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Horse Chestnut Seed Extract for the Treatment of Chronic Venous Insufficiency

By Philippe O. Szapary, MD and Michael D. Cirigliano, MD

CHRONIC VENOUS INSUFFICIENCY (CVI) DESCRIBES PERSISTENT incompetence of the deep and perforating veins in the lower extremities. Clinically, edema, hemosiderin deposition, atrophic skin changes, and ulcerations accompany leg pain, tiredness, and itching. CVI prevalence ranges from 10-15% in men and 20-25% in women.[1] Traditional treatment includes external compression (support stockings) and for some, vascular surgery (venous stripping or sclerotherapy).

Extracts of horse-chestnut seeds (HCSE) have been extensively studied and used in German-speaking countries in the treatment of CVI. The Commission E has approved the use of HCSE for the treatment of CVI, especially when used as an adjunct to compressive therapy.[2] The American College of Phlebology does not have an official position on the use of HCSE. There are good data to suggest HCSE's efficacy.

History

The horse chestnut tree (*Aesculus hippocastanum*) belongs to the same family as the sweet chestnut and Ohio buckeye trees. Only the fruit of the sweet chestnut is edible while the fruits of the others are toxic.

Native to Greece and Albania, the horse chestnut tree was introduced in the United States in the 1740s as a shade tree. Growing up to 35 meters high, it bears long clusters of white flowers in May and a prickly fruit in the fall. Inside the fruit lie one to three large seeds; the extract of these seeds has been used in Europe since the 1800s as an oral remedy for various venous diseases. Published reports from France starting in 1896 discuss its use in varicose veins with insufficiency, hemorrhoids, and phlebitis.[3]

Pharmacology

The medicinal portion comes from the dried leaves and seeds.[4] Most commonly, the dried seeds are pulverized and mixed with

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water and alcohol to yield a solution that contains triterpene saponins, hydroxycoumarins, flavonoids, and tannins.[4,5] The most active ingredients are thought to be in the saponin mixture and are called escins (a- and b-escin). The escin fraction, measured as a percent and reported in milligrams, has been standardized by some pharmaceutical manufacturers. The primary hydroxycoumarin isolated from horse chestnut seeds is aesculin, which is responsible for the majority of toxic side effects from this plant.[6]

Mechanism of Action

In general, escins are thought to act as anti-exudative and anti-inflammatory agents, decreasing vascular permeability and thus preventing edema formation. In vitro studies have shown that escins increase venous tone of isolated animal saphenous veins.[5] Pure escins have been shown to decrease capillary hyperpermeability induced by histamine or serotonin, and decrease the formation of chemically induced inflammation in rats.[7] Escins exhibit a dose-responsive inhibition of the early exudative stage of inflammation.

Human studies have shown that HCSE inhibits three serum lysosomal enzymes.[8] These enzymes are important in the pathogenesis of CVI as they degrade proteoglycans in capillary walls allowing proteins to leak into the interstitium. By inhibiting these enzymes, HCSE may decrease capillary permeability and fragility. A "veno-tonic" effect lasted up to 14 days after HCSE was discontinued in one case series,[9] demonstrating a significant carryover effect.

Clinical Trials

To date, there are approximately 18 published randomized controlled clinical trials (RCTs) evaluating the safety and efficacy of HCSE in patients with CVI. These studies have all been performed and published in Germany or France between 1973 and 1996.

A recent criteria-based systematic review of 13 of the best RCTs suggests the benefit of oral HCSE over placebo both in objective and subjective measurements in patients with CVI.[1] HCSE was equally as effective as O-(b-hydroxyethyl) rutosides in three RCTs and to compression therapy in one trial. Most RCTs used a standardized HCSE preparation containing 50 mg of escins given twice a day. RCTs lasted between two and 12 weeks and used a wide variety of subjective (complaint scales) and objective (leg volume) endpoints. Two of these RCTs merit special consideration.

Rudofsky et al reported on the effects of 50 mg escin bid vs. placebo over 28 days in 40 subjects (67% women) with grade I or II CVI as defined by strict clinical and plethysmographic criteria.[10]

The results showed a statistically significant reduction in leg volume by 78 ml in the evening as measured by liquid plethysmography, while leg volume increased by 34 ml in placebo treated patients. While this study failed to show a significant effect on venous capacity, it did show a statistically significant change in both calf and foot circumference at 28 days ($P < 0.01$). Also, a Likert scale showed significant improvements in pain, pruritus, fatigability, and fullness in the HCSE treated group.

Diehm et al[11] conducted a 12-week single-blind trial comparing 50 mg escin bid vs. compression stockings vs. placebo in 240 patients with varying degrees of CVI. The primary endpoint was logarithmically transformed leg volume as measured by water displacement plethysmography. Subjects assigned to compressive therapy also received a seven-day course of a thiazide diuretic prior to being individually fitted with a class II compression stocking.

Compliance with HCSE was better (98%) than with compressive therapy (90%). While the compression group achieved a peak effect at four weeks, the HCSE group achieved a similar effect at 12 weeks. At the conclusion of the study, there was a non-significant trend favoring compression (47 ml decrease) over HCSE

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Table 1

Comparison of therapies for CVI available in the United States

Product	Description	Recommended Dose or Usage	Cost[#]
Venastat (Pharmaton)	300 mg HCSE, 16% TTG[*]	48 mg PO bid	$20/month
Horse-Chestnut (Nature's Life)	300 mg HCSE, 16-20% TTG[*]	56 mg PO bid	$10/month
Support hosiery	anti-embolism elastic stockings (TED)	18 mm Hg worn during waking hours	$15/pair[°] knee high
	fitted, compressive stockings (Jobst)	20-30 mm Hg or 30-40 mm Hg worn during waking hours	$60/pair[°] knee high
Surgical therapy	sclerotherapy	localized injections PRN	$300/session
	vein ligation and stripping	one-time surgery	$10,832

[*]TTG = triterpene glycosides

[#]For HCSE and stockings, cost is average retail cost. For sclerotherapy, cost depends largely on the number of treatments needed (average of three). Surgical cost includes physician and hospital charges at a university hospital.

[°]One pair of support hosiery provides reliable compression for up to three months.

(44 ml decrease), but both therapies were clearly superior to placebo (10 ml increase). Whether changes in leg volume were clinically significant is unknown, as there was no mention of symptom or function changes.

Most trials, including the latter two, were in part sponsored by Klinge Pharma, makers of Venostasin (a German brand of standardized HCSE). The lack of uniformity in the definition and grading of CVI, and the lack of standardization of endpoints diminish somewhat the scientific value of these studies.

The results of clinical trials on HCSE in CVI support each of the following statements *except*:

a. HCSE is superior to placebo in reducing leg symptoms.
b. HCSE is superior to O-(b-hydroxyethyl) rutosides in reducing leg symptoms.
c. HCSE was equally effective to compression stockings in reducing leg volume.
d. HCSE decreases ankle circumference compared to placebo.

Adverse Effects and Drug Interactions

While horse chestnut pollen is allergenic in sensitized individuals, oral HCSE appears to be well-tolerated.[12]

The most common side effects are pruritus, nausea, dyspepsia, headache, and dizziness.[1] Most studies show no difference when compared to placebo. A recent observational study found that adverse events occurred in 0.6% of 5,000 patients treated with HCSE in therapeutic doses.[13] There are no studies on the use of HCSE in pregnancy or lactation, and no reported drug-drug interactions.

However, there are two reports of toxic nephropathy and one report of hepatic injury in patients given large doses of escins.[4] When given in supratherapeutic doses to animals, escins have also been reported to cause fatal hemolysis.[4] It is possible that HCSE may interfere with warfarin, as HCSE possesses some coumarin constituents.

Formulation and Dosage

Oral HCSE preparations vary in their total milligram dosage, but usually report a % triterpene glycosides (calculated as escin) ranging from 16-21%. The recommended dose is 50 mg escins PO bid, with a maximum daily dose of 150 mg/d. Occasionally, HCSE is a component of a multiherbal preparation that often includes *Ruscus aculeatus* or butcher's broom, for which there are few good clinical data.

Three combination products that contain HCSE rank among the most commonly prescribed herbal remedies in Germany.[3] Until recently, standardized HCSE preparations were only available in Europe. In 1998, Pharmaton, a division of Boehringer Ingelheim Pharmaceuticals, released Venastat in the United States for the "promotion of leg vein health." This standardized HCSE represents one of the first examples of large pharmaceutical companies producing herbal preparations.

Topical HCSE solutions also exist but there are few clinical data to support their use.[14]

Conclusions

Standardized HCSE appears to be an effective treatment for the edema and symptoms associated with CVI. While there is mounting clinical evidence to suggest that HCSE is better than placebo, there is only one trial comparing HCSE to the current gold standard treatment of compressive therapy.

When used at the recommended dose, HCSE appears to be both safe and effective and compares favorably to

other currently available therapies for CVI in the United States. (*See Table 1.*)

Recommendation

Standardized HCSE should be considered in the treatment of non-pregnant, non-lactating patients with CVI. HCSE can be used alone, and probably in combination with compressive therapy. While compression stockings are still considered first-line therapy, HCSE can be used as monotherapy in patients who cannot tolerate or comply with compressive therapy. Because of the lack of data, HCSE should not be used in patients with acute or chronic DVT, in patients on coumadin, or in patients with renal or hepatic insufficiency. Longer clinical trials in patients with similar grade CVI, using validated symptom measures and standardized leg volume measurements are still needed prior to HCSE becoming part of standard medical formularies. ❖

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Which of the following statement(s) on HCSE is/are true:

a. HCSE can cause allergic rhinitis.
b. HCSE was better tolerated than compression therapy in one study.
c. HCSE can cause nausea and dyspepsia.
d. b and c
e. a, b and c

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Garlic for the Treatment of Topical Infections: Does It Help?

By Vance Dietz, MD, MPH, TM

"Five things have been said about garlic: it assuages hunger, warms the body, brings joy, increases virility, and destroys intestinal lice. There are those who say it engenders love and dispels envy."

Babylonian Talmud: Baba Kama

SKIN INFECTIONS! WHETHER FUNGAL OR BACTERIAL IN origin, they are some of the most common medical problems that a person has to deal with.

Garlic! Whether slivered or minced, or used as whole cloves or crushed, it is probably one of the most common aromatics used in cooking. Garlic not only gives flavor to food, but according to some is good for other uses as well. For example, when worn around the neck

during a full moon, it has been reported to keep vampires at bay. Others suggest that garlic is better for treating infections than dealing with vampires.

Garlic in Medicine

Allium sativum, also known as poor man's treacle or clove garlic, is said to have originated in Central Asia. Eventually introduced into the Mediterranean area, it is now cultivated worldwide.

The medicinal parts of garlic are the whole fresh clove, the dried clove, and the oil prepared from the clove. The ancient Egyptians, Greeks, Romans, Babylonians, and Chinese all knew of garlic's healing ability.[1] In Egypt, the *Codex Ebers Papyrus* (1550 B.C.) mentions the healing power of garlic. Pliny the Elder wrote about the medicinal uses of garlic. In 3000 B.C., Herodotus mentioned the medicinal use of garlic.[2]

Hippocrates is said to have used garlic in the fifth century B.C. to treat infections, including leprosy. In 1722, citizens of Marseilles were reported to be protected from the plague if they used an internal preparation of garlic vinegar. In 1858, Louis Pasteur reported favorably on the antibacterial activity of garlic. Currently, garlic is said to aid in the lowering of serum lipids and to prevent age-dependent vascular changes.[3]

Folklore

Garlic was used in Europe for bronchitis, colds, and hay fever.[1] In parts of Mexico, garlic is used to treat snake bites and, when taken internally, for the treatment of pertussis. In American folklore, garlic was put into old socks and worn around the neck to cure colds and to ward off evil spirits. When taken internally, it has also been used for atherosclerosis, high blood pressure, bloating, menstrual pains, and as a tonic. External uses include the treatment of corns, warts, calluses, otitis externa, muscle pain, neuralgia, arthritis, and sciatica.[4]

Mechanism of Action

The exact mechanism of action is unclear. Garlic contains alliins, ajoene, fructosans, and saponins.[4] An alliin, diallyl thiosulfinate, is thought to be responsible for garlic's antibacterial and antifungal properties.[5] In China, another alliin, diallyl trisulfide, is used for the treatment of bacterial and fungal infections. Garlic intake in humans has been reported to enhance natural killer cell activity and immune activity.[6,7]

Sorrentino reports, "When raw garlic is cut or crushed, the enzyme allinase interacts with the cysteine compound alliin to produce allicin. Allicin gives garlic its typical aroma and taste.... Allicin is also thought to be one of the most important medicinal substances in garlic, although little or no allicin is present in the intact garlic clove. The garlic plant produces allicin as a natural defense against bacteria and other organisms. Allicin is highly irritating and has been shown to be bactericidal in in vitro studies." (See *Alternative Medicine Alert*, September 1998, pp. 97-99.)

Laboratory Studies

A review of the literature revealed numerous laboratory studies demonstrating antifungal activity[8-14] as well as antibacterial activity.[1] Several reports on the effectiveness of garlic in humans were also found.[15-17]

For example, researchers in Japan studied the antifungal properties of garlic by taking a garlic extract obtained from crushed cloves and applying it to agar mediums inoculated with different fungi of clinical importance.[8] The extract, containing allicin, was highly effective against *Candida*, *Cryptococcus*, *Trichophyton*, *Epidermophyton*, *Microsporum*, and less so against *Aspergillus*. Allicin was found to inhibit both germination of spores and growth of hyphae.

The effect of garlic on *Cryptococcus* also has been reported.[9] In China, when given intravenously, garlic extracts reportedly have been used with success in the treatment of cryptococcal meningitis.[10] Researchers in New Mexico obtained and studied this Chinese extract, i.e., diallyl trisulfide or allitridium, and found it to contain properties for in vitro killing against *C. neoformans* and to work synergistically with amphotericin B.

Other researchers have taken fungal isolates from clinical cases and have tested garlic extracts' antifungal ability. For example, of 88 isolates of dermatophytes from cases of tinea capitis, tinea corporis, and tinea cruris, 76 were sensitive to a garlic extract at a dilution of 1:150 and all at 1:100.[11] In comparison, when the isolates were tested with ketoconazole, 71 were sensitive at a concentration of 1 mcg/mL and all at 5 mcg/mL. Similarly, 22 cultures of *C. albicans* isolated from active vaginal yeast infections were tested for sensitivity to garlic extract.[12] The garlic extract was found consistently to inhibit the growth of *C. albicans*.

The effect of garlic extracts on otomycosis has also been studied.[13] Otomycosis is a common condition seen in pediatric practice. Researchers at the University of New Mexico compared the antifungal properties of aqueous garlic extract (AGE) and concentrated garlic oil (CGO) with three commercial preparations commonly used in practice, i.e., cresylate otic solution, Lotrimin, and ketoconazole cream. Using agar disks inoculated with the fungi, the authors demonstrated a dose response of both garlic extracts against the three dermatophytes studied, i.e., *Aspergillus fumigatus*, *A. niger*, and *A. ter-*

reus. When compared to the commercial products, CGO was found to have greater inhibitory activity than the three antifungal agents. AGE had less activity than Lotrimin but greater activity than cresylate and equal activity to ketoconazole cream. In the treatment of keratomycosis, however, other researchers failed to demonstrate an effect of garlic extract.[14]

Thus, garlic extracts have been demonstrated to be effective against a wide variety of fungi, including fungi isolated from clinical cases, and have been shown to be as effective in vitro as conventional therapeutic agents for otomycosis. In addition to lab studies on fungi, a Boston study demonstrated a broad spectrum of activity of garlic extracts against gram-positive and gram-negative organisms.[1] The authors also used an extract that was 40% concentrated.

Clinical Studies

Unfortunately, there have not been any well-controlled trials in humans. There are, however, several case reports and one case series in which the therapeutic effect of garlic has been studied. One case report involved a culture confirmed lesion of *Microsporum canis* on the arms of a young women.[15] Freshly cut garlic was applied to the lesions on one arm and tolnaftate to the lesions on the other arm. The arm treated with garlic took 10 days to heal; the other took four weeks. Another case report cites the successful treatment of culture-confirmed sporotrichosis.[16] The patient was monitored for six months and had no recurrence.

Clinicians in Venezuela reported on the efficacy of a garlic extract, such as ajoene, in the treatment of culture-confirmed tinea pedis in 34 soldiers living in conditions that favored dermatophytosis, i.e., humid conditions and occlusive foot wear.[17] On the seventh day of treatment, 27 of the 34 had no clinical signs, and cultures taken immediately and one week later were negative. The remaining seven soldiers were treated for an additional seven days with success. All 34 soldiers were culture negative at 90 days.

A young mother brings her two-year-old son to your office for otitis externa. You determine that the likely cause is fungal. What do you recommend?

a. Lotrimin and ketoconazole creams are common useful ointments. Herbal preparations are, in general, not advisable.
b. Lotrimin and ketoconazole creams as well as garlic extract and garlic oil have been shown to be effective against the fungi responsible for otitis externa.
c. None of the above.

Adverse Effects

Raw garlic may be caustic to the skin. Several cases of dermatitis following the topical application of sliced garlic cloves have been reported.[2,18] Raw garlic can also cause stomach upset, reflux and GI upset. If this should occur it would indicate the need to stop treatment and re-evaluate.

Drug Interactions

Garlic taken internally may potentiate the effects of anticoagulants, antihypertensives, and antidiabetic agents.[19] Garlic may have antithrombotic activity so it is not recommended for patients taking anticoagulants.[20]

Formulation

Many companies promote preparations containing garlic. Some come as oil, some as capsules, some as dried powders, some as extracts. Internal and external preparations are used for topical infections; topical is preferred.

Dosage

Topically, sliced cloves or commercial garlic oil is applied two to three times a day. Lesions may need to be treated for one to two weeks. The usual dose for internal administration of allicin extracts is 2-5 mg per day.

Conclusion

Medicinal preparations of garlic have existed for thousands of years. Garlic has a strong history as a remedy for skin infections, particularly for fungus. Numerous laboratory-based studies have demonstrated a significant fungicidal effect of garlic extracts. Importantly, this effect has been demonstrated on multiple isolates obtained from clinical cases. Data from human studies are limited but suggest a positive antifungal effect.

Recommendation

When questioned by their patients about garlic, clinicians could advise that laboratory studies suggest both fungicidal and bactericidal effects. Although clinical studies are limited in number and in scope, they do suggest potential benefit in the treatment of fungal infections. Clinicians should advise their patients that if used as an external remedy, the patient should observe for the development of contact dermatitis which, on rare occasion, has been reported. ❖

There is good evidence that garlic extract has antifungal properties when applied on the skin. True or false?

a. True
b. False

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Pyruvate for the Treatment of Obesity

By Dónal P. O'Mathúna, PhD

HAVE YOU NOTICED THAT YOUR PATIENTS' WEIGHTS keep climbing? More than half of those 20 and older are overweight, now defined as a body mass index (BMI) of 25-29.9 kg/m^2.[1] Roughly one quarter of U.S. adults are obese (BMI > 30), as are many children and adolescents.[2] Your overweight patients have substantially increased risks of coronary disease, hypertension, type II diabetes, osteoarthritis, cholecystitis, stroke, and sleep apnea. In the words of the World Health Organization, the escalating epidemic is "one of the greatest neglected public health problems of our time."[2]

Obesity is a complex problem, involving social, behavioral, emotional, cultural, physiological, metabolic, and genetic factors.[1] Drug therapy offers some promise, but was set back by the greater-than-previously-reported serious complication rate of fenfluramine, often used in combination with phentermine as "Phen/Fen." Memories of fenfluramine and dexfenfluramine's market withdrawal, and all those worrisome cardiac ultrasounds in otherwise healthy young women now makes prescription of sibutramine and orlistat just that much less appealing.

Claims

Among alternative approaches, pyruvate is the hottest supplement around. Internet sites proclaim it as the newest and best "fat burner." It is said to boost overall weight loss by 37% and enhance fat loss by 48%.[3] Promoters say it lowers cholesterol levels, improves cardiovascular health, and increases athletic endurance. They also claim the support of 25 years of extensive scientific research published in peer-reviewed journals.

So should physicians recommend that overweight patients add pyruvate to their dieting regimens? Not if they look closely at the reported studies.

Pharmacology

Pyruvate (or pyruvic acid) is a metabolite of glucose you encountered in biochemistry as a product of glycolysis. Pyruvate forms an important junction in carbohy-

drate catabolism, being reduced to lactic acid under anaerobic conditions. Aerobic conditions bring it into the citric acid cycle, allowing its complete oxidation to CO_2 and H_2O.

Dietary interest in pyruvate began in the late 1970s when animal studies revealed that large quantities of different natural metabolites altered lipid and carbohydrate metabolism.[4] Rats raised on ethanol failed to develop fatty liver steatosis when fed pyruvate and/or dihydroxyacetone (DHA). DHA is closely related to another glucose metabolite, DHA-phosphate, and was one of a number of metabolites tested in these studies. Subsequent studies showed that adding pyruvate and DHA to animal diets produced the largest reductions in weight gain and body fat, while increasing heat production and energy expenditure.[4]

Mechanism of Action

Pyruvate's mechanism of action in weight loss is unknown. One proposal is based on the reversible conversion of pyruvate to phosphoenolpyruvate, another glucose metabolite. This may be a "futile cycle" where the reaction runs forward and backward, continuously expending energy.[5] This theory is supported by the greater heat production and energy expenditure found in animal studies.

Pyruvate also appears to improve glucose uptake by skeletal muscle. Rats fed pyruvate have lower plasma insulin levels, without increased plasma glucose concentrations. Human studies showed that pyruvate and DHA increased glucose extraction by muscles, but plasma insulin levels remained unchanged.[6,7]

Clinical Studies

Claims that pyruvate suppresses appetite are based on one animal study.[4] The authors state that pyruvate's taste could also account for their observations. A Medline search (using "pyruvate," "weight loss," and "human") revealed four clinical studies, all coordinated by the same researcher, Ronald T. Stanko, MD, at the University of Pittsburgh Medical Center. Three 1998 reviews revealed no additional studies.[8,9,10]

The first weight-loss study reported by Stanko et al was conducted on 13 obese women (average BMI 38.9 kg/m^2; average age 48 years).[11] Subjects were confined to bed in a metabolic ward, observed continuously, and allowed no exercise. Participants were randomly divided between two groups, although the number in each group was not reported. All were placed on a severely restricted liquid diet (500 kcal/d) for 21 days, with one group receiving a placebo while the other received pyruvate (26 g) plus DHA (12 g) daily. Those taking pyruvate-DHA showed greater overall weight loss (6.5 kg vs. 5.6 kg; $P < 0.05$) and greater fat loss (4.3 kg vs. 3.5 kg; $P < 0.05$).

Stanko's second study was done with 14 obese women (average BMI 39.9 kg/m^2; ages not reported) confined under similar circumstances but given 1,000 kcal/d for 21 days.[12] Exactly half the subjects received 30 g pyruvate and showed greater overall weight loss (5.9 kg vs. 4.3 kg; $P < 0.05$) and greater fat loss (4.0 kg vs. 2.7 kg; $P < 0.05$), than those who simply endured the diet. Bioelectrical impedance, as in all Stanko's studies, was used to measure body composition. This study's conclusion is frequently quoted: "Patients in the pyruvate group increased weight loss by 37% and fat loss by 48%."[12]

The third Stanko study investigated pyruvate's ability to reduce cholesterol levels. An earlier Stanko study had shown a 4% reduction in plasma cholesterol while hyperlipidemic patients were maintained at the same weight on a high-cholesterol, high-fat anabolic diet while taking 36-53 g pyruvate.[13] In the study of interest here, 34 hyperlipidemic patients (average BMI 28.3 kg/m^2; average age 57 years) consumed a low-cholesterol, low-fat diet for six weeks.[14] Half the subjects, randomly assigned, received 22-44 g pyruvate daily. Com-

Table 1

Summary of weight change differences between pyruvate and control groups

Study	n	Subject Average Weight	Diet (Cal/d)	No. Days	Dose of Daily Supplements	Differences in Weight Changes*	Differences in Body Fat Changes*
Ref 11	13	220 lb	500	21	Pyruvate (26 g) + DHA (12 g)	2.0 ± 1.1 lb#	1.8 ± 0.7 lb#
Ref 12	14	237 lb	1000	21	Pyruvate (30 g)	3.5 ± 2.2 lb	2.9 ± 1.5 lb
Ref 14	34	232 lb	Weight-based	42	Pyruvate (22-44 g)	1.3 ± 0.9 lb	0.9 ± 0.7 lb
Ref 15	17	230 lb	2500-2700	21	Pyruvate (15 g) + DHA (75 g)	2.4 ± 0.9 lb	2.2 ± 0.9 lb

*(Average weight loss of test subjects) – (Average weight loss of control subjects) and converted to pounds using 1 kg = 2.20 lb.

#(Average weight gain of control subjects) – (Average weight gain of test subjects) and converted to pounds using 1 kg = 2.20 lb.

Table 2

Sample pyruvate prices

Brand	Formulation	Recommended Dose	Price/Count
Pinnacle	1000 mg pyruvate per tablet (calcium and sodium salts of pyruvic acid)	2-6 tablets daily	$39.99/60 tablets
Kal	5 g creatine pyruvate per scoop	1 scoop 1-3 times daily	$39.98/500 g powder
Twinlab	750 mg calcium pyruvate monohydrate per capsule	3 capsules daily	$36.95/60 capsules
Natrol	1000 mg calcium pyruvate per capsule	3 capsules daily	$26.99/60 capsules
MET-Rx	500 mg calcium pyruvate per capsule	4-10 capsules daily	$24.95/60 capsules
Natural Balance	500 mg calcium pyruvate per capsule	6-8 capsules daily	$19.99/90 capsules
Advanced Research	500 mg calcium pyruvate/100 mcg chromium per capsule	4 caplets daily	$19.99/60 caplets

Source: Online mail-order firms

pared to controls who consumed the same diet but no pyruvate, no differences in cholesterol levels were found, in contrast to the results in Ref. 13. However, those taking pyruvate had greater overall weight loss (0.7 kg vs. 0.1 kg; $P < 0.05$) and greater fat loss (0.5 kg vs. 0.1 kg; $P < 0.05$).

Stanko's fourth weight-related study examined whether pyruvate would slow weight gain when a normal diet was resumed after a severely restricted liquid diet.[15] Seventeen obese women (average weight 232 lb, average height 63 in; BMI 41.3 kg/m^2; average age 43 years) were confined as in Stanko's first two studies. After 310 kcal/d for 21 days, they were randomized to two groups and everyone received a weight-gaining diet (2,500-2,700 kcal/d) for 21 days. Nine subjects receiving pyruvate (15 g) plus DHA (75 g) gained significantly less weight overall than the eight who received the placebo (1.8 kg vs. 2.9 kg; $P < 0.05$) and gained less fat (0.8 kg vs. 1.8 kg; $P < 0.05$). The authors concluded that pyruvate and DHA "will inhibit weight gain by 36% and body fat deposition by 55% during hyperenergetic feeding in obese humans."[15]

In all these studies, very little additional weight was lost by those taking pyruvate. (*See Table 1.*) But the small benefits are exaggerated in reports by statistical manipulation. For example, the widely cited 37% greater weight loss while taking pyruvate was derived from a 3.5 lb difference between the pyruvate and control groups.[12] It only seems large when expressed as a percentage. While the results appear statistically significant, their clinical significance is questionable. The reliability of available techniques for measuring such small changes in body composition is also in question, as Stanko acknowledges.[15] Further, placing research subjects on a 500 kcal/d diet is highly problematic, not to mention making meaningful comparison with everyday clinical situations difficult.

Formulation and Dosage

Supplement manufacturers package pyruvate as the bulk powder or as 500 mg capsules, sometimes adding 10 mg DHA. Being anionic, pyruvate is compounded with a variety of cations, usually sodium or calcium. Newer "enhanced" pyruvate products include other supplements like creatine, carnitine, or chromium.

Providers recommend taking 1-5 g pyruvate daily, usually broken into 2-3 doses. Pyruvate can be added to flavored drinks, either by breaking the capsules or using bulk powder. However, these recommended doses remain much lower than the 15-44 g used in animal and clinical trials. The ratio of pyruvate to DHA in commercial products is completely different than in the reported research. Also, the studies used liquid formulations, which could impact absorption, although no bioavailability reports were found. (*See Table 2 for price comparison.*)

Adverse Effects

All four clinical studies reported pyruvate producing "some" diarrhea, intestinal rumblings, and flatus. Two studies were more specific. Almost half the subjects taking pyruvate (26 g) plus DHA (12 g) had diarrhea and borborygmi,[11] while 35% of those taking 22-44 g pyruvate had diarrhea.[14] No other adverse effects were reported.

Conclusion

Preliminary studies show that pyruvate provides, at most, a very small benefit to a select group of obese women attempting to lose weight in highly controlled environments. These studies need to be replicated and others performed by different researchers with larger numbers of subjects. No studies have been reported on the commonly recommended doses or on pyruvate's long-term effectiveness or safety.

Recommendation

Until long-term effectiveness and safety studies are reported, pyruvate should not be recommended as a weight-loss supplement. Pyruvate supplementation as obesity treatment may delay patients from dealing with the complex, difficult problems underlying weight gain.

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Pyruvate's effectiveness as a weight-reducing aid has been tested:

a. with moderately overweight people consuming normal weight-loss diets.
b. with obese women on restricted diets in controlled circumstances.
c. with obese men and women observed for a number of months.
d. with obese women consuming their usual diets in home environments.

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Note to Readers

Thank you for responding to the reader survey. We appreciate your feedback and will begin incorporating some of your suggestions in future issues. The editors invite you to submit questions about articles in *Alternative Medicine Alert*. We will publish the questions and answers in future issues.

Please send questions to Reader Questions, *Alternative Medicine Alert*, c/o American Health Consultants, P.O. Box 740056, Atlanta, GA 30374. Or you may send your questions via e-mail to leslie.coplin@medec.com. We look forward to hearing from you.

Editor's Note

By January 21, when the U.S. FDA finally asked manufacturers to withdraw gamma butyrolactone (aka RenewTrient), reports of unconsciousness in 19 people had been filed. Seizures and bradycardia had also been reported, as had one death. Our Clinical Comments last November (1:131), after a *New England Journal of Medicine* letter the previous month, read in part "Gamma-butyrolactone is a dangerous 'dietary supplement' that appears to induce coma. It is billed as a bodybuilding aid. Discourage its use."

Acupunture for HIV-Related

With Comments from John La Puma, MD, FACP

Peripheral Neuropathy

Source: Shlay JC, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: A randomized controlled trial. *JAMA* 1998;280:1590-1595.

PERIPHERAL NEUROPATHY IS COMMON in persons infected with HIV but few data on symptomatic treatment are available. We conducted a randomized, placebo-controlled multicenter clinical trial to evaluate the efficacy of a standardized acupuncture regimen (SAR) and amitriptyline hydrochloride for the relief of pain due to HIV-related peripheral neuropathy. The interventions were SAR vs. control (sham acupuncture) points; amitriptyline 75 mg nightly vs. placebo, or both for 14 weeks. Of 250 patients enrolled, 125 were in a modified double-blind 2 x 2 factorial design of SAR, amitriptyline, or the combination compared with placebo; 114 were in SAR vs. control; and 11 were in amitriptyline vs. placebo.

Patients in all groups showed reduction in mean pain scores at six and 14 weeks compared with baseline values. For both the acupuncture/amitriptyline comparisons, changes in pain scores were not significantly different between the two groups. At six weeks, the estimated difference in pain reduction for patients in the SAR group compared with those in the control points group was 0.01 (P = 0.88, 95% CI -0.11 to 0.12) and for patients in the amitriptyline group vs. those in the placebo group was 0.07 (P = 0.38, CI -0.22 to 0.08). At 14 weeks the difference for those in the SAR group compared with those in the control points group was -0.08 (P = 0.26, CI -0.21 to 0.06) and for amitriptyline compared with placebo was 0 (P = 0.99, CI -0.8 to 0.19).

In this study, neither acupuncture nor amitriptyline was more effective than placebo in relieving pain caused by HIV-related peripheral neuropathy.

COMMENT

Supported in part by the National Institute of Allergy and Infectious Diseases, this well-designed multicenter national trial found a modest decline in pain scores in all groups. The investigators attributed their results to a placebo effect or time of entry in the trial.

The acupuncture treatments were administered twice weekly for six weeks, and once weekly for eight weeks thereafter. Exclusion criteria included taking a tricyclic or a MAOI two weeks before randomization. There were no statistically significant differences in adverse effects or discontinuations.

Consensus on the SAR was reached by nine acupuncturists before protocol implementation, but some believe that acupuncture of even "nonclassical points" may have analgesic effects. Studying standardized points allows a conclusion to be drawn about acupuncture as a whole, say the authors, but not individualized treatments. The control (sham) points chosen were three in a line on the back of the calf. The usefulness of sham acupuncture has been debated, even as a blinded research technique.

A statistically significant number of patients who reported moderate or more relief at 14 weeks tended to guess they were receiving SAR and not the control (sham) acupuncture. In contrast, regardless of their level of pain relief, those who took amitriptyline also correctly guessed the study treatment.

Latin for "I shall please," a placebo can be a powerful medicine. Here, two systems of pain control, representing two powerful belief systems, demonstrated no more effect than placebo. Whether placebos can improve symptoms by reducing stress, creating specific biochemical reactions, or playing on the brain's conditioning and expectancy no one knows. But the idea that the mind and body are separate is probably false—some of the time, for some people, and some diseases.

Recommendation

This difficult-to-treat disease awaits effective medical therapy. Much lower dose amitriptyline (10 mg nightly) and off-label use of gabapentin for treatment of peripheral neuropathy are common in primary care. ❖

Spinal Surgical Alternative: Exercise?

Source: Nelson BW, et al. Can spinal surgery be prevented by aggressive strengthening exercises? A prospective study of cervical and lumbar patients. *Arch Phys Med Rehabil* 1999;80:20-25.

TO DETERMINE IF PATIENTS RECOMmended for spinal surgery can avoid it through an aggressive strengthening program, a privately owned medical clinic treated consecutive referred patients. Study entry criteria included a physician's recommendation for lumbar or cervical surgery, no medical condition preventing exercise, and willingness to participate in an outpatient 10-week program.

Intensive, progressive resistance exercise of the isolated lumbar or cervical spine was practiced and continued to failure, and patients were encouraged to work through their pain. Forty-six of 60 participants completed the program; 38 were available for follow-up (average 16 months, range 12-30 months after discharge); three required surgery after completing the program.

COMMENT

Back pain hurts. It is the leading cause of disability in the United States, and a pile of frustration among practitioners and patients alike. It is also expensive—early 1990s data from the Worker's Compensation Back Pain Claim Study show that "the average cost per industrial back injury in the U.S. is now more than $24,000." Here, the authors present surgical cost data of $60,000 for a cervical laminectomy and

more than $168,000 for a lumbar fusion.

Of 651 patients referred for rehab, 62 with chronic pain (mean 28 months) met the inclusion criteria. Sixty began the outpatient program; 14 dropped out. Twenty-eight men and 18 women, mean age 42, completed the 10 weeks in an average of 21 visits, most to physical therapists. Nearly all patients—90%—had already tried and failed some type of exercise program.

The program emphasized progressive resistance, and used lumbar and cervical extension devices to isolate and strengthen lumbar extensors, cervical extensors and rotators, and thoracic rotators. A self-monitored maintenance program was also taught to maintain strength, vigor, self-care, and newly improved body mechanics.

Statistically significant gains in strength for lumbar and cervical extensor and rotator muscles in men and women were reported, and only three patients underwent surgery.

These Minneapolis area authors acknowledge their methodologic limitations—unblinded, no control group, no randomization, selection bias, variable follow-up, only regrets offered for the nearly one-quarter drop-out. Yet they observe that even patients recommended for spinal surgery can tolerate intensive, specific exercise. By specific they mean isolated musculature; by intensive they mean muscular exercise against dynamic resistance to volitional failure, through a full range of motion.

These bold investigators take a hands-on approach to patients famed for fragility, who "develop a keen sense of fear when it comes to spinal motion ... few understood that literally millions of people develop the same radiologic diagnoses with few or no symptoms." Provided there is no physical deterioration, emphasizing activity tolerance as a means to symptom relief is sensible, empowering, and precise.

Recommendation

Committed motivated patients who wish to avoid back or neck surgery may be able to do just that. This innovative program deserves better evaluation. ❖

Calcium for PMS

Source: Thys-Jacobs S, et al. Calcium carbonate and the pre-menstrual syndrome: Effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1988;179:444-452.

PREVIOUS REPORTS HAVE SUGGESTED that disturbances in calcium regulation may underlie the pathophysiologic characteristics of premenstrual syndrome (PMS) and that calcium supplementation may be an effective therapeutic approach. To evaluate the effect of calcium carbonate on the luteal and menstrual phases of the menstrual cycle in PMS, a prospective, double-blind, placebo-controlled, parallel group, mulitcenter randomized national clinical trial was conducted.

The study screened 720 healthy premenopausal women (ages 18-45) for moderate to severe, cyclically recurring premenstrual symptoms, prospectively documented over two menstrual cycles. Women were randomly assigned to either calcium supplements (1200 mg) or placebo for three menstrual cycles. Daily documentation of symptoms, adverse effects, and compliance with medications were monitored, with a resulting 17 parameter score.

Data were reported for 466 of the 497 women enrolled. The calcium treated group had a significantly lower premenstrual (luteal phase) symptom score for the second ($P = 0.007$) and third ($P < 0.001$) treatment cycles. By the third treatment cycle, the calcium group was associated with a 48% reduction in total symptom scores from baseline, compared with a 30% reduction in the placebo group.

COMMENT

This New York St. Luke's-Roosevelt Hospital Center study found that irritability, depression, food craving, aches and pains, and water retention all improved with calcium carbonate supplementation. With the exception of aches and pains, however, the placebo group improved nearly as much in each category. The salutary effects were not apparent until the second month.

Why should calcium work in PMS? Evidence of secondary hyperparathyroidism in women with PMS has been demonstrated by the same principal investigator, who postulates serotonergic dysregulation in PMS.

Partially funded by SmithKline Beecham, makers of TUMS®, questions of blinding (TUMS®' texture and flavor are difficult to emulate) and adequacy of pain relief (analgesics were allowed but not tracked) mar this study's methods. The strong placebo effect is comparable to that observed in trials of fluoxitene for premenstrual dysphoria and alprazolam for PMS.

Calcium carbonate is the least expensive form of supplemental calcium, and if not compounded from oyster shells, is unlikely to contain lead, as do some "natural" calcium supplements. Calcium supplements should be taken with food. Some of the best food sources of calcium include a cup of plain nonfat yogurt (450 mg), 3 ounces of sardines with bones (370 mg), a cup of calcium fortified orange juice (300-350 mg), and a cup of cooked turnip greens (200 mg).

Recommendation

A three-month therapeutic trial of 1200 mg of calcium daily for women with moderate or severe symptoms of premenstrual syndrome should be investigated more carefully. It also will, with weight-bearing exercise, reduce the chance of osteoporosis, especially in Caucasian women. Whether calcium acts as a placebo or changes biochemistry, it is an inexpensive and safe approach. ❖

In Future Issues:

Vitamin B_6 for Carpal Tunnel Syndrome
Peppermint Oil for Irritable Bowel Syndrome
Feverfew for Migraine