Support Care Cancer. Author manuscript; available in PMC 2012 June 1.
Published in final edited form as:
Support Care Cancer. 2011 June; 19(6): 859–863.
Published online 2011 January 27. doi: 10.1007/s00520-011-1099-7
PMCID: PMC3085555
NIHMSID: NIHMS277868

A pilot phase II trial of magnesium supplements to reduce menopausal hot flashes in breast cancer patients

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Abstract

Background

We tested if magnesium would diminish bothersome hot flashes in breast cancer patients.

Methods

Breast cancer patients with at least 14 hot flashes a week received magnesium oxide 400 mg for 4 weeks, escalating to 800 mg if needed. Hot flash score (frequency×severity) at baseline was compared to the end of treatment.

Results

Of 29 who enrolled, 25 women completed treatment. The average age was 53.5 years; six African American, the rest Caucasian; eight were on tamoxifen, nine were on aromatase inhibitors, and 14 were on antidepressants. Seventeen patients escalated the magnesium dose. Hot flash frequency/week was reduced from 52.2 (standard error (SE), 13.7) to 27.7 (SE, 5.7), a 41.4% reduction, p=0.02, two-sided paired t test. Hot flash score was reduced from 109.8 (SE, 40.9) to 47.8 (SE, 13.8), a 50.4% reduction, p=0.04. Of 25 patients, 14 (56%) had a >50% reduction in hot flash score, and 19 (76%) had a >25% reduction. Fatigue, sweating, and distress were all significantly reduced. Side effects were minor: two women stopped the drug including one each with headache and nausea, and two women had grade 1 diarrhea. Compliance was excellent, and many patients continued treatment after the trial.

Conclusions

Oral magnesium appears to have helped more than half of the patients and was well tolerated. Side effects and cost ($0.02/tablet) were minimal. A randomized placebo-controlled trial is planned.

Keywords: Menopause, Hot flashes, Breast cancer, Survivorship, Drug treatment

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Introduction

Hot flashes are common with menopause from chemotherapy, tamoxifen, raloxifene, or aromatase inhibitors. As many as 90% of perimenopausal women have bothersome hot flashes [1], and 40% of breast cancer survivors rate the bother as “quite a bit” to “severe” [2]. Several treatments are moderately effective including clonidine, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors [3, 4], megestrol acetate [5], and medroxyprogesterone acetate [6], but all have potential side effects.

Based on clinical observations in two patients [7] and anecdotal experience (http://reviewstream.com/reviews/?p=81861, magnesium may be effective in reducing severity and frequency of hot flashes. Magnesium has been used for years to treat hypertension [8], eclampsia [9], and other cardiovascular [10] or nerve disorders [11] and is safe in patients with normal renal function. This pilot study was designed to evaluate the effectiveness of magnesium oxide as a natural, inexpensive, non-prescription, readily available treatment for patients experiencing hot flashes.

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Methods

The primary objective was to determine if magnesium oxide supplements would decrease the frequency and severity of hot flashes (the hot flash score) by 50% as done in trials conducted at the Mayo Clinic [12]. Secondary objectives were to evaluate the effect on overall quality of life and toxicities.

We enrolled patients with bothersome hot flashes (defined by their occurrence ≥14 times per week for ≥1 month, and sufficient severity to make the patient desire therapeutic intervention prior to study entry) after undergoing treatment for cancer. To be eligible, patients had to have good performance status (ECOG Performance Status 0, 1, or 2). We excluded patients with decreased renal function or hypersensitivity to magnesium; who were pregnant or nursing; or using antineoplastic chemotherapy or other investigational drugs within 4 weeks prior to study entry. We excluded patients who had the addition or change of androgens, estrogens, progestins, gabapentin, or antidepressants within 4 weeks prior to study entry; or any change in dose of tamoxifen, raloxifene, or aromatase inhibitors within 4 weeks.

The first week was used as baseline without magnesium supplementation for comparison. Patients were asked to start magnesium oxide 400 mg at bedtime for the

next 2 weeks. If that provided adequate symptom relief (reduction in hot flash frequency or severity of about half, or 50%), then they stayed on that dose for the full 4-week period. If symptom relief was not adequate after 2 weeks, the dose of magnesium was increased to 400 mg twice a day.

Based on previous pilot studies [12], a sample size of 25 was considered adequate to detect 50% reduction in outcome with significance level of 0.05 and power greater than 97%. Prospective hot flash diary entry was used to collect data for 5 weeks of study period. Questionnaires and definition of severity validated by previous studies [12] were used to assess frequency and severity of hot flashes. Linear analog scale quality-of-life questionnaires, the Symptom Assessment scale (21 questions), and Self-Assessment Scale (six questions) questionnaires (all provided by Dr. Charles Loprinzi) were used to assess quality of life during the study period. The magnesium oxide 400 mg tablets (elemental magnesium, 250 mg/tablet) were purchased through the hospital purchasing system, at $2.50 per bottle of 120 tablets. Each patient was given one bottle of pills dispensed by the Investigational Drug Pharmacy. Usage was confirmed by pill count at the end of the study period.

The hot flash score was defined as the product of the daily frequency and average hot flash severity. The hot flash scores were summed for the week; that is, week 1 represents the total for the first week without treatment, and week 5 represents the total for the fourth week on treatment. Sums of weekly hot flash frequency and score at baseline survey were compared with those at the end of the 5 weeks using the two-tailed paired *t* test. Greater than a 50% reduction in outcomes was determined to be clinically significant reduction prior to analysis. A *p* value of 0.05 or less was considered statistically significant, and specified in the protocol beforehand. The study protocol was reviewed by the Protocol Review and Monitoring System of Massey Cancer Center and Institutional Review Board of at Virginia Commonwealth University. The National Clinical Trial number was NCT01008904.

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Results

A total of 31 patients were enrolled, all women with a history of breast cancer and ECOG performance status of 0, 29 received pills for treatment, and 25 completed the 4-week study with full data. One patient was lost to follow up and three patients discontinued treatment before any assessments of their hot flashes; two patients due to possible side effects, and one patient due to an unexpected surgery during study period not related to the treatment. All patients returned all of the survey forms. Three patients took approximately 70% of the pills, and the rest reported complete compliance.

Twenty-nine participants started treatment with the study drug, and 25 completed treatment. The average age was 53.5 (range, 33~78) years. Six patients were African American, the rest Caucasian. Of the 29, eight were on tamoxifen, nine were on aromatase inhibitors, and 14 were on anti-depressants. Twenty-four patients were postmenopausal, and 15 patients reported duration of hot flash symptoms longer than

18 months. Of the 25, 17 patients escalated magnesium dose after 2 weeks of treatment.

Hot flash frequency and score were both reduced significantly. Results from 25 patients who completed the study treatment are shown in Table 1. Of 25 patients, 14 (56%) experienced a >50% reduction in hot flash score, and 19 (76%) had a >25% reduction at the end of the 4 weeks of study treatment compared with baseline. Average weekly hot flash frequency was 52.2 (SE, 13.7) at baseline and 27.7 (SE, 5.7) at week 5, a decrease of 41.4% with *p* value 0.009. Average weekly hot flash score decreased by 50.4% from 109.8 (SE, 40.9) to 47.8 (SE, 13.8), *p* value 0.02, as shown in Fig. 1.

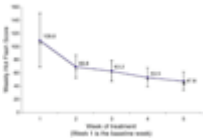

Fig. 1
Hot flash score reduction over time *N*=25 at all points

Table 1
Difference in weekly hot flash frequency, score, and quality-of-life measures at baseline (week 1) and week 5 (end of treatment)

	Week 1, baseline	Week 5, end of treatment	Difference	Changes (%)	*p* Value
Hot flashes					
Frequency (SE)[a]	52.2 (13.7)	27.7 (5.7)	24.6 (9.6)	−41.40	0.02
Score (SE)[b]	109.8 (40.9)	47.8 (13.8)	62.0 (28.5)	−50.40	0.04
Quality of life measures[c]					
Overall quality of life[d]	7.76 (0.3)	8 (0.3)	0.24	3.1	0.14
Level of fatigue	4.88 (0.72)	3.64 (0.61)	−1.24	−25.4	0.03
Abnormal	5.04	2.56 (0.56)	−2.48	−49.2	0.0004

Magnesium supplementation was found to have no statistically significant effect on overall quality of life. From the Symptom Assessment Scale, we observed a statistically significant decrease in three of 21 items: fatigue, perceived distress level due to hot flashes, and severity of abnormal sweating. There was no change in the degree of sleep disturbance.

We assessed toxicity with the Symptom Assessment Scale and CTEP toxicities scale. Side effects were minor; two women stopped the drug after several weeks for adverse effects including one person with migraine headache and one with nausea. Two women had grade 1 diarrhea but continued treatment. Among the 25 participants who completed the treatment, no significant difference in reported symptoms of diarrhea, headaches, or nausea before and after the treatment was observed.

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Discussion

Our findings suggest that oral magnesium supplementation is effective in reducing the severity and frequency of hot flashes in women after treatment of breast cancer. Magnesium appears to be a safe and inexpensive therapy for those with bothersome

hot flashes. The greater than 50% reduction in symptoms suggests that oral magnesium is likely more effective than placebo and meets pre-established criteria of sufficient success to test in a randomized, placebo-controlled trial. [12] We did not observe significant improvement in overall quality of life during the study period; however, symptoms associated with hot flashes, such as fatigue, abnormal sweating, and perceived distress from the hot flashes were significantly reduced. Reported side effects during the pilot study were very mild and tolerable. Oral magnesium can be obtained over the counter for $0.02 per day. The dose used here is well within therecommended national guidelines for supplements, and magnesium has a remarkable absence of major toxicity (see the NIH Office of Dietary Supplements fact sheet http://ods.od.nih.gov/factsheets/magnesium.asp#h7).

Many agents are used to control hot flash symptoms in breast cancer survivors, but most are expensive, have some side effects, and some patients are reluctant to take more medicines. While SSRIs are considered relatively safe, potential side effects include gastrointestinal symptoms, sexual dysfunction, and interaction with other medications, especially tamoxifen, by inhibiting CYP2D6 enzymes [13, 14].

The mechanism of magnesium in reducing hot flash symptoms is not known. Magnesium is known to be neuroactive, vasoactive, and influence serotonin in many body cells including the brain [11]. It is postulated that magnesium may interact with serotonergic agents in treating depression [15]. There are testable hypotheses why magnesium helps to diminish hot flashes. Hot flashes are mediated by an imbalance in serotonin and norepinephrine in the brain that causes vasomotor instability; drugs that increase serotonin availability in the brain, such as venlafaxine and citalopram, decrease hot flashes [16]. Magnesium deficiency has been correlated with severe depression in some studies and successful therapy with anti-depressants such as sertraline led to increases in erythrocyte magnesium, which is used as a non-invasive proxy for brain magnesium [15]. These increases were measurable (an increase of 56.9±3.2 mg/L after sertraline, $p<0.05$) and highly reproducible. Other studies have not shown changes in serum or erythrocyte magnesium even with successful therapy; supplemental magnesium 340 mg daily for 6 months significantly improved pulmonary function, quality of life, and asthma symptoms, but there were no changes in magnesium levels [17].

It is not known whether the serum or intracellular magnesium level is associated with hot flash symptoms. We did not measure serum, red cell, or cerebrospinal fluid magnesium levels of the participants in this practical pilot trial. We did not have a large enough sample size to perform subgroup analysis to determine whether antide-pressant use was associated with magnesium effect in reducing hot flashes, and this requires further evaluation.

There are weaknesses and strengths to this trial. This was a pilot study done at a single academic cancer center. Although we did not plan to limit our study population to breast cancer, only women with a history of breast cancer were studied due to a high prevalence of symptoms and rapid enrollment by that group. Strengths include the use of the Mayo Clinic trial framework and valid, reliable instruments to assess patient-reported symptoms [12], and an expert clinical trial staff with much experience in grading effect and toxicity.

In summary, magnesium appears to safely reduce hot flashes with few side effects at minimal cost. A phase III randomized controlled trial is planned to further evaluate effectiveness of magnesium supplementation for hot flash symptoms in a larger patient population, with biologic correlates to determine mechanism of action.

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Acknowledgments

The authors are grateful to the VCU Department of Internal Medicine Residency Program for dedicated research time of HP; the Cancer Prevention and Control team at Massey; Dr. Charles Loprinzi, Mayo Clinic, for providing a trial framework, symptom assessment instruments, and guidance; and Dr. Mary Helen Hackney for assistance with patients.

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Footnotes

Conflicts of interest The authors hereby indicate that they do not have a financial relationship with any organization that sponsored the research. Research support for the investigators comes from the Massey Cancer Center NCI Core Grant 5 P30 CA16059 (TJS, GLP, MM, and CHB); salary support for TJS comes from GO8 LM0095259 from the National Library of Medicine and R01CA116227-01 from the National Cancer Institute. The pilot trial research was sponsored by the VCU-Massey Cancer Center, which has no financial interest in the publication or the results. Indeed, the low cost of oral magnesium (US $0.02 per tablet) precludes any commercial interest and was one of the attractive features of the therapy. The authors note that they have full control of all primary data, which is stored in the secure VCU-Massey ONCOR system, and that they agree to allow the journal to review their data if requested. All authors meet standards for authorship and have made important contributions to the study.

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