

Intravenous Micronutrient Therapy (Myers' Cocktail) for Fibromyalgia: A Placebo-Controlled Pilot Study

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Abstract

Objectives: Intravenous micronutrient therapy (IVMT), and specifically the Myers' Cocktail, is a popular approach for treating fibromyalgia syndrome (FMS) among complementary and alternative medicine practitioners, but its efficacy is uncertain. This trial assessed the feasibility, safety, and provided insights into the efficacy of this therapy.

Design: This was a randomized, double-blind, placebo-controlled pilot study.

Locations: The study locations were an academic research center, teaching hospital, and affiliated Integrative Medicine Center in Derby, CT.

Subjects: The subjects were 34 adults with American College of Rheumatology (ACR)-defined FMS.

Intervention: Subjects were randomly assigned either to treatment (weekly infusions of IVMT) or to placebo (weekly infusions of lactated Ringer's solution) for 8 weeks.

Outcome measures: Primary outcome was change in the Tender Point Index, assessed 8 and 12 weeks after initiation. Secondary measures included a Visual Analog Scale to assess global pain, and validated measures of physical function (Fibromyalgia Impact Questionnaire), mood (Beck Depression Index), and quality of life (Health Status Questionnaire 2.0).

Results: Clinically significant improvements were noted (of a magnitude similar to other effective interventions). However, in part because of the high placebo response and the small sample size, no statistically significant differences were seen between groups, in any outcome measure, at 8 and 16 weeks. Statistically significant within-group differences were seen in both the intervention and placebo groups, demonstrating a treatment effect for both IVMT and placebo. At 8 weeks, the IVMT group experienced significantly improved tender points, pain, depression, and quality of life directly following treatment (all $p \leq 0.02$), while the placebo group experienced significantly improved tender points only ($p \leq 0.05$). The treatment effects of IVMT persisted at 4 weeks postintervention for tender points, pain, and quality of life, while placebo effects persisted only for tender points. A single minor adverse event was noted in one subject in the intervention group.

Conclusions: This first controlled pilot study established the safety and feasibility of treating FMS with IVMT. Most subjects experienced relief as compared to baseline, but no statistically significant differences were seen between IVMT and placebo. The efficacy of IVMT for fibromyalgia, relative to placebo, is as yet uncertain.

Introduction

Fibromyalgia syndrome (FMS) is a common clinical disorder of unknown etiology characterized by widespread pain and muscle tenderness often accompanied by chronic

fatigue, sleep disturbance, and depressed mood.¹ Approximately 3.4% of women in the United States suffer from FMS, 10 times the prevalence in men.²

The uncertain etiology of FMS² complicates a rational approach to pharmacotherapy. Several recently completed tri-

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als demonstrate promise, though not without concern for serious adverse effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly utilized,³ despite the fact that they have been found to have negligible effectiveness,⁴ along with potential gastrointestinal and renal toxicity.⁵ In clinical trials, the atypical opioid, tramadol, has shown some promise in controlling pain with inconsistent results in functional improvement,⁶ although a combination with acetaminophen has shown promising results in a randomized trial.^{7,8} A recent series of treatment guidelines expresses caution in the use of tramadol for FMS due to the potential for opiate dependence.⁶ A controlled trial of prednisone⁹ resulted in no improvement; most measured variables showed a trend toward deterioration. The limited data available on the use of selective serotonin reuptake inhibitors have shown them to be less effective than the tricyclic agents.¹⁰ Pregabalin was found to be efficacious for FM symptoms in various doses in randomized trials lasting between 8 and 14 weeks; the initial trial resulted in the first U.S. Food and Drug Administration (FDA) approval for a drug to treat FM.^{11–13} Of note, the most recent trial of pregabalin excluded “placebo responders,” limiting external validity and biasing away from the null.¹³ Duloxetine, a serotonin–norepinephrine reuptake inhibitor, demonstrated efficacy in two 12-week randomized controlled trials^{14,15} as well as a 6-month randomized clinical trial (RCT) on pain and self-perceived improvement. In the treatment arm with the highest dose (120 mg/d), 27.2% of patients discontinued the study due to adverse effects.¹⁶ Duloxetine was approved for fibromyalgia in June 2008.

Dietary interventions have demonstrated some promise; FMS symptoms decreased in patients eating predominantly raw vegetarian diets.^{17,18} Other open-label trials using nutritional supplementation consisting of whole food extracts, plant constituents, or single vitamins^{19,20} reported an increase in pain tolerance and overall quality of life.

As is true of many conditions that are poorly understood and rather resistant to conventional treatments, FMS often compels those afflicted to seek complementary and alternative medicine (CAM).^{21,22} These CAM interventions include nutritional and herbal supplements, spiritual practices, visits to alternative practitioners, dietary modifications, acupuncture, and osteopathy. While patient satisfaction with these treatments is ranked moderate to high, there currently exists limited evidence of the efficacy of any specific intervention.^{23–26} Several small trials have shown promise for a combination of malic acid and magnesium,²⁷ and S-adenosylmethionine.^{26,28}

Intravenous micronutrient therapy (IVMT), and specifically use of the “Myers’ Cocktail,”²⁹ a solution of water-soluble vitamins and minerals, is a popular approach among CAM practitioners. Interest in and use of IVMT is growing as evidenced by the number of clinics across the United States offering IVMT as a principal treatment. Members from a wide range of national medical associations including The American College for Advancement in Medicine (ACAM), The American Association of Naturopathic Physicians, the American Holistic Medical Association, the American Academy of Pain Management, the Great Lakes College of Clinical Medicine, and the International Society of Orthomolecular Medicine (ISOM) report using IVMT. Data from over 12,000 patient encounters obtained by an online survey of members of these organizations suggest that IVMT is widely used for a variety of conditions, most often FMS and chronic

fatigue syndrome, with consistently positive results.³⁰ Despite its popularity, no controlled trials of IVMT, and only one trial investigating the mechanism of action of the Myers’ Cocktail³¹ have been conducted. A single, small-sample, open-label study of the Myers’ cocktail for FMS was recently published suggesting therapeutic efficacy.³² We therefore performed the first controlled clinical trial of IVMT for FMS.

Methods

Participants

The Yale University (New Haven, CT) Human Investigation Committee and Griffin Hospital (Derby, CT) Institutional Review Board approved the protocol. All enrolled participants provided informed consent.

Eligible subjects were English-speaking between 18 and 75 years old who fulfilled the criteria for FMS, as defined by the American College of Rheumatology, namely: (1) continuous presence of widespread (in all four quadrants of the body, including axial) musculoskeletal pain of undefined etiology for 3 months or more, and (2) pain in 11 of 18 tender point sites on digital palpation.¹

As occasion requires (PRN) use of NSAIDs and/or Cox II inhibitors was permitted provided that total dosing did not vary on average more than 50% from 1 week to the next over any given month during the past 90 days, and that no new PRN pain medication was introduced within 90 days of study enrollment. All medication and supplement use was documented during the screening process.

Exclusion criteria included narcotic analgesic use, rheumatologic disease, chronic infections, untreated endocrine disorders, unstable seizure disorders, previously diagnosed psychiatric disorders, acute peptic ulcer disease, congestive heart failure, chronic liver disorders and/or bleeding diathesis. Pregnant women and those unwilling to stop vitamin and mineral supplementation prior to and during the course of the study were excluded.

Prescription medications for conditions unrelated to FMS were included, provided a stable dosing regimen for 60 days prior to enrollment. A minimum of 90 days of stable dosing was required for all classes of antidepressants and anxiolytics.

Other modalities of treatment specifically for FMS, such as acupuncture or osteopathy, were discontinued for 2 weeks prior to enrollment. Subjects agreed to discontinue all vitamin/mineral supplementation throughout the study period.

Potential subjects exhibiting allergy to thiamine, as determined by a visible wheal following intradermal injection of 0.1 mL of diluted thiamine, were excluded as well as previous treatment with the Myers’ Cocktail.

Interventions

The intervention is based on the current Myers’ cocktail³³ containing:

- 5 mL of magnesium chloride hexahydrate (20%)
- 3 mL of calcium gluconate (10%)
- 1 mL of hydroxocobalamin (1,000 µg/mL)
- 1 mL of pyridoxine hydrochloride (100 mg/mL)
- 1 mL of dexpanthenol (250 mg/mL)
- 1 mL of B-complex 100 containing:

- 100 mg of thiamine HCl, 2 mg of riboflavin, 2 mg of pyridoxine HCl, and 2 mg of panthenol
- 100 mg of niacinamide, 2% benzyl alcohol
- 5 mL of vitamin C (500 mg/mL)
- 20 mL of sterile water.

The solution is bright yellow and contains 37 mL of relatively high doses of water-soluble vitamins and minerals and sterile water. Prior to study inception, an Investigational New Drug (IND) application to the FDA was submitted and approved (IND 66,885).

Intervention solutions were prepared within 1 hour of administration, under a sterile hood, and double-checked for accuracy by the Joint Commission on Accreditation of Healthcare Organizations–accredited Griffin Hospital Inpatient Pharmacy. The placebo infusion consisted of 37 mL lactated Ringer’s solution. Preparation costs for one dose of IVMT was \$18 US.

Subjects received intervention or placebo solutions intravenously in the antecubital fossa using a slow-push infusion delivered over approximately 10 minutes using a 25-gauge butterfly needle. Subjects received infusions, once weekly for 8 weeks, at the Integrative Medicine Center at Griffin Hospital, Derby, CT.

Objectives

This pilot study was designed to assess safety and feasibility, and to provide preliminary data regarding efficacy of IVMT for FMS as compared to an intravenous lactated Ringer’s placebo.

Outcomes

The primary outcome measure was change in the Tender Point Index (TPI)^{1,34} assessed by a single board-certified rheumatologist. Secondary corroborative measures included

a Visual Analogue Scale (VAS) to assess global pain, the Fibromyalgia Impact Questionnaire (FIQ)³⁵ to assess physical function, the Beck Depression Inventory (BDI)^{36,37} and Health Status Questionnaire 2.0 (HSQ 2.0)³⁸ to assess subjects’ self-perceived mood and general well-being.

Outcomes were measured at baseline, end of treatment period (8 weeks), and after a 4-week washout period (12 weeks) (Table 1).

Sample size

The sample size was determined to allow for 20% attrition and noncompliance and provide at least 80% power to detect a minimal difference of 2.0 points in the TPI between the experimental and placebo group with a maximum allowable type I error of 5%. A standard deviation of 2 points in the TPI was used to compute the sample size.

Randomization

Subjects went through a 2-week run-in period to assess the stability of FMS medication use. Those demonstrating the ability to successfully complete the run-in period (i.e., maintain stable dosing of FMS medications) were assigned by balance allocation to either IVMT or placebo. Randomization was performed by the data manager with gender stratification in blocks of two to assure optimal balance between groups using SAS Software (SAS Institute, Cary, NC). Subjects were enrolled by a study coordinator unblinded to group allocation.

Study design

This pilot study was a randomized, double-blind, placebo-controlled clinical trial. Once deemed eligible, subjects were randomized to receive eight weekly intravenous infusions of either IVMT (intervention) or lactated Ringer’s solution (control).

TABLE 1. EVALUATION TOOLS AND OUTCOME MEASURES

	Description
Pain	
Primary: Tender Point Index (TPI)	Manual assessment at 18 tender point sites 0 = no reported tenderness 2 = tenderness reported with an objective physical response. 10 = untouchable pain TPI-SS: sum of the 18 sites scores FMIS: Fibromyalgia Impact Scale—mean site score = (TPI-SS)/18 10-cm line ranging from “no pain” to “pain as bad as possible”
Visual Analog Scale (VAS)	Respondents mark the location on the line corresponding to the amount of pain they experience
Psychologic	Description
Beck Depression Inventory (BDI)	21-item questionnaire to assess subjects’ degree of depression Response options: 0–3 BDI: sum of the scores of the 21 items
Quality of life	Description
Fibromyalgia Impact Questionnaire (FIQ)	Ability to perform muscular tasks: 10 items # of days in the past week felt good # of days in the past week missed work Seven visual analog scales FIQ: questions normalized to a max score of 10 and total up the 10 questions
Health Status Questionnaire 2.0 (HSQ)	39-item questionnaires to assess subjects’ functional status, well being, and general perceptions of health HSQ: sum of the scores of the 39 items

Blinding

The infusion nurse and subject were blinded to treatment assignment by means of placing an opaque sheet over the syringe and cannula between the nurse and subject. All tender point examinations were performed by a single board-certified rheumatologist who was blinded to treatment assignment. Other self-report instruments were delivered by a study coordinator and research assistant unblinded to treatment assignment.

Statistical methods

Data were analyzed using SAS software for Windows version 9.1. Validated scoring techniques were used to calculate total survey scores for the BDI, HSQ, and FIQ. Responses for individual survey questions were scored and then added to produce a total survey score for each study participant. The Fibromyalgia Intensity Score for each patient was calculated by dividing the TPI Total Survey Site Scores by 18 tender-point sites tested in the survey. Individual patient readings for the VAS were converted to scores ranging from 0 to 100, based on a linear scale of 10 segments and each segment 10 mm in length. Comparisons of all survey scores for the IVMT and Placebo groups were done at three time points: baseline, 8 weeks after the start of intervention, and 12 weeks after the start of intervention. Descriptive analyses of individual surveys showed that the data were not normally distributed. Therefore, nonparametric statistics were used to analyze the outcomes of interest. Within-group changes in the

outcome measures were calculated by subtracting each score at 8 weeks and at 12 weeks from the baseline score. Differences in the change in outcome measures between the two groups were assessed using the Wilcoxon rank-sum test. In all analyses, a two-tailed α of less than 0.05 was considered statistically significant. The continuous data are presented as means \pm standard deviation in the text and tables.

Results

Participant flow (Fig. 1)

A total of 263 potential subjects were screened by phone; 55 were eligible for clinical screening. Approximately 40% of those deemed ineligible after phone screen were taking narcotic analgesics, while approximately 20% cited distance from study center or disinterest in participating. Other subjects were excluded due to a pre-existing health condition, a lack of stability on medications, unwillingness to discontinue vitamins, or lack of FMS diagnosed by a board certified rheumatologist. Clinical screening consisting of TPI examination was performed by a board-certified rheumatologist on 44 candidates; 35 were randomized to IVMT or placebo. Of those eligible for clinical screen, 11 were not interested in continuing with the study, or could not be reached to schedule an appointment. Of the 9 that were excluded after clinical screen, 4 exhibited sensitivity to thiamine, and 5 were found to be unstable on their medication (Fig. 1). One subject in the IVMT group and 2 subjects in the placebo group

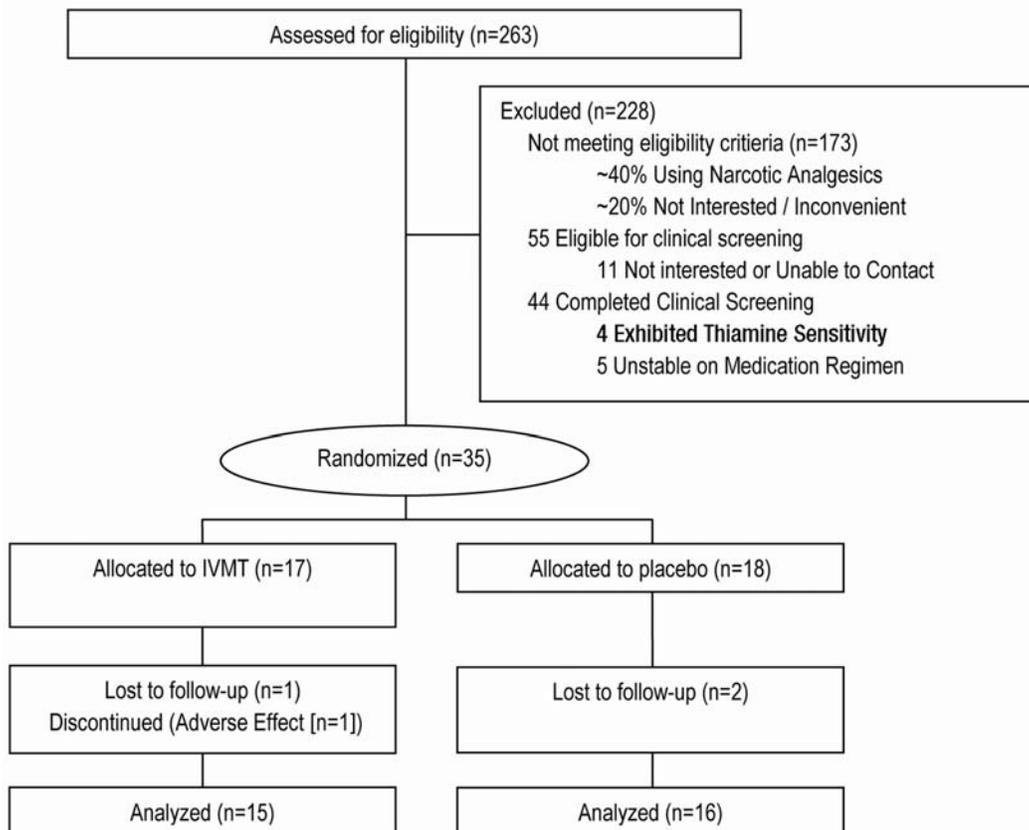


FIG. 1. Flow of participants through the trial. IVMT, intravenous micronutrient therapy.

dropped out prior to the 12-week assessment; all were unwilling to travel to the study site. Ultimately, 31 subjects completed the 8-week intervention and follow-up assessment.

Recruitment

Subjects were recruited by internet announcements, press releases, newspaper advertisements, presentations to FMS support groups, and mailings to rheumatologists and naturopathic physicians between September 2003 and October 2005 in south central Connecticut. Screening and data collection took place at Yale-Griffin Prevention Research Center in Derby, CT.

Baseline data

The two groups were comparable in terms of demographic and baseline characteristics (Table 2). All but 1 subject were female; 1 male was in the IVMT group. Mean ages were 51.7 ± 12.1 years and 50.7 ± 8.2 years, for the IVMT and placebo groups, respectively.

Numbers analyzed

Thirty-four (34) subjects enrolled and completed at least one of the two follow-up assessments: 16 in the IVMT group and 18 in the placebo group. Analyses were based on the intention-to-treat principle, by substituting missing values with the reported values from the 8-week evaluation for the subjects who dropped out prior to completing the study.

Outcomes

Between-group comparisons of individual variables did not reach statistical significance (all *p*-values > 0.05) (Tables 3 and 4); no significant differences were seen in participants assigned to IVMT or lactated Ringer's solution. Following the treatment period (8 weeks), mean Total Survey Sites Score (intervention -18.7 ± 26.5; placebo -16.6 ± 31.2; *p* = 0.60) and mean Fibromyalgia Intensity Score (intervention

-1.1 ± 1.4; placebo -0.9 ± 1.7; *p* = 0.50) decreased in both groups indicating improvement in tender points.

Tables 3 and 4 summarize the results for 8-week and 12-week evaluations, respectively.

Ancillary analyses

The within-group decreases in TPI scores was significant in the IVMT arm (-18.7 ± 26.5, *p* = 0.02 in Total Survey Site Scores and -1.1 ± 1.4, *p* = 0.02 in the Fibromyalgia Intensity Score) as well as in the placebo arm (-16.6 ± 31.2, *p* = 0.04 in Total Survey Site Scores and -0.9 ± 1.7, *p* = 0.05 in the Fibromyalgia Intensity Score) (Table 3). At the 12-week assessment, TPI scores remained improved from baseline in both IVMT (-17.1 ± 24.6, *p* = 0.01 in Total Survey Site Scores and -1.0 ± 1.4, *p* = 0.01 in the Fibromyalgia Intensity Score) and placebo groups (-20.7 ± 25.4, *p* = 0.01 in Total Survey Site Scores and -1.1 ± 1.4, *p* = 0.02 in the Fibromyalgia Intensity Score) (Table 4; Figs. 2 and 3).

Significant within-group improvement was observed in mean BDI score in the IVMT group at 8 weeks (-4.1 ± 4.3, *p* < 0.01), but not at 12 weeks of assessment (-3.2 ± 5.8, *p* = 0.06). Changes in mean BDI score for the placebo group were not statistically significant at either time point (-3.2 ± 8.9, *p* = 0.07 at 8 weeks and -1.3 ± 7.4, *p* = 0.45) (Fig. 4).

Mean within-group HSQ scores significantly increased at 8 weeks in the IVMT group (4.0 ± 5.1, *p* = 0.01), but not in the placebo group (1.9 ± 7.2, *p* = 0.23) (Table 3, Fig. 5). The IVMT group maintained statistically significant improvement in self-reported health status at 12 weeks of assessment (4.1 ± 7.2, *p* = 0.04), with no improvement in the placebo group (0.3 ± 5.9, *p* = 0.76) (Table 4, Fig. 5).

Mean VAS scores significantly decreased within-group in both arms at the 8-week assessment (IVMT: -21.6 ± 25.9, *p* = 0.01; placebo: -15.7 ± 24.8, *p* = 0.02), indicating improvement in self-reported levels of pain (Table 3, Fig. 6). At 12 weeks, the IVMT arm reported overall sustained improvement in pain (-8.9 ± 16.6, *p* = 0.03), whereas the placebo group did not (-7.1 ± 20.3, *p* = 0.27) (Table 4, Fig. 6).

TABLE 2. DEMOGRAPHIC CHARACTERISTICS AND OUTCOMES OF INTEREST AT BASELINE

Variable	IVMT (n = 16)	Placebo (n = 18)	p-value
Gender <i>n</i> (%)			
Male	1 (6.3)	0 (0.0)	—
Female	15 (93.8)	18 (100.0)	
Race <i>n</i> (%)			
White	15 (93.8)	18 (100.0)	—
African American	1 (6.3)	0 (0.0)	
Age (mean ± SD)	51.7 (12.1)	50.7 (8.2)	0.7850*
BMI (mean ± SD)	28.7 (6.2)	30.7 (7.5)	0.3980*
BDI score (mean ± SD)	12.9 (8.3)	13.6 (9.2)	0.8490**
TPI (mean ± SD)			
Total Survey Site Scores (SS)	108.3 (19.1)	109.0 (22.5)	0.9250*
Fibromyalgia Intensity Score (SS/18)	6.0 (1.0)	6.0 (1.2)	0.9450*
HSQ 2.0 total score (mean ± SD)	102.1 (6.3)	101.7 (8.6)	0.8620**
VAS (mean ± SD)	69.1 (14.6)	64.5 (14.4)	0.3650*
FIQ (mean ± SD)	54.9 (18.5)	58.6 (15.3)	0.5320*

BMI, body-mass index; BDI, Beck Depression Inventory; TPI, Tender Point Index; HSQ, Health Status Questionnaire; VAS, visual analog Scale; FIQ, Fibromyalgia Impact Questionnaire; SD, standard deviation.

**p*-value obtained from two-tailed Student's *t*-test.

***p*-value obtained from Wilcoxon rank-sum test.

TABLE 3. CHANGE IN OUTCOME MEASURES AT 8 WEEKS FOLLOWING TREATMENT (INTENT-TO-TREAT)

Variable	IVMT (n = 16)	Placebo (n = 18)	p-value**
TPI			
Total Survey Site Scores (SS)	-18.7 (26.5)	-16.6 (31.2)	0.60
Within-group p value*	0.02	0.04	
Fibromyalgia Intensity Score (SS/18)	-1.1 (1.4)	-0.9 (1.7)	0.50
Within-group p value*	0.02	0.05	
BDI score			
BDI score	-4.1 (4.3)	-3.2 (8.9)	0.35
Within-group p value*	<0.01	0.07	
HSQ 2.0 total score			
HSQ 2.0 total score	4.0 (5.1)	1.9 (7.2)	0.50
Within-group p value*	0.01	0.23	
VAS			
VAS	-21.6 (25.9)	-15.7 (24.8)	0.49
Within-group p value*	0.01	0.02	
FIQ			
FIQ	-12.0 (15.3)	-11.2 (25.4)	0.50
Within-group p value*	0.02	0.11	

BDI, Beck Depression Inventory; TPI, Tender Point Index; HSQ, Health Status Questionnaire; VAS, visual analog scale; FIQ, Fibromyalgia Impact Questionnaire.

*p-value obtained from Wilcoxon signed-rank test.

**p-value obtained from Wilcoxon rank-sum test.

Self-reported level of physical function, as measured by mean FIQ score, improved in both arms following the beginning of treatment. At 8-week assessment, a decrease in mean FIQ scores from baseline, indicating fewer reported restrictions on physical function, was significant in the IVMT group (-12.0 ± 15.3 , $p = 0.02$), but not in the placebo group (-11.2 ± 25.4 , $p = 0.11$) (Table 3, Fig. 7), though the magnitude of change did not differ between groups. This treatment effect waned by 12 weeks (Table 4, Fig. 7).

Adverse events

One (1) subject reported feelings of dyspepsia, insomnia, depression, and a rise in blood pressure, gradually over the course of 3 weeks. The principal investigator and Data Safety Monitoring Board agreed the symptoms were unusual given the intervention, but treated them as causal. Symptoms ameliorated after voluntary withdrawal from the study. No other adverse effects were reported. All subjects

tolerated the infusion well, with no complaints of discomfort or pain.

Discussion

This pilot study, the first controlled trial of IVMT for fibromyalgia, demonstrated feasibility and safety of testing an intravenous vitamin solution in a randomized, controlled trial. All outcome measures improved at the end of the 8-week treatment period, both in intervention and placebo groups. At 12 weeks, 4 weeks after treatment had ceased, some but not all of the apparent treatment benefits had abated.

A strong placebo effect was noted, with minimal between-group differences on all outcome measures. The impact of an invasive placebo such as weekly infusions in a health care setting are generally greater than oral placebos.^{39,40} However, the consistency and magnitude of treatment effects was greater in the IVMT group. There was a statistically signifi-

TABLE 4. CHANGE IN OUTCOME MEASURES AT 12 WEEKS FOLLOWING TREATMENT (INTENT-TO-TREAT)

Variable	IVMT (n = 16)	Placebo (n = 18)	p-value**
TPI			
Total Survey Site Scores (SS)	-17.1 (24.6)	-20.7 (25.4)	0.39
Within-group p value*	0.01	0.01	
Fibromyalgia Intensity Score (SS/18)	-1.0 (1.4)	-1.1 (1.4)	0.50
Within-group p value*	0.01	0.02	
BDI score			
BDI score	-3.2 (5.8)	-1.3 (7.4)	1.00
Within-group p value*	0.06	0.45	
HSQ 2.0 total score			
HSQ 2.0 total score	4.1 (7.2)	0.3 (5.9)	0.07
Within-group p value*	0.04	0.76	
VAS			
VAS	-8.9 (16.6)	-7.1 (20.3)	0.50
Within-group p value*	0.03	0.27	
FIQ			
FIQ	-3.6 (20.7)	-7.1 (27.5)	0.24
Within-group p value*	0.33	0.42	

IVMT, intravenous micronutrient therapy; TPI, Tender Point Index; BDI, Beck Depression Inventory; HSQ, Health Status Questionnaire; VAS, visual analog scale; FIQ, Fibromyalgia Impact Questionnaire.

*p-value obtained from Wilcoxon signed-rank test.

**p-value obtained from Wilcoxon rank-sum test.

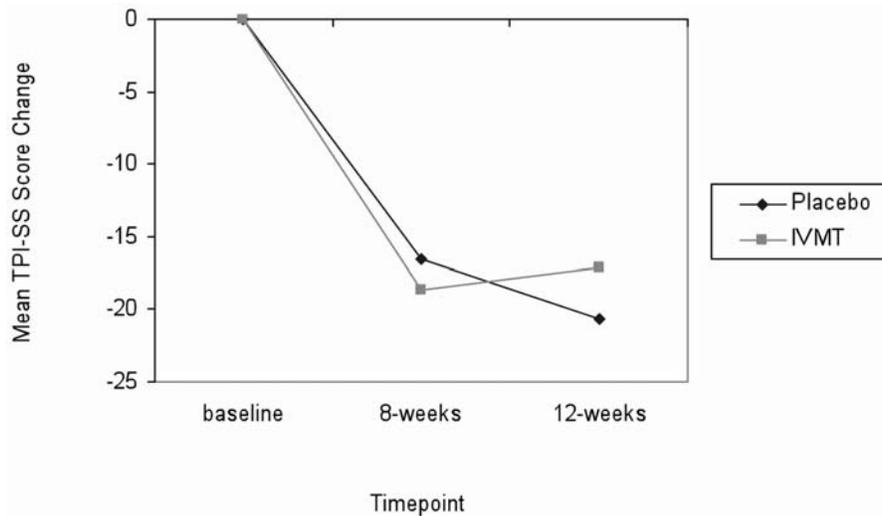


FIG. 2. Change from baseline in mean Tender Point Index (TPI) total survey sites (TSS) scores. IVMT, intravenous micronutrient therapy.

cant improvement in all outcome measures in the IVMT group at 8 weeks, and persistent significant improvement from baseline in most measures at 12 weeks. In comparison, only the TPI showed significant improvement at 12 weeks in the placebo group. Immediately following the treatment period, the IVMT group had significantly improved pain, depression, and quality of life. IVMT effects persisted at 1 month postintervention for pain and quality of life, but was marginal for depression.

The suggested therapeutic effects seen in this trial are commensurate with other modalities considered promising. The magnitude of change seen with IVMT with the FIQ, the standard measure of global function in patients with FMS,⁴¹ exceeds or is similar to the benefits seen in recently completed RCTs in both conventional and CAM domains, though the effect sizes (Cohen's *d*)⁴² vary. Pre-post changes in the FIQ in a recent trial of patient education and exercise resulted in a 3.38-point change (*d* = 0.4) in the intervention group.⁴³

Other interventions such as written emotional disclosure resulted in a 5.6-point (*d* = 0.5) change after 3 months;⁴¹ acupuncture resulted in a 7.6-point (*d* = 0.7) change after 1 month.⁴⁴ The magnitude of change was strongest in trials of guided imagery and pramipexole with 13.2-point (*d* = 5.7) change after 6 weeks⁴² and 13.3-point (*d* = 5.7) changes after 14 weeks,⁴⁵ respectively. A recent trial of pregabalin, the first FDA-approved drug for the treatment of fibromyalgia, found a 13.08-point (*d* = 0.72) change after 14 weeks (600-mg dose). Subjects receiving IVMT in our study improved by a mean 12.0 points (*d* = 0.8) after 8 weeks; subjects receiving intravenous lactated Ringer's solution (placebo) improved by a mean 11.2 (*d* = 0.4) points after 8 weeks.

This trial was one assessing prevailing practice. IVMT is in widespread use by CAM physicians for a variety of conditions, particularly FMS. There is scant theoretical understanding of the formulation nor any definite mechanistic understanding of any apparent clinical effects. Much of

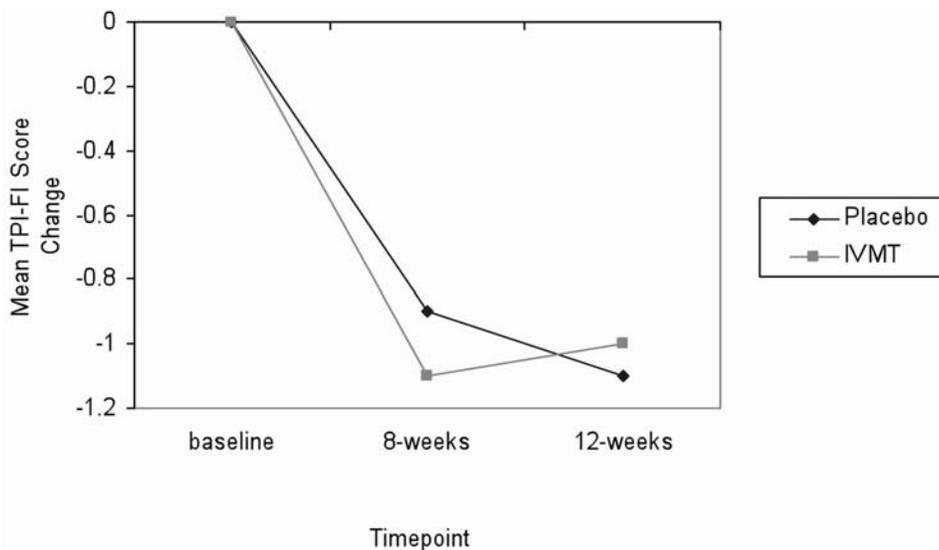


FIG. 3. Change from baseline in mean Tender Point Index (TPI) fibromyalgia intensity (FI) score.

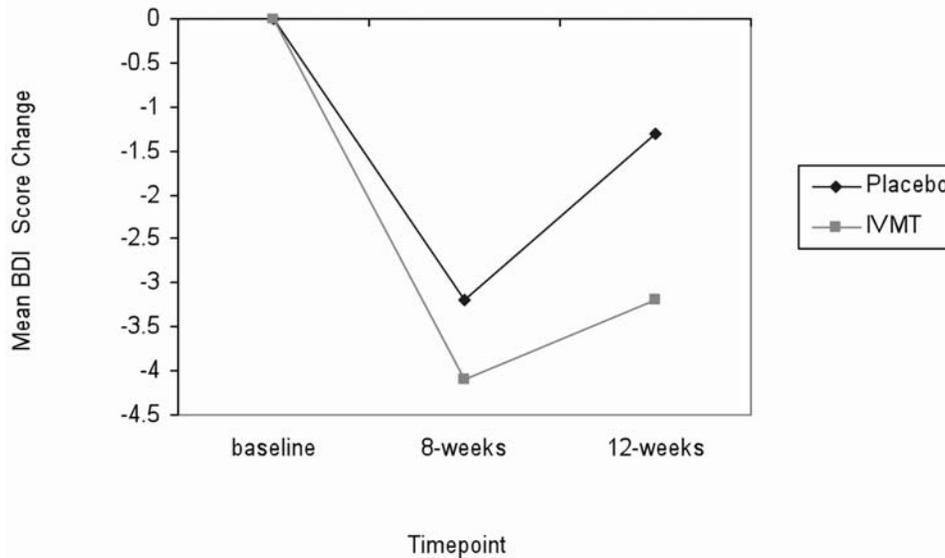


FIG. 4. Change from baseline in mean Beck Depression Inventory (BDI) score. IVMT, intravenous micronutrient therapy.

the benefit of Myers' Cocktail in the treatment of FMS may be derived from the magnesium content.²⁹ Magnesium administered intravenously has been shown to ameliorate pain in a number of conditions.⁴⁶ Patients with fibromyalgia may be deficient in serum magnesium,⁴⁷ and low serum magnesium is associated with increased fatigue in FMS.⁴⁸ Most other constituents of the IVMT solution have not been investigated extensively, although vitamin B₁₂ injected intramuscularly has been used experimentally to treat chronic fatigue syndrome,⁴⁹ which is closely associated with FMS.⁵⁰

Among the limitations of this pilot study is a small sample size, initially based on an effect size and variance in a randomized trial assessing the efficacy of ibuprofen for FMS pain.⁵¹ Study power may have been insufficient to identify

significant between-group differences in light of the strong placebo effect observed. Alternatively, if modest volume expansion is a therapeutic mechanism of IVMT, the placebo in this study may have been a poor choice, overlapping with the active treatment. A comparison to IV insertion without volume expansion and/or oral placebo may be warranted in follow-up study.

The external validity of the study is limited as well, due to the homogeneous nature of the population studied. Subjects were primarily middle-aged white women, similar in demographics to participants in other FMS clinical trials. This is in part attributable to an increased prevalence of FMS in women compared to men.² In addition, men with fibromyalgia may have less severe symptoms than women and are less likely to seek medical care for the condition.⁵²

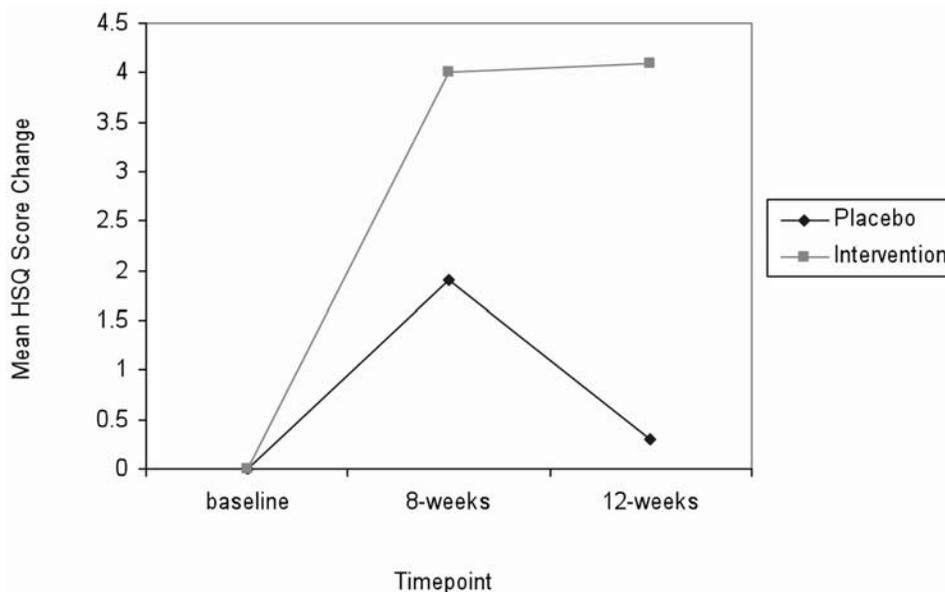


FIG. 5. Change from baseline in mean Health Status Questionnaire (HSQ) score.

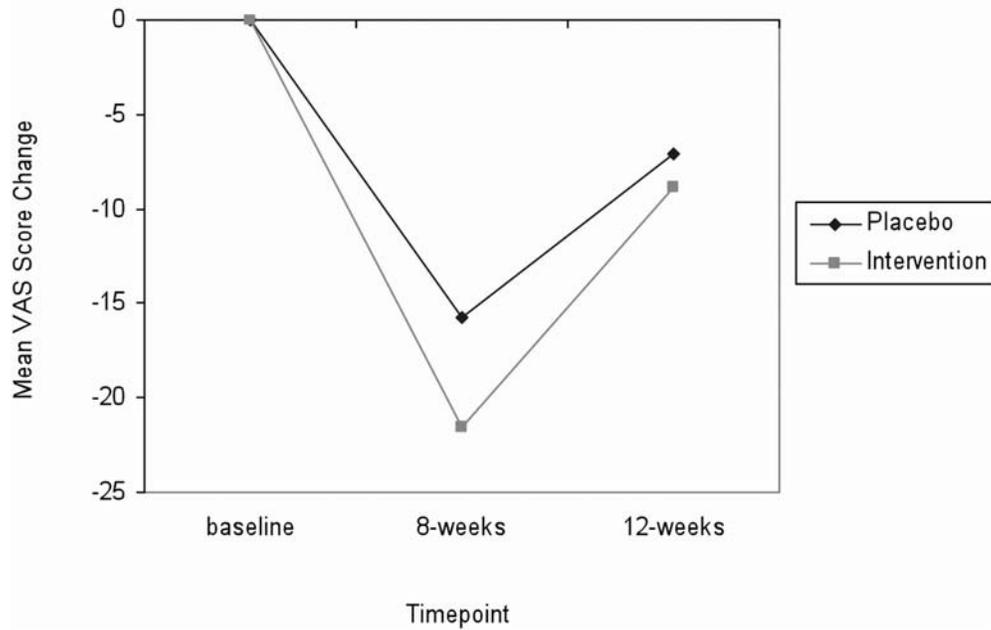


FIG. 6. Change from baseline in mean visual analogue scale (VAS) score.

Of 263 people telephone screened for the current study, only 14 were male.

Conclusions

In conclusion, this pilot study established the safety and feasibility of treating FMS with IVMT. No significant differences in outcome measures between IVMT and placebo were demonstrated. Preliminary data regarding the efficacy of IVMT show a strong placebo effect, with both intervention and placebo groups experiencing strong symptomatic relief after 8 weeks of treatment. The efficacy of IVMT relative to placebo remains uncertain.

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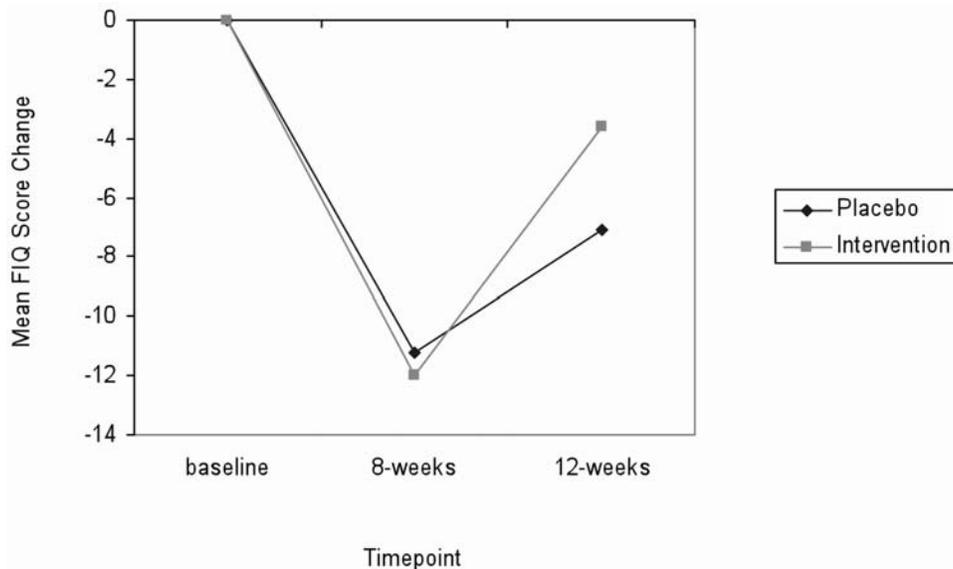


FIG. 7. Change from baseline in mean Fibromyalgia Impact Questionnaire (FIQ) score.

Authors' Contributions

A.A. analyzed and interpreted the data, drafted the manuscript, critically revised the manuscript for important intellectual content, and provided administrative, technical, and material support.

V.Y.N. analyzed, interpreted the data and performed statistical analysis and critical review of the manuscript.

V.N. analyzed and interpreted the data, drafted the manuscript, and performed statistical analysis.

A.B.S. was involved in acquiring data and provided administrative, technical, and material support.

A.L.W. was involved in study concept and design, obtained funding, and provided administrative, technical, and material support.

L.S.L. provided administrative, technical, and material support.

A.I.P. was involved in study concept and design and critically reviewed the manuscript.

H.A. was involved in study concept and design and obtained funding.

D.L.K. was involved in study concept and design, analyzed and interpreted the data, edited the manuscript, critically revised the manuscript for important intellectual content, obtained funding, and supervised the study.

Disclosure Statement

The authors declare that they have no competing interests. This trial was conducted under Trial Registration: clinicaltrials.gov Identifier: NCT00067405.

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