Protocol Submission Template

Please check the Focus Research Team funding source:

☒ **Cancer** ☐ **Comprehensive** ☐ **Digestive Diseases** ☐ **Heart-Lung**
☐ **Neuroscience** ☐ **Transplant–Regenerative Med.**

Title of the study: A Randomized, Placebo Controlled, Single Blinded Trial of 400mg of Magnesium Glycinate BID investigating the body's structure/function role of Hot Flashes.
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Funding Requested: MCF Cancer Focus Research Team

Abstract

DESCRIPTION: Hot flashes are one of the most common symptoms that are experienced in women during perimenopause, menopause, and as a result of treatment of cancer such as breast cancer. Hot flashes, also known as vasomotor symptoms (VMS) may decrease a woman's quality of life due to discomfort, disruption of daily life, interruption of sleep, and worsening of depression. Previously, estrogen-based therapy was the primary treatment choice for VMS. However, in recent years, this has been considered less favorable due to the increased risk of breast cancer associated with estrogen-based therapy.

While medications such as certain antidepressants, gabapentin and clonidine are available as non-hormonal treatment options, they appear to be less effective in comparison to estrogen therapy with reported adverse effects.

Magnesium supplementation has been found to have very promising results in alleviating VMS in patients with a history of breast cancer. The goal of this study is to further investigate the effects of administering magnesium supplementation in reducing the effects of hot flashes in this targeted population. Our aim is to create a controlled trial using different dosages of magnesium glycinate in the management of hot flashes. Participants will be asked to complete surveys for data collection and analysis.

Research Plan

I. Specific Aims

The goal of this study is to further evaluate the effect of magnesium on the symptoms of menopause, specifically vasomotor symptoms (VMS) in breast cancer patients and/or women at an elevated risk of breast cancer.

Aim 1: To perform a dose-response evaluation of magnesium glycinate 400 mg twice daily dose versus placebo

Aim 2: To determine any adverse effects of magnesium glycinate in the study population

Aim 3: To assess the impact of VMS on the overall quality of life (QOL) in this patient population and the effectiveness of magnesium glycinate versus placebo in reducing the impact on quality of life as it relates to other therapy options as measured by the MD Anderson Symptom Inventory (MDASI).

II. Background and Significance

Vasomotor symptoms (VMS) or "hot flashes" are experienced by many women in menopause. Up to 75% of women, including women with a history of cancer experience VMS1. For some women, VMS can begin during the perimenopausal period. Studies have demonstrated that VMS will dissipate after approximately 2-4 years in many women. In approximately 20% of women, hot flashes will persist for at least 15 years2. One study showed that a longer duration of VMS inversely correlated to positive mood. A longer duration of VMS led to a lower than average positive mood score3. In addition, VMS may negatively impact a woman's quality of life by disrupting her sleep, worsening her anxiety and depression, and interrupting work-related responsibilities and hampering leisure activities4.

Patients with a history of cancer, specifically breast cancer, may encounter menopause prematurely. Tamoxifen and aromatase inhibitors are endocrine forms of treatment that are known to cause hot flashes in many women5. Additionally, breast cancer patients who experience menopause have been shown to be more likely to experience VMS than those without a history of cancer6.

Previously, estrogen-based therapy was the gold standard for the management of VMS. However, estrogen-based treatment is not a favorable option for women with a history of hormone receptor positive breast cancer or women at an elevated risk of breast cancer due to the associated increased risk of cancer recurrence or developing breast cancer7. Because estrogen therapy should be avoided in this population, non-hormonal therapy medications are routinely used to alleviate hot flashes in women with active breast cancer or a history of breast cancer. These alternatives include antidepressants, gabapentin, and clonidine1. For many women, these medications can facilitate up to a 40% reduction in VMS symptoms8. However, there are adverse effects associated with these pharmacologic treatment options. Some SSRIs are contraindicated with concomitant tamoxifen use due to CYP2D6 metabolism. Additionally, SSRI and SNRI antidepressants are known to have a common sexual side effect of decreased libido and for some patients, the stigma of taking an antidepressant may also be a barrier to treatment. Gabapentin is known to cause dizziness and drowsiness, while Clonidine may cause orthostatic hypotension.

A lesser studied option for the body's structure/function role of VMS in menopausal women, including those with a history of breast cancer, is the use of magnesium supplementation. A recent pilot study investigated the effect of magnesium on VMS in breast cancer patients. More than half of the participants had a favorable response with minimal side effects and cost9. While some forms of magnesium may lead to loose stools or even diarrhea, magnesium diglycinate has a decreased risk of diarrhea and superior bioavailability. In fact, a study evaluating the bioavailability of magnesium diglycinate versus magnesium oxide in patients status post ileal resection found that a portion of magnesium diglycinate is absorbed intact. Additionally, magnesium diglycinate was found to have less of a cathartic response in comparison to magnesium oxide10.

Based on this information, we have designed a study to further evaluate the effect of magnesium diglycinate (also known as magnesium glycinate) on VMS in breast cancer patients. Data will be collected on the effect of magnesium glycinate on other menopausal symptoms such as sleep disturbances, depression, vaginal dryness, sexual function, arthralgias, and cognitive function to identify possible areas for further research.

III. Research Design and Methods

a. Study Design or Overview – After the consent process takes place, the patient will complete a baseline Hot Flash Diary from memory to record the severity, duration, and intensity of their hot flash symptoms for the seven days prior to joining the study as a baseline rating, and the MDASI, a patient-reported symptom inventory to monitor other symptoms. The MDASI is a series of uniscales in which the severity of each of ten symptoms (fatigue, pain, nausea, sleep disturbance, shortness of breath, memory, appetite, drowsiness, vomiting and distress) is indicated by filling in the appropriate circle on an 11-point scale, from 0 (not present) to 10 (as bad as you can imagine). The MDASI will be completed a total of five times throughout the study: at Baseline, and by phone with the Coordinator at 2, 4, 6, and 8 weeks. Then the coordinator will randomly assign the patient to one of two investigational arms: placebo or magnesium glycinate 400 mg to be taken by mouth twice (BID) a day for 8 weeks +/- 4 days. Investigational assignment will be done using the Pocock-Simon dynamic allocation procedure. Prescription for an 8 week supply (+/- 4 days) of study medication will be sent to the pharmacy for patient pick up. Study Coordinator will then dispense study diaries (Supplementation Diary and Hot Flash Diary) with instructions on how to complete for the eight week study duration. Study Coordinator will discuss upcoming phone calls on Weeks 2-8 to complete the MDASI by phone and the best times to do so with the patient. Coordinator will schedule a return visit with the Patient approximately 9 weeks after the start of the study for follow-up. At follow-up, Coordinator will retrieve Patient Diaries (Hot Flash Diary and Medication Diary), perform supplement reconciliation, and exit Patient from the study. Below is the Patient Care Schedule for the study.

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	End of Investigation
Randomization	x									
MDASI	x		x*		x*		x*		x*	
Complete Hot Flash Diary	x	x	x	x	x	x	x	x	x	
Study Diary Dispensation	x									
Supplement Dispensation	x									
Supplement Consumption		x	x	x	x	x	x	x	x	
Return Visit										x
Supplement Reconciliation										x
Study Diary Collection										x

*Indicates will be performed over the phone with Study Coordinator

b. Study Subjects - The study will target women who have with a history of breast cancer and are experiencing vasomotor symptoms. Recruitment of participants will be from the Mayo Clinic's Breast clinic from patients who consent to participate in the trial.

Inclusion Criteria:

- Age: 25-85 years.
- Women with a history of invasive breast cancer, DCIS, or LCIS
- Creatine labs drawn within 90 days as part of Standard of Care.
- Bothersome hot flashes (defined by their occurrence of two or more hot flashes a day and/or of sufficient severity to prompt the patient to seek therapeutic intervention).
- Presence of hot flashes for >30 days prior to study entry.
- Ability to complete questionnaire(s) by themselves or with assistance.
- Ability to provide informed written consent.
- Life expectancy ≥6 months.
- Willing to work with the enrolling institution for follow-up (during the Active Monitoring Phase of the study).
- ECOG Performance Status (PS) = 0, 1.

Exclusion Criteria:

- Pregnancy (Assessed on Intake Questionnaire. Positive Answer exclusionary)
- Any of the following current (≤4 weeks prior) or planned therapies:
- Antineoplastic chemotherapy (anti-HER2 agents allowed)
- Androgens
- Estrogens (any delivery route)
- Progestogens
- Tamoxifen, raloxifene and aromatase inhibitors are allowed, but patient must have been on a constant dose for at least 28 days and must not be expected to stop the medication during the study period
- SSRIs/SNRIs
- Gabapentin
- Clonidine
- Oxybutinin
- Stage IV or V renal disease or GFR<30 in the last 90 days

c. Sample Size – The sample size for this study is fixed at 40 patients (20 patients per arm). The primary analysis for this study is a two independent sample z-test comparing the difference in the percent change in hot flash frequency from baseline to week 8 of the body's structure/function role between the magnesium and placebo investigational arms. The following table provides some power analysis for various differences in proportions with α=0.05, power=80% and assuming equal variances.

Difference in proportions	0.05	0.1	0.2	0.3	0.4
Power (%)	6	10	26	55	87

Having 20 patients per investigational arm will give us 86% power to detect a difference of at least 0.4 (40%) in the percent change from baseline to week 8 between the magnesium and placebo arms.

d. Data Collection and Handling– Survey and other study data will be collected and inputted into a password secured REDCap database. Only research staff designated by the PI will have access to the data. Hardcopy data will be kept in locked filing cabinets within secured department areas. All study data will be entered by a staff member designated by the PI.

e. Data Analysis - The primary endpoint of this study will be the percent change in hot flash frequency from baseline to week 8. A two independent sample z-test (assuming equal variances) or a Wilcoxon rank-sum test will be used for the analysis of this endpoint. As a secondary analysis, we will also look at the average change in hot flash frequency from baseline to week 8 and compare these means using a two-

sample t-test or a Wilcoxon rank-sum test. Adverse events (as captured using the NCI CTCAE version 4) will be compared between the two investigational arms using summary statistics. Frequencies of adverse events will be compared using chi-square tests or Fisher's exact tests. Change in QOL (as measured by the MDASI) from baseline to week 8 will be compared for each question between the investigational arms using two sample t-tests or Wilcoxon rank sum tests.

f. Strengths - Based on the design of this survey, we will be able to assess the body's effect of magnesium glycinate on the vasomotor symptoms of this patient population. The study will also reveal the effects of magnesium glycinate on other common symptoms of menopause such as depression, insomnia and sexual function. The pilot study as a whole will provide the preliminary data needed to apply for extramural funding to research the effect of magnesium glycinate in alleviating hot flashes and other vasomotor symptoms in a much larger population of post-menopausal women.

IV. Human Subjects

Population- This study will target women aged 25-85 recruited from Mayo Clinic's Breast Clinic who consent to participate in the study and are currently experiencing bothersome hot flashes. Women younger than 25 will be excluded as these women are typically younger than the age range of women with medically-induced menopause or physiologic menopause. Women older than 85 will be excluded.

Recruitment of Subjects: Participants meeting Inclusion/Exclusion criteria will meet with a clinical coordinator to review the study consent form. They will be given ample opportunity to ask any questions they may have and to discuss their potential participation with friends or family members if they so desire.

Potential Risks: The potential risk to subjects for participating in the study is low due to the fact that side effects of magnesium glycinate are mild and mainly include gastrointestinal distress such as abdominal cramping, nausea and diarrhea.

Benefits: Based on previous studies on the effects of magnesium supplementation of reducing vasomotor symptoms in the setting of a very mild side effect profile, there is the high potential for promising outcomes from the data and analysis from this study. This will also be an alternative for those patients who have contraindications for other VMS therapy options such estrogen therapy. This study will also further investigate other potential benefits of magnesium supplementation on other menopausal symptoms.

V. Gender/Minority Mix

The study subjects will be women ages 25-85 recruited from Mayo Clinic's Breast Cancer Center who consent to participate in the study. Women younger than 25 will be excluded as these women are typically younger than the age range of women with medically- induced menopause or physiologic menopause. Women older than age 85 will be excluded.

VI. References:

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