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INSIDE

Efficacy of Acupuncture for Treating Knee Osteoarthritis

By Yoon-Hang Kim, MD, MPH, DABMA

OSTEOARTHRITIS IS THE MOST COMMON JOINT DISORDER IN THE world. Radiographic evidence of knee osteoarthritis (OA) is found in the majority of people by age 65 and in about 80% of those age 75 and older.[1] Approximately 11% of persons age 64 and older have symptomatic OA of the knee.[2] In addition to decreased mobility due to pain and emotional suffering, patients with knee OA are at an increased risk for falls.[3] With the continued growth of the elderly population in the United States, OA is becoming a major medical and financial concern.

Conventional medical approaches to treating knee OA range from conservative management with nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy modalities to invasive interventions such as steroid injection, arthroscopic procedures, and knee replacement surgery. The safety of NSAIDs has been questioned on many levels. Acute renal failure secondary to NSAID use is well documented. Stiefelhagen reported a case of a patient with acute renal failure caused by NSAIDs and concluded that successful treatment of knee pain had been achieved, but the patient had died.[4]

Bjordal et al conducted a meta-analysis on the efficacy of NSAID medications for osteoarthritic knee pain and concluded that NSAIDs can reduce short-term pain in OA of the knee slightly better than placebo, but long-term use of NSAIDs for this condition should be avoided.[5] As serious adverse effects are associated with oral NSAIDs, only limited short-term use can be recommended.

In 2001, Hochberg called for the re-evaluation of NSAIDs as the first-line OA agent, urging clinicians instead to consider glucosamine sulphate, and expressed hope for the role of COX-2 inhibitors.[6] However, in 2004, the FDA issued a Public Health Advisory recommending limited use of COX-2 inhibitors in light of the possible associated increased cardiovascular risk.[7]

Acupuncture is one of the most popular forms of complementary and alternative medicine and is rapidly gaining acceptance in the United States. In 1997, the National Institutes of Health (NIH)

Consensus Panel concluded that acupuncture is effective for adult postoperative and chemotherapy-related nausea and vomiting and probably for the nausea of pregnancy.[8] Furthermore, the panel concluded that there are reasonable studies showing relief with acupuncture on such diverse pain conditions as menstrual cramps, tennis elbow, and fibromyalgia. Since then, a number of well-designed, high-quality randomized, controlled trials clarified the efficacy of acupuncture for treating many entities including cocaine dependence, back pain, and osteoarthritic knee pain.

Mechanism of Action

Since the late 1970s, acupuncture analgesia has been demonstrated to activate the endogenous opioid peptide system and influence the body's pain regulatory mechanism by changing the processing and perception of noxious information at various levels of the central nervous system.[7]

It is widely believed that acupuncture analgesia is initiated by stimulation of small diameter nerves in muscles, which send impulses to the spinal cord, midbrain, and pituitary gland, resulting in the release of neurotransmitters such as monoamines and endorphins, which in turn block pain signal transduction.[9]

Two model systems of acupuncture analgesia have been proposed:

Endorphin-dependent system: The discovery of naloxone, an endorphin antagonist, helped elucidate the role of endorphins in acupuncture. Naloxone was shown to block acupuncture analgesia in human volunteers in a randomized, double-blind study.[10] A subsequent study produced the same results, fashioned a dose-response curve for naloxone, and found that increasing doses created increasing blockade.[11] The endorphin-dependent system can be activated through low-frequency, high-intensity electrical stimulation of acupuncture needles. The pain relief is characterized by a slow onset throughout the body and cumulative effect upon subsequent stimulation.[9]

Monoamine-dependent system: In addition to endorphins, monoamines such as serotonin and norepinephrine have been shown to be involved in acupuncture analgesia. Microinjections of serotonin antagonists and norepinephrine antagonists have blocked the effect of acupuncture analgesia.[12,13] The monoamine-dependent system can be activated through high-frequency, low-intensity electrical stimulation of acupuncture needles. Pain relief is rapid in onset and segmental, and offers no cumulative effect upon subsequent stimulation.[9]

Systematic Review

Ezzo et al published a systematic review of seven randomized controlled trials (RCTs) and concluded that strong evidence exists that acupuncture is more effective than sham acupuncture for pain relief but not for functional improvement.[14] Three studies with sham acupuncture as a control were reviewed; two studies found more significant improvements in pain with acupuncture compared to sham, while the third did not. Ezzo et al noted that in the two studies that showed benefit, the sham acupuncture consisted of needles placed at distal non-acupuncture points, which they refer to as "minimal sham." In the third study, which did not show a benefit for sham acupuncture, the sham acupuncture was at sites one inch adjacent to the real points, which the authors note may have inadvertently elicited an analgesic response.

Clinical Trials

In 2001, Singh et al conducted an RCT with 73 patients with symptomatic OA of the knee.[15] Patients self-scored on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Lequesne Algofunctional Index at baseline and at weeks 4, 8, and 12. Results demonstrate that patients' scores on both indices improved at weeks 4, 8, and 12. Scores

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were stable regardless of the baseline severity of the OA. However, the group with the least disability and pain rebounded to original levels to a greater degree than did those who initially were more hindered by the condition. The more disabled groups retained the benefits of acupuncture treatment through the 12-week period. Singh et al concluded that acupuncture for patients with OA of the knee may best be used early in the treatment plan, with a decrease in treatment frequency once the acute treatment period is completed to avoid a rebound effect.

Tillu examined the effects of acupuncture on patients with advanced OA of the knee awaiting total knee joint replacement.[16] Forty-four patients were randomly assigned to two groups. The first group received acupuncture to the most affected knee only and the other group received acupuncture to both knees. A blinded observer assessed knee function before starting treatment, and at months 2 and 6. Analysis showed a significant reduction in symptoms in both groups, and this improvement was sustained for six months. However, there was no statistically significant difference between the groups. The author concluded that unilateral acupuncture is as effective as bilateral acupuncture in increasing function and reducing the pain associated with OA of the knee. However, this research design did not control for nonspecific effects of needling.

In 2003, Ng et al performed an RCT of the effectiveness of electro-acupuncture (EA) vs. transcutaneous electrical nerve stimulation (TENS) in alleviating OA-induced knee pain.[17] Twenty-four subjects were assigned to EA, TENS, or a control education group. After eight sessions of treatment, there was significant reduction of knee pain in the EA and TENS groups compared to the control group. The results obtained by Ng et al are consistent with the conclusion of a Cochrane Database System Review prepared by Osiri et al,[18] in which TENS and EA were shown to be more effective in pain control than placebo.

In 2004, four trials were conducted investigating the effectiveness of acupuncture for treating OA of the knee. Tukmachi et al conducted an RCT in which subjects were assigned to one of three groups.[19] The first group received acupuncture alone, the second group received acupuncture plus medication, and the third group used medication for the first five weeks and then added a course of acupuncture to the medication. Repeated measure analyses revealed a highly significant improvement in pain (VAS) after the courses of acupuncture in patients receiving acupuncture alone ($P = 0.012$) and patients receiving medication and acupuncture ($P = 0.001$) vs. the wait-list control group. There was no change in the control group until after the course of acupuncture was added to the medication; the improvement was significant ($P = 0.001$). These benefits were maintained for one month after the course of acupuncture. The authors concluded that manual acupuncture and EA cause a significant improvement in the symptoms of OA of the knee, either on their own or as adjunct therapy, with no loss of benefit after one month.

Vas et al completed two studies in 2004. The first was a large case series consisting of 563 patients treated with acupuncture as an adjunctive treatment for OA.[20] Their results showed that 75% of the patients achieved a reduction in pain of 45% or more with the addition of acupuncture. In the second study, an RCT, 97 patients were randomly assigned to two groups, the first group receiving acupuncture plus diclofenac ($n = 48$) and the second receiving placebo acupuncture plus diclofenac ($n = 49$).[21] Patients in the intervention group experienced a greater reduction in pain than did the control group (mean difference 23.9; 95% confidence interval [CI] 15.0-32.8) using the WOMAC scale. The same result was observed in the pain visual analog scale, with a reduction of 26.6 (95% CI 18.5-34.8). Vas et al concluded that acupuncture plus diclofenac is more effective than placebo acupuncture plus diclofenac for the symptomatic treatment of OA of the knee.

Perhaps the most significant study assessing the effect of acupuncture to treat OA of the knee was conducted by Berman et al in 2004.[22] The study was the largest randomized, controlled phase III clinical trial of acupuncture ever conducted. Five hundred seventy patients with OA of the knee were divided into two groups: a true acupuncture group and a sham acupuncture group. Primary outcomes were changes in pain and function scores (assessed using WOMAC) at weeks 8 and 26. Participants in the true acupuncture group experienced greater improvement in WOMAC function scores than the sham acupuncture group at week 8, but not in WOMAC pain score. However, at week 26, the true acupuncture group not only experienced significantly greater improvement than the sham group in the WOMAC function score, but also in WOMAC pain score and patient global assessment. The authors concluded that acupuncture provided improvement in function and pain relief as an adjunctive therapy for OA of the knee when compared with credible sham acupuncture and control education groups. This trial seems to infer that acupuncture treatment may need to continue longer than eight weeks.

The impact of Berman's study is best described by Stephen E. Straus, MD, Director, National Center for Complementary and Alternative Medicine, NIH:[23]

"For the first time, a clinical trial with sufficient rigor, size, and duration has shown that acupuncture reduces the pain and functional impairment of osteoarthritis of the knee. These results also indicate that acupuncture can serve as an effective addition to a standard regimen of care and improve quality of life for knee osteoarthritis sufferers."

In 2003, Centers for Medicare and Medicaid Services (CMS) commissioned a Technology Assessment to review evidence regarding the use of acupuncture for OA. The results of Berman et al lend support to the decision to provide greater access to acupuncture and to include acupuncture as a covered benefit through CMS.

Adverse Effects/Safety Trials

The safety of acupuncture is well documented. Ernst and White conducted a systematic review to determine the incidence of adverse events associated with acupuncture.[24] The most common adverse events were needle pain, tiredness, and bleeding. Feelings of faintness and syncope were uncommon. Pneumothorax was rare, occurring only twice in nearly a quarter of a million treatments. However, the use of non-sterile needles may cause infections. One overview identified 126 documented cases of hepatitis associated with acupuncture.[25]

Conclusion

A significant amount of data exists supporting the effectiveness of acupuncture for treating OA of the knee. The recently completed phase III trial strongly supports the role of acupuncture for treating knee OA.

Recommendation

Knee OA is a prevalent medical problem with huge social, economic, and medical implications. Given the risk of currently available medical therapy, physicians may choose to employ a trial of acupuncture for their patients with OA, especially for those most at risk for adverse drug events associated with NSAID use. ❖

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Magnets for Musculoskeletal Symptoms

By Sharon L. Kolasinski, MD, FACP, FACR

NATURALLY OCCURRING MAGNETIZED STONE HAS BEEN used in traditional medical practice for hundreds of years.[1] More recent uses of magnets in medicine include nuclear magnetic resonance imaging and the use of bone stimulators to enhance the healing of nonunion fractures. Currently, considerable interest exists in the use of magnets for the treatment of arthritis and musculoskeletal pain, and many devices are commercially available through retail outlets and web sites. In fact, magnet sales approached $5 billion in 1999 according to *U.S. News and World Report*.[2]

Although theoretical arguments can be made as to why pulsed electromagnetic fields may have a beneficial effect in ununited fractures, a rationale for the use of static magnets in painful conditions is less clear. Laboratory work, largely from the orthopedic realm, provides a relevant physiologic framework for discussion of therapeutic magnet use, but clinical trials are lacking.

Mechanism of Action

Pulsed electromagnetic fields (PEMFs) of 1-10 mTesla have been in use as bone-growth stimulators for more than two decades. Their success rests on certain physiologic concepts in the functioning of normal bone and cartilage. First, compression of bone during normal activities results in the generation of negative charge along the compressed surface. In other words, mechanical compression leads to the formation of an electrical potential via a piezoelectric effect.[1] Hydroxyapatite and collagen are known to be piezoelectric in nature and contribute to this generated potential. The electric potential, in turn, affects cell functioning. Bone differentiates and chondrocytes synthesize proteoglycan in response to compressive forces via this electrical transduction.

Externally applied electric fields can alter the electrical environment of bone and cartilage as well. Exogenous electromagnetic fields can induce currents through ionic solutions, influencing cell behavior in ways similar to that seen with the normal response to mechanical compression. Stimulation of chondrogenesis and enhancement of glycosaminoglycan production are among the effects that have been demonstrated in response to PEMFs, suggesting a mechanism through which PEMFs may lead to fracture union. Others have suggested that anti-inflammatory effects may be possible with PEMF because DNA synthesis can be modulated in certain immune cells.[3]

Externally applied static magnets would not be expected to induce an electric current in a stationary conducting medium. However, it has been hypothesized that the movement of ions associated with blood flow could induce an electric current in soft tissues and joints when exposed to a static magnet. This could lead to effects on chondrocytes and cells within the soft tissues. Some investigators have suggested that application of permanent magnets could, therefore, alter the course of osteoarthritis (OA).

Recently, investigators reported on a canine model of OA.[4] Dogs underwent transection of the anterior cruciate ligament and were then cared for in pens with floors covered with: no mattress and no foam; a foam floor mattress with nonmagnetized ceramic pieces between two layers of foam; or a foam floor mattress with magnetized pieces. The magnetized floor mattress delivered 45-50 mTesla at the surface of the mattress. At the end of 12 weeks, the investigators histologically examined the cartilage of each dog. They reported that magnet-treated dogs had qualitatively less severe cartilage surface changes than did the other groups, as well as lower levels of matrix metalloproteinases. These findings led the investigators to suggest that further studies are warranted to delineate how magnetic fields might be used to reduce the severity of OA.

Static magnets may have additional effects. Constant magnetic stimulation may desensitize sensory neurons by modifying cell membrane potentials. This could lead to an analgesic benefit suggested in clinical trials.

Clinical Studies

Although early reports suggested that static magnets may be of benefit for diabetic neuropathy and postpolio syndrome, it was not until recently that well-designed trials appeared in the literature reporting more rigorous evaluations of the efficacy of static magnets in painful conditions. One of the earlier well-designed trials was carried out with patients with low back pain.[5] In this randomized, double-blind, placebo-controlled, crossover pilot study, participants were enrolled at a Veterans Affairs hospital through the primary care and rehabilitation services. Only 24 subjects enrolled with a mean age of 60 years and a mean pain duration of 19 years. Patients had spondylosis confirmed radiographically,

with three subjects having had prior laminectomies. The primary outcome measure was a visual analog score (VAS) for pain. Subjects wore a device made of a flexible rubber-like material impregnated with active magnetic material that either remained magnetized or was demagnetized to provide a sham device. The magnetic strength of the active device was 30 mTesla. No statistically significant differences between the active and sham treatments were seen in VAS for pain, nor using the McGill Pain Questionnaire.

Mattress pads embedded with ceramic magnets were used with subjects enrolled in a trial to assess the effectiveness of magnets on fibromyalgia symptoms.[6] The investigators used two "functional" pads, one rated by the manufacturer to have a magnetic strength of 395 mTesla, which was placed between the mattress and box spring, and the other 75 mTesla within an eggcrate foam pad, placed on top of the mattress. Two identical sham pads were used and a usual care group received no active intervention. A total of 119 subjects were spread among the five groups and were assessed after three and six months of use. Over the six-month time period, all subjects improved in terms of quality of life, measured by the Fibromyalgia Impact Questionnaire (FIQ), and in the number of tender points. No statistically significant differences were noted between any of the groups, although the group that was exposed to the strongest magnetic field had a reduction in pain intensity levels (measured by one question of the 19-question FIQ).

Magnetic insoles were studied at the Mayo Clinic for use in a group of subjects suffering for at least 30 days from foot pain with maximal tenderness on physical examination over the medial plantar fascia.[7] All participants wore an insole made of magnetic foil embedded in foam under the proximal arch of the foot. The active treatment group wore insoles with a magnetic strength of 245 mTesla and the placebo group wore identical demagnetized insoles for 4 hrs/d, 4 d/wk for eight weeks. The investigators could not demonstrate any benefit attributable to the magnetic insoles. Both treatment and placebo groups reported improvements in morning foot pain and over a third in each group had virtually complete symptom resolution at week 8.

The largest trial published to date assessed the effectiveness of a magnetic bracelet commercially available in Great Britain for control of symptoms of hip and knee OA.[8] Patients with radiographically confirmed OA were randomly assigned to wear one of three identical appearing bracelets: one with a magnetic field strength of 170-200 mTesla; one with a strength of 21-30 mTesla (intended to be an undetectable placebo); and one nonmagnetic. A manufacturing defect led to the use of weak-strength magnetic bracelets that were considerably more magnetized than intended; most had a magnetic field strength of 69-196 mTesla when tested at the end of the trial. Participants wore the bracelets for 12 weeks and their responses to questionnaires assessing their pain and functioning were cataloged; differences were minimal. Although positive effects were noted with the standard magnetic bracelet on both WOMAC A and WOMAC B scales, only the difference in VAS for pain between the standard magnetic bracelet and the dummy bracelet reached statistical significance. Furthermore, about a third of patients in the standard and dummy groups were able to correctly identify whether they wore a magnetized bracelet and the authors did not directly calculate the effect of this unblinding. Two participants in each group reported dizziness, increased pain, or increased stiffness.

Adverse Effects

Concern has been expressed in the popular press about a possible link between exposure to magnetic fields from high currency wires and cancer based on scattered reports of increases in leukemia and childhood cancers. No clear body of data has emerged, since confounding environmental and socioeconomic variables have made interpretation of these observations difficult. Nonetheless, the American Physical Society has gone on record with the opinion that there is no evidence that power lines cause cancer.[9]

Contraindications and Precautions

No systematic survey of the long-term safety of PEMFs or locally applied static magnets exists. It has been recommended that PEMFs not be used by those with cancer or pacemakers, or by pregnant women.

Within the pediatric literature, there are reports of ingestion of steel beads from magnetic bracelets by children causing intestinal obstruction, perforation, and fistula formation.[10]

Product Specifications

Thousands of web sites sell hundreds of products that are magnetized, including bracelets, rings, mattress pads, face masks, neck collars, and supports for knees, elbows, and ankles. Product prices range from $10-$20 for a bracelet to $250-$500 for a mattress pad. Magnetized materials may include gold, silver, copper, neodymium, or ceramic ferrite.

Conclusion

Although pulsed electromagnetic fields are commonly used in orthopedics to help heal nonunion fractures,

the wider medical use of pulsed or static magnets in the prevention or treatment of arthritis or musculoskeletal pain syndromes is not well substantiated. What little clinical evidence exists is largely anecdotal and the few well-designed trials show scant benefit.

Recommendation

Patients and physicians are concerned about side effects associated with nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors, and continue to search for treatment options for a variety of musculoskeletal complaints and arthritis. Pulsed electromagnetic fields have important beneficial effects on cartilage and bone, but the benefits of static magnets are less clearly defined. Static magnet use may be associated with analgesia in some patients and appears to be safe based on short-term studies. ❖

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Mistletoe Extract in Cancer: An Anthroposophic Remedy

By Melinda Ring, MD

WHILE MANY COMPLEMENTARY PRACTICES, SUCH AS mind-body therapies, have little downside for cancer patients receiving treatment, the issue of safety with concomitant use of dietary supplements remains paramount. Not only can some supplements fail to help, but in certain cases they may lessen the efficacy of proven chemotherapy and radiotherapy regimens. Some patients forego conventional medical approaches to cancer treatment in favor of only using supplements, even when conventional approaches have been shown beneficial. Extreme caution should be taken, therefore, when approving the use of supplements in this setting, and then only when sufficient efficacy and safety data exist.

Mistletoe, *Viscum album* L., garnered significant attention in the U.S. cancer community after it was employed by actress Suzanne Somers in her fight against breast cancer in the 1990s.[2] Mistletoe is one of the most widely used nontraditional cancer treatments in Europe; 74% of cancer patients acknowledged using mistletoe therapies in a recent survey in Switzerland.[3] This herb is the most commonly prescribed cancer therapy in Germany, with associated costs topping $30 million per year. The appeal of mistletoe therapy is far from waning in Europe; expenditures have increased 20% annually in recent years.[4]

Proponents of mistletoe claim it stimulates the immune system, promotes cancer cell reversion to more differentiated forms, improves overall well-being, and may extend survival in certain cancers.[5] Additionally, it is used for cancer prevention in high-risk patients, such as those with ulcerative colitis, cervical dysplasia, papillomatosis of the bladder, and intestinal polyposis.

History

Mistletoe's history as a medicinal can be traced back to the time of the Celtic druids. However, it was not until the 1920s that the Austrian philosopher-scientist Rudolf Steiner, PhD, drew attention to the use of mistletoe as a cancer therapy.[6] Steiner was struck by a perceived parallel between the mistletoe plant's parasitic nature and cancer's parasitic invasion of the human body. He hypothesized that mistletoe extracts could stimulate the body's innate healing processes to battle cancer from precancerous to invasive stages.

Steiner is credited with the formation of a healing science known as anthroposophic medicine, a field still

thriving in Germany and Switzerland, and with a growing presence in other European countries and the United States. Currently, physicians in specialized anthroposophic clinics use mistletoe extracts most extensively. Since the establishment of the clinics in the 1920s, more than 80,000 patients have been treated, primarily for cancer.

Anthroposophy blends spiritual and scientific principles and applies them to healing practices. A central concept is that humans are composed of the interactions of physical body (*materia*), inner life body (*forma*), soul (*anima*), and spiritual ego (*geist*). Illness is the result of disharmony and imbalance among these systems. Anthroposophic treatment might include conventional medication accompanied by any of the following complementary therapies: dietary manipulation, natural remedies (herbs, essential oils, potentized metals), medicinal baths, external compresses or ointments, artistic therapies, therapeutic eurythmy (movement therapy), rhythmical massage (a light-touch massage), and psychological counseling.

Anthroposophic natural remedies, including mistletoe, are prepared according to classic homeopathic principles of "like cures like" and dilutional potentization (the more diluted the substance, the greater its potency). The strong belief in an integral human connection to nature is evidenced by the use of natural elements, with special attention to timing and biological rhythms when making and administering these medicines.

Laboratory Evidence/Active Constituents

Since Steiner popularized mistletoe extract, research to identify its active components and anticancer properties has proliferated. Mistletoe augments immune system activation in vitro, including stimulation of the quantity and activity of NK-cells, monocytes/macrophages, and T-cells (especially T-helper cells), and stimulation of cytokine release, including interleukin-1, interleukin-6, and tumor necrosis factor.[7] Studies using human and animal cancer cell systems have identified effects such as increased DNA stability, induction of cell apoptosis, and inhibition of cell growth. The cytotoxic effect appears most pronounced during the G0 (resting) phase of the cell cycle.[8]

Lectins and viscotoxins are the two major active components in mistletoe preparations. Lectins are glycoproteins that can bind sugar portions on cell surfaces; of the four identified in mistletoe, ML-1 (also known as viscumin) is thought most critical to the biologic activity of the plant. When ML-I was selectively removed from mistletoe extracts, a marked reduction in measured activity was noted.[9] Actions of ML-1 include: interference with intracellular protein synthesis, stimulation of cytokine production, and activation of leukocytes. Additionally, ML-1 may therapeutically influence the processes of metastasis and apoptosis.

In contrast, viscotoxins work primarily by damaging the cell membrane and inducing cell necrosis, rather than through immune system modulation. It was suggested in one study that mistletoe itself could promote cancer development; however, subsequent studies have disputed this concerning claim.[10]

Clinical Evidence

Mistletoe has been evaluated as a treatment for cancer in more than 30 clinical studies, about half of which were randomized controlled trials. The majority were performed in Germany and Austria, and published exclusively in foreign language journals. The mistletoe products tested include Iscador, Eurixor, Helixor, Lektinol, and recombinant lectin ML-I. Although most studies concluded positive efficacy in at least one major endpoint (survival, time to tumor recurrence, quality of life), they have been criticized for weaknesses that cast significant doubt on the reliability of the findings.

In 2003, Ernst et al conducted a systematic review of all randomized clinical trials found in eight databases.[11] Ten trials met the inclusion/exclusion criteria; however, prominent weaknesses and heterogeneity precluded a pooled analysis. A narrative summary concluded that some weaker studies implied benefits of mistletoe extracts, particularly in terms of quality of life. However, none of the methodologically stronger trials exhibited efficacy in terms of quality of life, survival, or other outcome measures.

Published in the same year, Kienle et al performed a search of 11 electronic databases, reference lists, and expert consultations.[12] Twenty-three studies were identified: 16 randomized, two quasi-randomized, and five nonrandomized. Cancer sites included breast, lung, stomach, colon, rectum, head and neck, kidney, bladder, skin, brain, and genitals. Like Ernst, the reviewers identified substantial study design differences and biases, and did not perform a quantitative synthesis. Of the 23 studies examined, 12 showed one or more statistically significant positive result (survival or quality of life), another seven studies showed at least one positive trend (survival, disease-free survival, tumor remission), three showed no effect, and one had a negative trend.

Stauder et al performed a review limited to mistletoe extracts standardized to mistletoe lectin.[13] The authors concluded that the clinical database does not support direct anticancer action or improvement in time to tumor progression or overall survival.

Some of the more rigorous studies explored in these reviews are summarized below.

Steur-Vogt et al studied the clinical effectiveness of adjuvant mistletoe extract in 477 patients with head and neck squamous cell cancer in a phase III trial.[14] The patients first were divided into two groups after TNM (tumor, node, metastasis) staging, either undergoing surgery alone (n = 202) or surgery combined with postoperative radiotherapy (n = 275). Both sets then were randomized to standard treatment alone (control group), or standard treatment plus Eurixor, an extract standardized to ML-I. Eurixor was given in four treatment cycles; each cycle lasted 12 weeks and was followed by a four-week break period. During each cycle, Eurixor was administered by subcutaneous injection twice a week. Statistical analysis after an average of four years of follow-up showed no significant improvement in disease-free survival or tumor-related mortality. Additionally, no changes were noted in cellular immunity as measured by lymphocyte subsets or quality-of-life scores. The investigators concluded that Eurixor cannot be recommended as adjuvant treatment in head and neck cancer patients.

In another phase III trial, the German Cancer Society studied patients with high-risk melanoma, defined as a primary tumor greater than 3 mm diameter with negative regional lymph nodes or any size primary tumor with 1-2 positive regional nodes and no distant metastases.[15] After potentially curable surgery, 407 patients were randomized to receive adjuvant treatment for one year with subcutaneous injections of interferon-alpha, interferon-gamma, or Iscador M, or no further treatment. Analysis after eight years of follow-up showed no prolongation in time to tumor recurrence or improvement in overall survival with any of the tested adjuvant treatments.

In 2002, a prospective, randomized phase II trial explored whether adjuvant Eurixor therapy could reduce recurrence of noninvasive bladder cancer.[16] After surgery, 45 patients were randomly assigned to receive either three cycles of treatment with Eurixor or no further therapy. Three cycles of Eurixor treatment were given; each consisted of three months of twice-weekly subcutaneous injections, followed by a three-month break. After 18 months of follow-up, no difference in recurrence rate or disease-free interval was noted. Some critics have identified a lack of weight-based dosing of the extract as a potential reason for the failure to see benefits.

In contrast to these results, a large cohort study conducted in Germany found a positive therapeutic effect from mistletoe treatment.[17] Nonrandomized and randomized matched pairs were studied in the context of a prospective, long-term epidemiological study of cancer survival involving 10,226 patients. A total of 1,668 of these patients had used a mistletoe extract. In the non-randomized study of 396 matched pairs, mean survival time was 40% longer in the mistletoe group (4.23 years) compared to control (3.05 years; $P < 0.001$). Results of the two randomized matched-pair studies supported this finding. Survival time was prolonged in all cancer types studied: carcinoma of the colon, rectum, or stomach; breast carcinoma with and without axillary or remote metastases; and small cell or non-small cell bronchogenic cancer. The research also found that Iscador use tended to improve patient psychosomatic self-regulation, or ability to achieve a sense of well-being and control in a stressful situation. This study has been criticized primarily for the lack of consistency in determining compliance, as well as dose and types of Iscador used. The retrospective nature of the data is another major weakness.

Several studies have been published over the past year further examining the role of mistletoe extract in varied cancers with endpoints including tumor response, quality of life, and survival.

A phase II trial was designed to determine whether mistletoe extract can induce objective tumor response in patients with metastatic colorectal cancer resistant to 5-fluorouracil and leucovorin (5FU/LCV).[18] Twenty-five patients were given three weekly subcutaneous injections of Abnoba-viscum Quercus with gradual dose increases. Treatment was continued in 14 patients until they became bedridden, and 11 patients elected to stop treatment after their illnesses progressed. Median duration of therapy was 14 weeks (range 4-66). Objective tumor response was not seen in any of the 25 patients; symptomatic relief was reported by 10 (40%) patients.

Bock et al examined the efficacy of Iscador in reducing adverse side effects attributable to conventional chemotherapy.[19] A total of 1,442 patients with non-metastatic breast cancer were enrolled, 710 of whom received adjuvant subcutaneous mistletoe extract for three to 52 months. After three years of follow-up, the authors reported a significant reduction in adverse reactions from chemotherapy with mistletoe therapy (16.3% vs. 54.1%). They conclude that Iscador reduced disease and treatment-associated symptoms, and may prolong overall survival. However, the lack of consistency in dose duration, lack of placebo, and poor accountability is concerning.

Another trial also examined quality-of-life issues in breast cancer patients receiving CMF chemotherapy.[20] Two hundred seventy-two patients were randomized to placebo vs. low, medium, or high doses of a standardized mistletoe extract, PS76A2. After 15 weeks of

therapy, the researchers reported a significant improvement with mistletoe based on a self-assessed quality-of-life scores and Spitzer's quality-of-life scale for the medium dose only.

Preparation/Administration

Mistletoe is a semi-parasitic evergreen bush that grows on deciduous trees such as oak, pine, elm, and apple. Although mistletoe species are found in the United States (*Phoradendron leucarpum*) and Korea (*Viscum album coloratum*), only the European *Viscum album* Loranthacea is employed in cancer preparations.

Iscador is the trade name of the most commonly available extract of European *Viscum album*, manufactured by Weleda AG in Switzerland and West Germany. Weleda Inc. distributes it in the United States as a homeopathic remedy with the brand name Iscar. Iscador/Iscar is produced by taking an aqueous extract of the whole mistletoe plant. The extract is fermented with the bacterium *Lactobacillus plantarum*, mixed, filtered for bacteria removal, standardized, and packaged into ampules. Iscador is identified further by the host tree: pine (Pini-Iscador P), Oak (Quercus-Iscador Qu), and Apple (Mali-Iscador M). Anthroposophic practitioners believe different cancers respond better to mistletoe from specific host trees; for example, mistletoe from pine trees may be beneficial in the treatment of skin cancer.

Other mistletoe formulations (trade names: Helixor, Eurixor, Isorel, Plenosol, Vysorel, and ABNOB Aviscum) may be fermented or unfermented, standardized to one of the purported active constituents rather than including the whole plant, or modified by the addition of homeopathic doses of metals, such as mercury, silver, or copper. While most extracts are prepared according to homeopathic principles, some are not.

Iscador typically is injected subcutaneously into the abdominal wall, preferably near the tumor site. Some anthroposophic practitioners inject the substance directly into the tumor. Other routes include oral and intrapleural. The drug regimen is individualized for patients following a protocol established by Steiner, in which escalating doses are given 3-7 times weekly over several weeks to months.[21] The optimal dose is based upon a temperature rise after administration, felt to be an indicator that the immune system is responding. Maintenance-phase injections may be prescribed on an individual basis.

Oral preparations, far less commonly used in Europe, are the only commercially available form of *Viscum album* in the United States. The remedies are available in capsule form, liquid extract, and tea made from either the whole plant or only the leaf.[22]

Safety/Adverse Effects

Side effects related to subcutaneous mistletoe preparations have been minimal and non-life threatening in clinical studies. A few anaphylactic reactions have been reported in a case series.[23] More commonly, the injections lead to localized soreness and inflammation, with headache, fever, and chills. Anthroposophic practitioners view these reactions favorably as signs of immune system stimulation. Transient episodes of gingivitis, eosinophilia, and elevations in serum urea nitrogen and creatinine were noted in one clinical study in both control and test subjects.[24]

Contraindications for oral mistletoe extracts are pregnancy, intolerance to the extract, and hyperthyroidism.[22] Ingestion of toxic levels of mistletoe plants and berries can lead to seizures, bradycardia, blood pressure fluctuations, emesis, and death.[25]

Regulation

Viscum album is listed in the U.S. *Homeopathic Pharmacopoeia*, the standard accepted compendium.[26] However, it is only available commercially in oral preparations in the United States. Since the 2002 Bioterrorism Act, the FDA disallowed general importation or distribution of injectable mistletoe extracts, including homeopathic formulations. U.S. patients interested in receiving injections of mistletoe extract have three options. They may participate in FDA-approved Investigational New Drug studies on mistletoe as a treatment for cancer; currently at least two such projects are ongoing.[27,28] Individual patients may travel outside the United States to receive treatment. In regions such as Germany, where mistletoe remedies have the status of a biological standard therapy, injectable aqueous extracts are readily available by prescription. Finally, patients and physicians in the United States may apply for a three-month supply of the formulations under the FDA Compassionate Use Act, and order Iscador directly from Weleda.

Conclusion

The use of European mistletoe in cancer as an adjuvant therapy has been in vogue in Europe for the past several decades. Bench research points to two main actions of *Viscum album* L.: immunomodulation and cytotoxicity. However, clinical studies have failed to produce convincing data that mistletoe extract can positively affect relevant endpoints such as tumor recurrence, survival, or quality of life. Injectable mistletoe extract is not approved by the FDA as a cancer therapy. Two other organizations, the National Cancer Institute and the American Cancer Society, also caution against its use except in the setting of clinical trials.

Recommendation

The popularity of mistletoe extracts in Europe appears to rely on a weak evidence base. Although several higher-quality clinical trials have been published in the past few years, the results are by no means uniform. However, *Viscum album* and its associated lectins do have potential utility based on pre-clinical research. Given the large number of extracts available, and their variable effects in different tumors, it is unlikely that we will have an answer to the mistletoe conundrum in the near future. For now, it seems prudent to remind patients that mistletoe extracts should not replace conventional therapy, and should only be considered for adjuvant therapy in controlled settings. ❖

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CME Questions

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 certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

17. A large Phase III study has shown that acupuncture can reduce pain and functional impairment in osteoarthritis of the knee.
a. True
b. False

18. Static magnets have been proven clearly beneficial in which of the following medical settings?
a. Nuclear magnet resonance imaging
b. Enhanced healing of nonunion fractures
c. Musculoskeletal disorders
d. None of the above

19. Clinical trials of mistletoe have produced convincing evidence that it can affect relative endpoints such as:
a. tumor recurrence.
b. survival.
c. quality of life.
d. None of the above

Answers: 17. a, 18. d, 19. d.

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

Cup of Joe—No Go?

Source: Lee SJ, et al. Caffeine ingestion is associated with reductions in glucose uptake independent of obesity and Type 2 diabetes before and after exercise training. *Diab Care* 2005;28:566-572.

Goal: To determine the effect of a single exposure to caffeine on insulin-mediated glucose uptake in previously sedentary men, both lean and obese, the latter with and without Type 2 diabetes mellitus (DM). Also, to see whether three months of aerobic fitness training without weight loss influences the effects of caffeine on glucose uptake in these same men.

Design: Randomized, double-blind, 17-week trial.

Subjects: Sedentary lean (n = 8, BMI < 25 kg/m^2) and obese (n = 15, BMI > 27 kg/m^2, 7 with Type 2 DM) Caucasian, non-smoking Canadian men.

Methods: All subjects performed two trials, one with placebo and one with caffeine, before and after exercise training. The 13-week aerobic exercise program consisted of either walking or light jogging on a treadmill at moderate intensity for 60 min five times weekly. A weight-maintenance diet was undertaken prior to and during the exercise-intervention period, and detailed food intake records were completed. After fasting for 10-12 hours overnight, baseline blood samples were obtained and subjects then took the placebo pill (dextrose) or caffeine 5 mg/kg (equivalent to 2-3 cups of coffee) with 250 cc water. An IV of normal saline with glucose, insulin, and potassium was infused to maintain plasma glucose concentration at approximately 5 mmol/L, and blood samples were obtained every 30 min for three hours. Whole body MRI was performed to determine body fat (total and visceral) and skeletal muscle mass.

Results: Caffeine ingestion caused significant reductions in glucose uptake in all groups both prior to and after the exercise program. Impairments in glucose uptake ranged from 33-37% at baseline to 23-36% post-exercise, with the highest numbers occurring in men with Type 2 DM.

Conclusions: Caffeine ingestion reduces insulin-mediated glucose uptake independent of BMI or Type 2 DM. Caffeine's effect on glucose uptake is not attenuated through aerobic exercise that maintains body weight despite small reductions in visceral body fat.

Study strength: Thorough methodology.

Study weaknesses: Small sample; subjects were already moderate consumers of caffeine; results applicable only to white men.

Of note: Self-reported caffeine ingestion prior to the study was 1-5 cups/d; four men with DM were being treated with oral hypoglycemic agents; subjects were not permitted to use vitamins or supplements during the trial; to ensure normal muscle glycogen levels and control for known effects of exercise on glucose uptake, participants were asked to eat at least 200 g carbohydrate and to avoid strenuous exercise for at least four days prior to measurement of insulin sensitivity; it's interesting that the placebo pill was dextrose.

We knew that: Prior studies have shown that caffeine impairs glucose tolerance and insulin sensitivity; even a single episode of exercise is normally associated with improvements in glucose tolerance and insulin sensitivity; caffeine may impact skeletal muscle adenosine receptors or cause significant increases in epinephrine; recent studies suggest that high intakes of coffee (5-6 cups/d) may actually help prevent Type 2 DM (but coffee consumption alone may underestimate total caffeine consumption, and coffee contains magnesium, which increases insulin sensitivity).

Clinical import: Data regarding preventive effects of high coffee intake are interesting, but one would be hard pressed to recommend 5-6 cups of coffee daily as a therapeutic intervention. This small study adds to data strongly suggesting that regular consumption of caffeine heightens the risk for metabolic disorders, especially in those already at risk with a BMI > 25 kg/m^2. We should counsel our patients, especially those struggling to attain a healthy weight, to limit caffeine exposure, while allowing for the occasional splurge.

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