants in the intervention group used 1 heaping teaspoon of salt, ½ teaspoon of baking soda, and 1 pint of lukewarm water to create a homemade saline preparation. The primary outcomes were quality-of-life scores from a validated questionnaire, the Rhinosinusitis Disability Index (RSDI), and the Single-item Sinus-symptom Severity Assessment (SIA). Secondary outcomes were assessed every 2 weeks by recording compliance with the nasal irrigation (daily diary) along with the presence or absence of sinus symptoms, antibiotic use, and nasal spray use. After 6 months, the intervention group reported adherence to nasal irrigation during 87% of the study, and their questionnaire scores improved significantly as compared to the control group ($P <$ 0.001 for both measures). The number needed to treat to achieve a 10% improvement at 6 months was 2. The nasal irrigation intervention group reported fewer periods of sinus-related symptoms and less antibiotic use, and 93% reported overall improvement of sinus-related quality of life. None reported worsening and side effects were minor and infrequent.

Rabago et al continued to study the patients above in an uncontrolled 12-month follow-up that combined 40 participants from the intervention group from the previous study and 14 from the control group (all patients used nasal irrigation in this study).[6] They again followed the RSDI and the Sino-nasal Outcomes Test (SNOT-20). Secondary outcome measures were frequency and pattern of nasal irrigation use, side effects, and participant satisfaction. Prior intervention group RSDI scores continued to improve ($P < 0.001$), and their SNOT-20 scores remained stable. Prior control participants' RSDI scores improved similarly to the intervention group ($P < 0.001$) and the SNOT-20 scores decreased significantly ($P =$ 0.05); and as for anyone with nasal congestion, the less SNOT (scores in this case) the better. Mean nasal irrigation use for all participants was 2.4 times per week. Satisfaction was high and side effects were minor.

A third study by Pynnonen et al compared isotonic saline nasal irrigation with saline nasal sprays for the treatment of chronic nasal/sinus symptoms.[7] A total of 127 adults 18 years or older were enrolled. Each self-reported one or more of the following symptoms 4 or more days per week in the preceding 2 weeks if they had been present for at least 15 of the previous 30 days: nasal congestion, nasal dryness or crusting, or thick nasal discharge. Excluded were patients with recent sinus surgery, respiratory infection within the preceding 2 weeks, or who had previously used either of the study interventions. Participants were randomly assigned to either irrigation or spray and asked to do the assigned treatment twice daily for 8 weeks. Outcomes were measured at 2, 4, and 8 weeks via mail-in survey, including the SNOT-20 measure of symptom severity, a symptom frequency questionnaire, and a medication diary documenting compliance and use of prescription and nonprescription medications for nasal and sinus-related symptoms. Baseline SNOT-20 scores were similar in the two groups, and both groups showed significantly lower scores at 8 weeks. The irrigation group scores declined significantly more than the spray group at 8 weeks ($P =$ 0.002). Symptom frequency also decreased significantly in both groups but more in the irrigation group ($P =$ 0.01). There was no difference in medication (both oral and nasal) use between groups, but a significant decrease in medication use was noted for both groups compared to baseline. Compliance was higher in the spray group (97%, 93%, and 93%) than the irrigation group (92%, 81%, and 79%) at weeks 2, 4, and 8, respectively ($P = 0.03$).

Recently, an unpublished study presented at the American College of Allergy, Asthma, and Immunology Annual Meeting in Miami (2009) has cast some doubt upon the benefit of nasal saline irrigation for prevention

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Coles McKagen
DIRECTOR OF MARKETING: Schandale Kornegay
SENIOR MANAGING EDITOR: Paula Cousins
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

AHC Media LLC

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
$299 per year (Student/Resident rate: $165).
Add $17.95 for shipping & handling.
Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Outside the United States
$369 per year plus GST (Student/Resident rate: $180 plus GST).

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *24 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for physicians and researchers interested in complementary and alternative medicine. It is in effect for 36 months from the date of the publication.

For CME credit, add $50.

Questions & Comments

Please call **Paula Cousins,** Senior Managing Editor, at (404) 262-5468

of sinusitis.[8] The authors followed 68 people who used nasal saline irrigation for 12 months and then discontinued use for another 12 months. They reported a reduction in number of cases of sinusitis by 62.5% during the discontinuation phase. Researchers then compared the rates of sinusitis among the discontinuation group with another group of 24 adults using daily nasal saline irrigation for 12 months. Again, they found significantly higher (50%) rates of sinusitis among saline irrigation users than nonusers. The authors hypothesize that because nasal mucus acts as a first line of defense against infections, long-term nasal saline irrigation may interfere with this natural immune barrier. Although use of a neti pot for nasal saline irrigation may temporarily improve sinus infection symptoms, they say "its daily long-term use may result in an increased frequency of acute [sinusitis] by potentially depleting the nose of its immune blanket of mucus."

Seasonal Allergies in Children

In 2005, Garavello et al studied the relationship between nasal irrigation used during the seasonal allergy period and symptoms of allergic rhinoconjunctivitis in a pediatric population.[9] Children with seasonal grass pollen rhinoconjunctivitis were randomized to three times daily nasal irrigation with hypertonic saline during the 7 weeks of pollen season. Subjects in the treatment group were allowed to use oral antihistamines as needed. The mean rhinoconjunctivitis symptom score in the active group was reduced (graph shows approximately 3.5 vs. 10 in the control group) during the pollen period. Statistical significance was reported in weeks 6 and 7. A statistically significant reduction in antihistamine use among the treatment group was reported in 5 of the 7 weeks (0-2 in the treatment group and 2-5 in the control group). No adverse effects were reported, and the treatment was thought to be tolerable, inexpensive, and effective. Unfortunately, the authors did not report results numerically, and no *P*-values or confidence intervals are provided.

In 2003, Garavello et al evaluated the use of hypertonic saline nasal irrigation in the prevention of seasonal allergic rhinitis-related symptoms in pediatric patients.[10] Twenty children with allergic seasonal rhinitis to *Parietaria* sp. were randomized to nasal irrigation with hypertonic saline three times a day for the entire pollen season (6 weeks). Mean daily rhinitis scores were calculated (based on nasal itching, rhinorrhea, nasal obstruction, and sneezing) and patients were allowed to use oral antihistamines as needed. In the irrigation group, the mean daily rhinitis score was reduced during 5 weeks of the study period, and this became statistically significant at weeks 3-5. Graphs demonstrate rhinitis scores of 11-14 in the control group and 4-6 in the treatment group. The authors report less oral antihistamine use in the treatment group (0-2 tablets per week) than for controls (2-5 tablets per week) and this was statistically significant in weeks 3, 4, and 6. Unfortunately, numerical results, *P*-values, and confidence intervals are not provided. Nasal irrigation was reported to be tolerable, inexpensive, and effective in this trial.

The children in both the 2003 and 2005 studies ranged in age from 6 to 12 years.

Pediatric Upper Respiratory and Influenza Infection

In 2008, Slapak et al studied 401 children ages 6-10 years with uncomplicated cold and flu. Subjects were randomized to standard medication (antipyretics, nasal decongestants, mucolytics, and/or systemic antibiotics) or nasal irrigation with modified seawater.[11] The saline solution used was a commercially available isotonic product processed from Atlantic Ocean seawater (Physiomer; Goemar Laboratoire de la Mer, Saint Malo, France). Subjects used irrigation six times per day in the acute setting and three times per day for prevention and were observed for 12 weeks. Patients in the nasal irrigation group showed lower symptom scores (sore throat, cough, nasal obstruction) and decreased use of medication (antipyretics, 9% vs. 33%; nasal decongestants, 5% vs. 47%; mucolytics, 10% vs. 37%; and systemic antiinfectives, 6% vs. 21%). Nasal irrigators also reported fewer days with illness (31% vs. 75%), school absence (17% vs. 35%), and complications (8% vs. 32%). The authors reported faster resolution of nasal symptoms during acute illness and less frequent reappearance of rhinitis among children in the nasal irrigation group.

Adverse Effects

Nasal irrigation appears to be well tolerated. Reported side effects include post-treatment drainage, nasal irritation, nasal burning, bitter taste, and epistaxis. However, adherence-to-treatment rates are high, suggesting few side effects severe enough to lead to discontinuation of treatment. In our experience, irritation or burning can be eliminated with reduction of the irrigation solution salinity or buffering with baking soda. Post-treatment positioning such as forward flexion at the waist along with head rotation and exhalation through the nose seems to augment drainage of salt water out of the nasal passage. This may minimize the sensation of continued drainage experienced by some users after using nasal irrigation.

Discussion

For treatment of chronic rhinosinusitis, most recent studies show statistically significant improvement in

sinus symptoms and quality of life along with reduced antibiotic and nasal spray medication use. In general, the studies showed limited adverse effects and high patient compliance and satisfaction.

Whether the statistical improvement in symptoms translates into clinical benefit was addressed by Pynnonen et al. In their study, the improvement in SNOT-20 scores ranged from 12.2 to 16.2 points.[12] In comparison, a study that followed patients after sinus surgery showed an improvement of 19-22 points and patients with severe polyposis treated with oral prednisone improved by 10 points.[13]

Study strengths include generalizability and practicality, since they focused on community-based populations with reported chronic sinus symptoms that are commonly seen by primary care providers. A major challenge is the inability to blind subjects or researchers to a physical treatment like nasal irrigation. The studies evaluating chronic rhinosinusitis also did not have adequate power to evaluate subgroups, such as patients with allergic rhinitis, nasal polyposis, cystic fibrosis, or anatomic problems causing congestion.

With respect to chronicity of treatment, the negative study presented at a recent conference is interesting. It showed that possible long-term use (> 12 months) may not be recommended. More research is needed in this area before official recommendations can be given, but caution should be advised regarding long-term treatment for now.

Although supportive, the pediatric research on nasal irrigation also suffers from the above mentioned methodological weaknesses and more. For example, Garavello (in both 2003 and 2005) did not report numerical results, *P*-values, or confidence intervals. The studies were not blinded, and no placebo was used. The number of subjects were small, and treatment periods brief (ranging from 6 to 7 weeks). Slapak's study included large numbers of subjects, was randomized and partially blinded (physicians were aware of which patients used nasal wash and their assignment to particular groups, but were not informed about the composition and device used in these groups since the bottles were not labeled), and reported clear results. However, the study used six times a day irrigation, which is not the standard use pattern and likely to suffer from poor adherence in the general population.

Conclusion

Most recent published research supports the use of nasal saline irrigation for the prevention and treatment of chronic rhinosinusitis, pediatric seasonal allergies, colds, and flus. Further study is needed to determine the most effective solution for nasal irrigation (hypertonic saline solution, buffered saline solution, Dead Sea salts, etc.), frequency of irrigation, and duration of treatment in both acute and preventive settings.

Recommendation

Based on the positive outcomes and low side effect reports in the recent studies on saline nasal irrigation, we recommend it for allergic rhinitis, colds, and chronic sinusitis for patients ages 6 years and older. People can mix their own saline with table salt or purchase premade packets of salt. The most effective salinity level is undetermined, so we recommend using 0.25-0.5 teaspoons of salt for every 8 ounces of lukewarm tap water and using 8 ounces of water for each nasal cavity irrigated. Decreasing the amount of salt can help if a patient experiences irritation. If table salt is used rather than proprietary blends, more time may be necessary for it to completely dissolve in the water. Published studies suggest a good safety profile, but vigilance to the possibility of harm with regular, long-term use of nasal irrigation is recommended until clarified by further research. ❖

References

1. Rabago D, Zgierska A. saline nasal irrigation for upper respiratory conditions. *Am Fam Physician* 2009;80: 1117-1119.
2. Rabago D, et al. Qualitative aspects of nasal irrigation use by patients with chronic sinus disease in a multimethod study. *Ann Fam Med* 2006;4:295-301.
3. Homer JJ, et al. The effect of hypertonicity on nasal mucociliary clearance. *Clin Otolaryngol Allied Sci* 2000;25:558-560.
4. Tomooka LT, et al. Clinical study and literature review of nasal irrigation. *Laryngoscope* 2000; 110:1189-1193.
5. Rabago D, et al. Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: A randomized controlled trial. *J Fam Pract* 2002;51: 1049-1055.
6. Rabago D, et al. The efficacy of hypertonic saline nasal irrigation for chronic sinonasal symptoms. *Otolaryngol Head Neck Surg* 2005;133:3-8.
7. Pynnonen MA, et al. Nasal saline for chronic sinonasal symptoms: A randomized controlled trial. *Arch Otolaryngol Head Neck Surg* 2007;133:1115-1120.
8. Nsouli TM, et al. Long-term use of nasal saline irrigation: Harmful or helpful? *Ann Allergy Asthma Immunol* 2009;103:A27.
9. Garavello W, et al. Nasal rinsing with hypertonic solution: An adjunctive treatment for pediatric seasonal allergic rhinoconjunctivitis. *Int Arch Allergy Immunol*

2005;137:310-314.
10. Garavello W, et al. Hypersaline nasal irrigation in children with symptomatic seasonal allergic rhinitis: A randomized study. *Pediatr Allergy Immunol* 2003: 14:140-143.
11. Slapak I, et al. Efficacy of isotonic nasal wash (seawater) in the treatment and prevention of rhinitis in children. *Arch Otolaryngol Head Neck Surg* 2008; 134:67-74.
12. Colclasure J, et al. Endoscopic sinus surgery in patients older than sixty. *Otolaryngol Head Neck Surg* 2004;131:946-949.
13. Woodworth B, et al. Alterations in eotaxin, monocyte chemoattractant protein-4, interleukin-5, and interleukin-13 after systemic steroid treatment for nasal polyps. *Otolaryngol Head Neck Surg* 2004;131: 585-589.

Reports of Thrombocytopenia Associated with Herbal Remedies, Dietary Supplements, Foods, and Beverages

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: *Thrombocytopenia is a well-established adverse effect of many conventional drugs. This systematic review found few reports of such adverse effects associated with complementary and alternative medicines, herbal remedies, nutritional supplements, foods, and beverages.*

Source: Royer DJ, et al. Thrombocytopenia as an adverse effect of complementary and alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. *Eur J Haematol* 2010 Jan 5; Epub ahead of print.

THIS TEAM OF REVIEWERS HAS SIGNIFICANT EXPERIENCE evaluating reports of drug-induced thrombocytopenia, which they make available on the Internet and update every 2 years (www.ouhsc.edu/platelets/ditp.html).[1] Past reviews have excluded reports of thrombocytopenia associated with complementary and alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. This review focused on reports of this adverse effect associated with these products.

A wide search strategy was used to identify all reports of interest. Eleven databases were searched, including those focused on conventional medicine (such as Medline and EMBASE) and complementary and alternative medicine (CAM), such as the Natural Medicines Comprehensive Database. The bibliographies of all retrieved articles were also searched for additional reports.

Articles were included only if they contained primary data on patients of any age. Articles were excluded if insufficient patient data were included, the platelet count was not less than 100,000/μL, the substance used was a known toxin or illegal, or if an excessive amount of the substance was taken with the intention of causing harm.

Articles retrieved were independently appraised by the three authors. Data were extracted to determine the level of evidence for a causal association between the substances and thrombocytopenia. Explicit criteria for these determinations were reported and had been developed previously for the reviews of conventional drugs. Different assessments were resolved through discussions between the authors.

Six articles were identified that described seven patients with thrombocytopenia associated with quinine-containing beverages, such as tonic water. In six of the seven patients the causal association was determined to be definite. An additional 27 articles met the review's inclusion criteria. These articles reported 47 patients with thrombocytopenia who had consumed 25 different substances. The reports came from 12 different countries and their publications spanned 72 years.

The substances with definite evidence of causal association were milk, cranberry juice, Jui (a Chinese herbal tea with two cases reported), *Lupinus termis* (a North African bean), and tahini (pulped sesame seeds). Four substances had probable evidence of causal association, including bajiaolian (a potentially lethal Chinese herbal tea known better in Western medicine as podophyllum), mourning cypress, milk (again), and vitamin A (62,000 units per day mistakenly given to a newborn from 10 days old to 3 months). Five articles described five patients with possible evidence of a causal association with thrombocytopenia. The substances here were a dietary supplement called Complete Thymic Formula, chromium picolinate, *Echinacea pallida*, St. John's wort, and nicotinamide. Eight patients were described with thrombocytopenia but the authors evaluated the causal association as unlikely. Reports of the remaining

24 patients were excluded after detailed evaluation of the complete text of the reports.

With the exception of quinine-containing beverages, the reviewers concluded that there were "surprisingly few" associations of thrombocytopenia and the products covered by this review.

■ COMMENTARY

Blood clotting problems and interactions with blood thinning drugs are commonly raised as potential concerns with herbs and dietary supplements. Thrombocytopenia, or a low platelet count, can be caused by several factors. A number of conventional drugs have been shown to cause thrombocytopenia. With increased attention being paid to the adverse effects of herbal remedies and dietary supplements, questions have been raised about whether such products might lead to thrombocytopenia. Quinine is known to cause thrombocytopenia, and in 2006 the FDA ordered unapproved quinine drugs off the market because of their "off-label" use for the treatment of leg cramps.[2]

This review involved a systematic and broad search for reports of thrombocytopenia associated with dietary supplements and similar products. The methodology used was thorough and explicit. The criteria used to determine the level of evidence for an association were explicit and determined prior to conducting the review. A wide variety of databases was searched, including those most likely to include CAM case reports.

In spite of their methodology and experience, the reviewers reported difficulty evaluating many of the reports. Many of the case reports were missing important information necessary to allow confidence about the level of evidence determined.

The lack of published reports of thrombocytopenia can be explained in a number of different ways. Such associations may be relatively rare, with quinine-containing beverages being the exception. On the other hand, the associations may be more common but not reported because clinicians do not ask about CAM products when investigating thrombocytopenia. Also, providers and users of CAM products may not be aware of the need to report adverse effects. Only further, longitudinal studies involving users of these products will be able to determine if thrombocytopenia is as rare an adverse effect of CAM products, foods, and beverages as this review has found.

This systematic review summarizes the evidence currently available, but also points to the importance of vigilance in this area. Since some definite associations were discovered, clinicians caring for patients with thrombocytopenia of unknown origin should ask about any supplements or beverages consumed and publish reports when associations are verified. ❖

References

1. Swisher KK, et al. Drug-induced thrombocytopenia. An updated systematic review, 2008. *Drug Saf* 2009;32:85-86.
2. FDA. FDA Advances Effort Against Marketed Unapproved Drugs. 11 December 2006. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108799.htm. Accessed Feb. 5, 2010.

Acupuncture vs. Venlafaxine for Hot Flashes in Breast Cancer Patients

ABSTRACT & COMMENTARY

By Judith L. Balk, MD, MPH, FACOG

Dr. Balk is Associate Professor, Magee-Women's Hospital, University of Pittsburgh; she reports no financial relationship to this field of study.

Synopsis: *This RCT compared acupuncture to venlafaxine for management of hot flashes in breast cancer patients. Both acupuncture and venlafaxine were given for 12 weeks, and then the subjects were followed. Both groups had improvements in their symptoms, but the venlafaxine group had side effects, and the acupuncture group did not.*

Source: Walker EM, et al. Acupuncture versus venlafaxine for the management of vasomotor symptoms in patients with hormone receptor-positive breast cancer: A randomized controlled trial. *J Clin Oncol* 2009 Dec 28; Epub ahead of print.

Vasomotor symptoms like hot flashes are common in breast cancer patients who are taking antiestrogen medications. Hormone therapy is contraindicated in these patients, so non-hormonal approaches are used. One popular non-hormonal approach is the medication venlafaxine, which is an antidepressant. However, some women experience side effects on this medication, and others simply choose not to use it. Thus, a non-pharmaceutical agent may be preferred by some women.

Fifty subjects with a history of hormone receptor-positive breast cancer were randomized to receive 12 weeks of either acupuncture or venlafaxine. After the 12-week treatment period, subjects were followed for up to 1

year. The primary outcome was hot flash frequency, and secondary outcomes included depressive symptoms and quality of life.

Both groups had significant improvements in hot flashes, depressive symptoms, and other quality-of-life symptoms. During the 12 weeks of treatment, the groups had similar outcomes. At 2 weeks post-treatment, the venlafaxine group had significant increases in hot flashes; the acupuncture group did not. At the other follow-up time points (3, 6, 9, and 12 months), the groups did not differ from each other, with both groups improving over time. The venlafaxine group had 18 incidences of adverse effects; the acupuncture group had none. In addition, in about 25% of women in the acupuncture group, improved libido was experienced.

Acupuncture appears to be at least equivalent to venlafaxine in reducing the frequency of hot flashes, without having adverse effects. Both groups improved over time after a 12-week course of treatment.

■ COMMENTARY

Effective treatment of hot flashes for breast cancer patients is an important problem. Women who have been diagnosed with breast cancer often have challenging menopausal symptoms, which can be due to discontinuing hormone therapy after their diagnosis, being placed into menopause from the chemotherapy, and taking anti-estrogen drugs like selective estrogen receptor modulators or aromatase inhibitors. Hormone therapy with estrogen and progestogens is contraindicated in women who have had breast cancer. Thus, finding nonhormonal treatment for menopausal symptoms is very important.

Many different pharmacologic and non-pharmacologic approaches have been studied, including clonidine,[1] fluoxetine,[2] venlafaxine,[3] gabapentin,[4] paroxetine,[5] relaxation training,[6,7] and acupuncture.[8] Clinical trials with medications can readily be placebo-controlled, but research on complementary modalities such as acupuncture and relaxation training is often plagued with difficulty in finding appropriate control groups. Recently, sham acupuncture has been questioned as to whether it is truly an inactive control group;[9,10] thus, identifying other appropriate control groups will manifest in better research on the effectiveness of various modalities. One approach to studying complementary modalities is to compare the modality with a known effective treatment. With this type of research, one can make an equivalency statement, i.e., whether one treatment appears to be equivalent to another treatment. However, whether the positive effects are due to attention or expectation (placebo effects) cannot be assessed with this type of study. Studying acupuncture relative to a known effective treatment for hot flashes, such as venlafaxine, is thus an excellent study design due to the limitations of sham-controlled acupuncture research.

Venlafaxine is effective for treating hot flashes.[3] One double-blind, placebo-controlled, randomized trial enrolled women who either had a history of breast cancer or were reluctant to take hormones, to study the effect of placebo or venlafaxine at different dosages: 37.5 mg, 75 mg, or 150 mg. The primary outcome variable was the hot flash score at 4 weeks. Subjects were stratified based on age, current tamoxifen use, duration of hot flash symptoms, and average frequency of hot flashes per day. One hundred ninety-one subjects had evaluable data over the entire study period. The groups receiving venlafaxine had a greater decrease in hot flashes than did the placebo group. Side effects that were significantly higher in the venlafaxine group compared to the placebo group include mouth dryness, decreased appetite, nausea, and constipation, and were more frequently reported at the 150 mg dosage than at the 75 mg dosage. Overall quality of life increased in all the venlafaxine groups, and decreased in the placebo group. Thus, it appears that venlafaxine is more effective than placebo, at least after 4 weeks, in treating hot flashes, but side effects may limit its utility.

Acupuncture also has placebo-controlled research supporting its effectiveness in treating hot flashes.[8,11] In one study, women on tamoxifen received 10 weeks of either true acupuncture or sham acupuncture. During the treatment period, the mean number of hot flashes at day and night was significantly reduced by 50% and almost 60%, respectively, from baseline in the true acupuncture group, and was further reduced by 30% both at day and night during the next 12 weeks. In the sham acupuncture group, hot flashes decreased 25% during the day over the 12 weeks of treatment, but this decrease was reversed during the following 12 weeks. No reduction was seen in hot flashes at night. In another study, 72 women with breast cancer experiencing three or more hot flashes per day were randomly assigned to receive either true or sham acupuncture. True acupuncture was associated with 0.8 fewer hot flashes per day than sham at 6 weeks, but this difference did not reach statistical significance (95% confidence interval, -0.7 to 2.4; $P = 0.3$). When participants in the sham acupuncture group were crossed over to true acupuncture, the frequency of hot flashes further decreased. The reduction in hot flash frequency persisted for up to 6 months after the completion of treatment. Thus, it appears that acupuncture is effective for hot flashes, and it appears to be well tolerated.

When advising a breast cancer patient regarding options to treat her hot flashes, one must consider both effectiveness and side effect profile. Direct comparisons, such as the study presented, which compare two viable options, often yield very helpful advice. This study has many strengths. First, the researchers employed randomized design with clear statements of the eligibility criteria. The outcome measures are well described, and the CONSORT diagram is clear. The acupuncture points are clearly stated, and the analysis is thorough and appropriate. Most importantly, this study has high clinical significance because it is a comparative effectiveness study, which can improve decision-making between two options.

This study also has limitations. First, the sample size is fairly small, including only 50 subjects. No power analysis is presented to determine the necessary sample size to detect a meaningful difference. The most important limitation is that while the acupuncture intervention likely mimics usual care, the venlafaxine arm does not. Patients may not electively choose to stop medication for hot flashes after 12 weeks, if the medication is tolerated and working well. That said, hot flashes rapidly returned after 12 weeks in the venlafaxine group, but the acupuncture effect was of longer-lasting duration. This is clinically significant, and it may be cost-effective to consider acupuncture rather than medication.

Overall, this is an excellent study that used a sound design to test a very significant question. The authors conclude the paper stating their hope that this study will lead to a change in the typical pattern of practice of treating vasomotor symptoms in patients with breast cancer. I agree with the authors, with the caveat that the small sample size precludes making equivalency conclusions. That said, acupuncture vs. venlafaxine? When conservatively weighing therapeutic risks and benefits, acupuncture comes out ahead. ❖

References

1. Nagamani M, et al. Treatment of menopausal hot flashes with transdermal administration of clonidine. *Am J Obstet Gynecol* 1987;156:561-565.
2. Loprinzi C, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20: 1578-1583.
3. Loprinzi C, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: A randomised controlled trial. *Lancet* 2000;356:2059-2063.
4. Guttuso T, Jr, et al. Gabapentin's effects on hot flashes in postmenopausal women: A randomized controlled trial. *Obstet Gynecol* 2003;101:337-345.
5. Stearns V, et al. Paroxetine controlled release in the treatment of menopausal hot flashes: A randomized controlled trial. *JAMA* 2003;289:2827-2834.
6. Freedman R, et al. Biochemical and thermoregulatory effects of behavioral treatment for menopausal hot flashes. *Menopause* 1995;2:211-218.
7. Irvin JH, et al. The effects of relaxation response training on menopausal symptoms. *J Psychosom Obstet Gynaecol* 1996;17:202-207.
8. Hervik J, Mjaland O. Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial. *Breast Cancer Res Treat* 2009;116: 311-316.
9. Lund I, et al. Minimal acupuncture is not a valid placebo control in randomised controlled trials of acupuncture: A physiologist's perspective. *Chin Med* 2009;4:1-27.
10. Balk J, Horn B. Why we should change the course of acupuncture research. *J Chinese Med* 2008;78:54-59.
11. Deng G, et al. Randomized, controlled trial of acupuncture for the treatment of hot flashes in breast cancer patients. *J Clin Oncol* 2007;25:5584-5590.

Energized Joints? Bracelets for OA

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *Results of this small double-blind RCT suggest that neither magnetic nor copper bracelets have a place in the treatment of osteoarthritis. These findings contradict those of a few other studies, but almost all suffer from small sample size and other methodological flaws. The lack of sound data regarding such therapy, however, has done little to dampen the enthusiasm of consumers hoping to realize symptom relief.*

Source: Richmond SJ, et al. Therapeutic effects of magnetic and copper bracelets in osteoarthritis: A randomized placebo-controlled crossover trial. *Complement Ther Med* 2009; 17:249-256.

THE AUTHORS OF THIS RANDOMIZED, DOUBLE-BLIND, placebo-controlled crossover trial sought to determine whether a specific type of commercially available magnetic wrist strap was effective in reducing symptoms in people with osteoarthritis (OA). Potential subjects were those older than age 40 years with documented OA who were taking pain medication (either

NSAIDs or opioids). They were recruited from general practices in both rural and urban areas of Yorkshire, United Kingdom, following review of their medical records and a home interview. A total of 300 people were initially approached regarding study participation, of which 45 made up the sample.

Subjects were then randomized to one of four 4-week treatment sequences, each associated with a distinct phase of treatment during which a specific device was employed. The devices were:

- A standard MagnaMax® wrist strap (the experimental device) consisting of two plastic-coated permanent neodymium magnets forming a single 23 mm insert attached to a leather strap and worn directly against the skin. Testing prior to randomization showed the average surface magnetic field to be 201 mT.
- An attenuated MagnaMax wrist strap, deemed the placebo, which appeared identical to the experimental wrist strap, but possessed a significantly weaker surface magnetic field of 45 mT. These straps would, for example, adhere to a refrigerator door, thus helping to maintain blinding.
- A demagnetized MagnaMax wrist strap (dummy) that also appeared identical to magnetic wrist straps, but were non-magnetic, and thus did not attract metal. The researchers believed most participants would be able to recognize this strap as inactive, a dummy device.
- A plain copper bracelet as sold by local pharmacies, also deemed a placebo, and with no magnetic properties.

The devices were distributed to the participants in sealed boxes that were labeled only with the order for distribution and study ID number. The devices were to be worn at least 8 hours of every day over the course of the trial, and each subject acted as her/his own control. Follow-up took place at the end of each of the four trial phases.

At trial's end, following one primary and eight secondary analyses, it was determined that subjects experienced pain relief with the experimental device, as well as with the attenuated and the demagnetized wrist straps, but tended to get somewhat worse with the copper bracelet. The reported changes in pain were small and essentially inconsequential, and no statistically significant differences between the four groups were identified. The findings were similar for measures of stiffness (WOMAC B), physical function (WOMAC C), and medication use as quantified from subjects' diaries. One finding of interest, however, was a statistically significant improvement with the true magnetic wrist strap (experimental device) on the PRI sensory pain subscale. No significant adverse events due to use of any of the devices occurred.

The authors conclude that both magnetic and copper bracelets are generally ineffective for management of the pain, stiffness, and physical impairments frequently seen with OA, and that reported benefits are likely a reflection of the placebo effect.

■ COMMENTARY

The popular use of magnetic bracelets continues to grow (more than $5 billion in annual sales), rivaled only, it seems, by the growth in claims of therapeutic benefit that appear in associated marketing materials. Many people profess to have benefited from the use of these bracelets, and a small number of studies suggests the potential for benefit in certain painful conditions. Keep in mind, however, that the total number of magnet therapy trials and subjects studied is very small. Keep in mind, too, that magnet therapy, while easily applied and without known significant side effects, can be a very expensive undertaking, and that a wide variety of products are available to the public.

Confidence in the results of this trial is lessened by the small sample size, testing of magnetic strength only at time of randomization, and determination of compliance by self-report. These are significant shortcomings, to be sure, but the study was otherwise well done. There was little attrition and very few data were lost, significant steps were taken to maintain blinding, and intention-to-treat analysis was employed. While some might suggest that the duration of the four phases of treatment was brief, other trials suggest that when magnet therapy is effective the relief is almost immediate.

Previous studies on static magnet therapy suggest that when therapeutic benefits are seen they occur only with strongly magnetized bracelets and not with weakly magnetized ones (under 50 mT), so the attenuated wrist strap may be a reasonable placebo. The wearing of copper bracelets for pain relief in OA has been even less well studied than magnetic bracelet use in this setting. As the authors point out, copper bracelets might be viewed as a valid placebo in light of data suggesting that while dermal absorption may occur with the wearing of such bracelets, there is no significant pain relief associated with their use. Still, a large number of patients swear by their effectiveness, and they may not be sharing that information with us unless we can discuss the science behind the therapy … non-judgmentally.

We practitioners are often dubious of the claims made by purveyors of magnet and copper bracelets, often with good reason, and rarely employ them, but a growing

population of people will be faced with the challenges of OA in the coming years. They have read about the shortcomings of NSAIDs, they are fearful about losing their independence, they want to avoid surgical intervention, and they are willing to try anything that might be safe and effective. The results of this trial are by no means definitive, but they can be shared with our patients when the question of magnet therapy comes up, as it will if our patients feel comfortable with us. We can quote from the small amount of existing data, let them know that scientific investigation into magnet therapy is still in its infancy and that existing trials have provided conflicting results, be honest regarding our concerns or positive experience with such therapy, and confidently state that use of these bracelets should not be dangerous to them. We need also share, however, that identifying credible manufacturers and reasonably priced products remains a challenge. ❖

Blowing Off Steam: Mindfulness and COPD

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *This well-done trial compared a combination of mindfulness-based breathing therapy (MBBT) and training in the relaxation response with participation in group support for elderly subjects, almost all men, with moderate-to-severe COPD. The results did not suggest any benefit of MBBT over group support, and in rare instances suggested superiority of group support. The dropout rate was high, but related data provide valuable insight into potential barriers to participation by patients in mind-body therapies.*

Source: Mularski R, et al. Randomized controlled trial of mindfulness-based therapy for dyspnea in chronic obstructive lung disease. *J Altern Complement Med* 2009;10:1083-1090.

THE AUTHORS OF THIS RANDOMIZED CONTROLLED TRIAL sought to test the efficacy of a mindfulness-based breathing therapy (MBBT) on improving dyspnea, other symptoms, and health-related quality of life in people with chronic obstructive pulmonary disease (COPD) as compared to participation in a support group. A total of 545 people recruited by clinician referral or posted advertisement from a single academic-affiliated veterans health care center were evaluated for eligibility, of which 86 were ultimately randomized (85 men; average age, 67 years; 50% Caucasian; 47% having completed at least some college; most of whom were ex-smokers). The study was billed as a "mind-body trial of shortness of breath in COPD." Those who did not participate either were excluded (n = 193) or refused (n = 266) based on a variety of factors (lack of interest, problems with transportation, other commitments). All participants had advanced and symptomatic COPD at enrollment.

The intervention group attended weekly group MBBT sessions for 8 weeks and were to practice MBBT daily on their own time. During the first 2 weeks they also received supplemental relaxation response training. The weekly sessions included practice in mindfulness meditation (body scan, seated and walking meditation, and mindful movement), the relaxation response, and group discussion. Sessions were scripted and protocolized. Tapes were provided for subjects to use in their home practice of both MBBT and the relaxation response, the times of which were to be recorded by participants in their personal diaries.

Instructors had specific training in mind-body therapies and a significant degree of clinical experience using them in practice. Additionally, all three instructors had completed an 8-week mindfulness-based stress reduction course together just prior to study initiation to "align intent and approach."

Support group participation was designed to parallel the personal attention and time commitment of those in the MBBT group, meeting weekly for 8 weeks for the same amount of time as the MBBT group. Subjects experienced group-facilitated discussions about various aspects of having COPD, had open time for group interaction, and submitted a matched collection of daily diary entries ("homework" was defined as time spent contemplating or discussing issues raised within the group that specifically dealt with COPD-related issues).

Medical records were reviewed to determine severity of COPD, and a combination of personal report and clinical database findings were monitored regarding exacerbations during the trial. Primary outcome measure of interest was the difference between pre- and post-trial 6-minute walking test (6MWT) Borg dyspnea assessment scores, essentially a self-rated score of dyspnea severity. Secondary outcome measures included 6MWT distance, symptoms scores, exacerbation rates, and a variety of measures of health-related quality of life. Stress levels were determined using the Perceived Stress Scale, mindfulness was assessed using the 5-Factor Mindfulness Questionnaire, and subject expectations were evaluated using adapted questions from the complementary and alternative medicine literature. A phone

interview was conducted at trial's end to better understand the subjects' unique experiences during the study period.

At baseline the groups were different in two respects: Support group members were on average about 7 years younger than MBBT group subjects, and had a significantly higher body mass index. Across both groups nearly all participants had little or no knowledge of mindfulness-based therapy, with about 60% believing it would be helpful, while 57% believed that support group therapy would be of benefit.

A significant number of people dropped out of the study (23 in the active group, 13 in group support), most before they had experienced even a single session.

Analyses, whether by intention-to-treat or on the subset of subjects who attended at least 75% of all sessions (n = 36), failed to reveal any benefit of MBBT over group support across all outcome measures. In fact, a few outcomes favored the support group over MBBT. Results of post-study telephone surveys suggested feasibility issues of interest that include difficulty with transportation and feeling too ill to participate. While less than 5% reported the sessions to be "weird or silly," 15% reported they did not believe the mind-body work they experienced during the trial was going to help them.

The researchers concluded that mindfulness meditation offers no measurable clinical benefit in patients with moderate-to-severe COPD over support group attendance.

■ COMMENTARY

While the study suffers from small sample size, lack of generalizability (only one female subject and the source of patients being a single VA medical center), not to mention the drastic dropout rate, it is nonetheless very

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

Upon completion of this educational activity, participants should be able to:

- describe evidence-based clinical analyses of commonly used integrative therapies;
- make informed, evidence-based recommendations about the usefulness and efficacy of integrative therapies to patients in their practice; and
- critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in integrative medicine as published in the scientific literature.

CME Questions

8. In their review of nasal saline irrigation, the authors recommend the practice for which of the following conditions?
a. Allergic rhinitis
b. Common colds
c. Chronic sinusitis
d. All of the above

9. Long-term use of nasal saline irrigation may result in increased frequency of acute sinusitis.
a. True
b. False

10. In clinical trials of nasal saline irrigation, adherence-to-treatment rates have been low due to irritation and burning caused by the saline solution.
a. True
b. False

11. Which of the following may result in a lack of published reports of thrombocytopenia associated with use of CAM therapies?
a. This type of adverse effect is rare.
b. This type of adverse effect is not reported.
c. Physicians and patients may not have discussed CAM use.
d. All of the above

12. Compared to venlafaxine, treatment of hot flashes with acupuncture resulted in:
a. greater improvement in hot flash frequency.
b. greater improvement in depressive symptoms.
c. sustained relief from hot flashes post-treatment.
d. All of the above

13. Conclusions about the use of magnet therapy for osteoarthritis are based on several large, well-designed clinical trials.
a. True
b. False

Answers: 8. d, 9. a, 10. b, 11. d, 12. c, 13. b.

well done. The results point not only to an apparent lack of clinical effectiveness of the MBBT intervention for those with markedly symptomatic COPD, but also underscore the realistic challenges of trying to offer mindfulness-based interventions to groups whose maladies (chronic pain comes to mind) the research shows mindfulness to be effective against. Even though participants were given $10 per session attended with the potential to collect $80 over the course of the study, compliance was poor. It is true that most of the dropouts did so without having experienced MBBT or a group support session, but the dropout rate among those who did was still relatively high at 19%.

Relaxation therapies have been touted as being potentially effective in select respiratory disorders, such as asthma and dyspnea, but the underlying problem in COPD, whether chronic bronchitis or emphysema, is damage to the pulmonary tissues, most often from smoking. One would think that relaxation strategies like mindfulness would help at least relieve anxiety related to a sense of dyspnea, since that sense is clearly impacted not only by the physical difficulty of breathing but also by mental distress. In that regard the findings of the trial are puzzling.

Might is be possible that mindfulness-based therapies are beneficial in those with mild COPD, or among women? Certainly. There being some suggestion that group support helps people with COPD at least on a psychosocial level, couldn't the relative equivalence of MBBT and group support in the current trial suggest some clinical merits of MBBT among those with moderate-to-severe COPD? Perhaps, but the current results showed minimal clinical improvement in either group, so any equivalence would have to be judged as equivalence of lack of efficacy. Further study is always of benefit, but to this reviewer's mind the current study's findings do not befit confidence in the potential benefits of MBBT in this setting ❖

Brief Note

Supersize My Bugs

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine,
Stanford University, Division of Infectious Diseases,
Santa Clara Valley Medical Center

Carol A. Kemper, MD, FACP, does research for GSK Pharmaceuticals, Abbott Laboratories, and Merck. This article originally appeared in the February issue of Infectious Disease Alert. *At that time it was reviewed by Connie Price, MD, Assistant Professor, University of Colorado School of Medicine; she reports no financial relationship to this field of study.*

Source: White AS, et al. Beverages obtained from soda fountain machines in the U.S. contain microorganisms, including coliform bacteria. *Int J Food Microbiol* 2010;137:61-66.

THIS ENGAGING EPIDEMIOLOGIC SURVEY ASSESSED microbial contamination of soda-fountain drinks, dispensed from nine different fountain machines, relative to current U.S. drinking water standards. Ninety drinks, including diet soda, regular soda, water, and ice were cultured. A follow-up survey examined the concentration of bacteria and other organisms found in an additional 27 drinks collected either in the morning or the afternoon. The beverages were self-dispensed or dispensed by a server.

Nearly half (48%) of the beverages contained coliforms, and one in 10 had more than 500 bacterial colony-forming units per mL. The most common pathogen identified was *Chryseobacterium meningosepticum*, found in 17% of the beverages, followed by *Escherichia coli* in 11%. Other microbes isolated included *Klebsiella*, *Staphylococcus*, *Serratia*, *Stenotrophomonas*, and *Candida* spp. Ice alone did not exceed current U.S. drinking water standards. No difference was observed in rates of bacterial contamination between self-dispensed drinks and those dispensed by a server, suggesting the machines are the source of the contamination. ❖