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• Research Article

Effects of transdermal magnesium chloride on quality of life for patients with fibromyalgia: a feasibility study

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ABSTRACT

BACKGROUND: Fibromyalgia is a syndrome characterized by chronic pain, fatigue, depression, and sleep disturbances. Its primary cause is unclear. Several studies have reported decreased intracellular magnesium levels in patients with fibromyalgia and have found negative correlation between magnesium levels and fibromyalgia symptoms.

OBJECTIVE: To gather preliminary data on whether transdermal magnesium can improve quality of life for women who have fibromyalgia.

DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS: This is a patient questionnaires and survey in a fibromyalgia clinic at a tertiary medical center. Forty female patients with the diagnosis of fibromyalgia were enrolled. Each participant was provided a spray bottle containing a transdermal magnesium chloride solution and asked to apply 4 sprays per limb twice daily for 4 weeks. Participants were asked to complete the Revised Fibromyalgia Impact Questionnaire, SF-36v2 Health Survey, and a quality-of-life analog scale at baseline, week 2, and week 4.

MAIN OUTCOME MEASURE: Questionnaire and survey scores, evaluated through intent-to-treat and per-protocol analyses.

RESULTS: Twenty-four patients completed the study (mean [SD] age, 57.2 [7.6] years; white, 95%; mean body mass index, 31.3 kg/m^2). With intention-to-treat analysis, Revised Fibromyalgia Impact Questionnaire subscale and total scores were significantly improved at week 2 and week 4 (total score, P = 0.001). Per-protocol analysis results were similar: all subscales of the Revised Fibromyalgia Impact Questionnaire were significantly improved at week 2 and week 4 (total score, P = 0.001).

CONCLUSION: This pilot study suggests that transdermal magnesium chloride applied on upper and lower limbs may be beneficial to patients with fibromyalgia.

TRIAL REGISTRATION: *ClinicalTrials.gov*.Identifier NCT01968772.

Keywords: fibromyalgia; magnesium chloride; Revised Fibromyalgia Impact Questionnaire; clinical trial

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1 Introduction

Fibromyalgia is a chronic pain syndrome with no known cause[1]. In addition to widespread pain, patients with fibromyalgia have fatigue, depression, and sleep problems[2]. About 3.5% of women and 0.5% of men in the United States have received the diagnosis of fibromyalgia[3,4]. The etiologic factors of fibromyalgia are unclear; however, some evidence shows that the widespread pain observed in patients with fibromyalgia is caused by abnormalities in the central nervous system. The pain threshold in fibromyalgia is lowered, and pain can be elicited with less stimuli than in the healthy state[5,6]. Higher levels of substance P in the cerebrospinal fluid[7], alterations in cerebral blood flow[8], reduced levels of serotonin and 5-hydroxytryptophan[9], and impairments of the hypothalamus-pituitary-adrenal axis[10] have also been associated with the presence of fibromyalgia.

With the various biological processes involved in and the uncertain clear cause of fibromyalgia, it is not surprising that its treatment includes multiple modalities such as education, exercise, medications (tricyclic antidepressants, selective serotonin reuptake inhibitors, dual serotonin and norepinephrine reuptake inhibitors, analgesics, and anticonvulsants), and complementary and alternative medicine (CAM) therapies[1]. CAM therapies have been reported to ease fibromyalgia symptoms[11], and their use is common in patients with rheumatologic disorders: more than 50% of patients with rheumatologic conditions, including fibromyalgia, use CAM therapies[12–14] and, as reported by Wahner-Roedler *et al*[14] in 2005, 98% of patients evaluated in a fibromyalgia clinic had used some form of CAM within the past 6 months. CAM therapies frequently used by patients with fibromyalgia include massage, meditation, acupuncture, hypnotherapy, and nutritional supplements.

Some preliminary evidence shows that fibromyalgia is an oxidative stress disorder and that deficiency in trace elements and antioxidants may have a role in the development of fibromyalgia symptoms[15–18]. A small study reported on a significant reduction of fibromyalgia symptoms after 9 months of treatment with coenzyme Q_{10}, a strong antioxidant[19]. Magnesium is a trace element with many important functions, including activation of almost all enzymes of the glycolytic and Krebs cycles. It is further needed for synthesis of adenosine triphosphate[20]. Some investigators have reported on the similarity in the clinical symptoms of fibromyalgia and magnesium deficiency, including the findings of tender points, indicating a possibility that magnesium has a part in fibromyalgia pathogenesis[21–24].

Several studies have shown that intracellular magnesium levels are decreased in fibromyalgia patients, with serum magnesium levels staying within the reference range[22–26] or decreased[27]. Abraham and Flechas[27] postulated that low magnesium levels in muscle cells may be a factor in fibromyalgia development. They also reported that daily supplementation of 300 to 600 mg of magnesium malate improved fibromyalgia symptoms. Bagis *et al*[28] noted that in their study, serum and erythrocyte magnesium levels were significantly lower in patients with fibromyalgia than in control subjects. They also reported a significant negative correlation between magnesium levels and fibromyalgia symptoms, with the number of tender points and the scores of tender point index, Fibromyalgia Impact Questionnaire (FIQ), and Beck Depression Inventory decreasing significantly with magnesium citrate treatment. Sendur *et al*[29] reported an association between serum magnesium levels and fatigue in patients with fibromyalgia, indicating a potential therapeutic role of magnesium supplementation in fibromyalgia symptoms.

The primary aim of the present study was to gather preliminary data on whether transdermal magnesium chloride ($MgCl_2$) can improve quality of life (QOL) in women who have fibromyalgia as measured with the Revised Fibromyalgia Impact Questionnaire (FIQR), the SF-36v2 Health Survey, and a QOL analog scale. The secondary aim was to assess the feasibility of recruiting 40 women with fibromyalgia into a study of a transdermal $MgCl_2$ product.

2 Patients and methods

This pilot study was approved by the Mayo Clinic Institutional Review Board and was registered as NCT01968772 on *ClinicalTrials.gov*. Each participant provided written informed consent.

2.1 Study population

Patients with a diagnosis of fibromyalgia at the Mayo Clinic Fibromyalgia Clinic were identified through the fibromyalgia clinic database. To participate, women had to be postmenopausal or to have undergone a hysterectomy. Patients were excluded from the study if they were receiving dialysis or had coronary artery disease, chronic cardiac arrhythmias, bipolar disorder, schizophrenia, or dementia.

2.2 Study design

This was a single-arm pilot study.

2.3 Intervention

Each participant was given a spray bottle containing transdermal $MgCl_2$ solution (Fibro Flex [formerly DermaMag]; Magnesium Direct) and asked to apply 4 sprays per limb 2 times daily for 4 weeks. After spraying the solution into the palm of the hand 4 times, the participant rubbed the amount on 1 limb and then repeated the steps for each limb. The suggestion was made that the spray be applied evenly. A wait of 4 h between doses was believed to be ideal, and a minimum of 1 h on the skin was requested before showering or washing the product off. For best results, the product was to be left on the skin throughout the day and then showered off before bedtime to avoid its transfer to the bed sheets. Use of cool, rather than warm, water for rinse-off within 1 h before bedtime was advised to avoid negative impact on sleep hygiene. Participants were further advised to rinse the solution off with water if

certain areas of skin became irritated and to avoid applying the solution to open wounds (simple scratches were believed not to be a problem).

According to the manufacturer (Mitch Pelavin, written communication, December 18, 2014), the magnesium formula contains 31% $MgCl_2$ by volume. It is "a clear, odorless liquid that dries rapidly", has a shelf life of years, and needs no refrigeration. Ingredients are water, $MgCl_2$, and, to aid absorption, a proprietary blend of trace minerals, including "boron, selenium, manganese, calcium chloride, potassium chloride, and sodium chloride. One fluid ounce contains approximately 3 000 mg of elemental magnesium; 8 sprays equal 100 mg elemental magnesium". There are no known adverse effects to dermally applied $MgCl_2$ other than possible skin irritation.

2.4 Instruments used

Participants were asked to complete the FIQR, the SF-36v2 Health Survey, and a 6-question QOL analog scale at baseline (before initiation of topical treatment), week 2, and week 4. The study coordinator called each patient weekly, inquiring about compliance and questions or concerns. Participants also were given a diary to keep track of the daily intervention. At the end of the study, the amount of unused $MgCl_2$ product was measured.

The FIQR has 21 questions rated on a scale of 0 to 10, with 10 being "worst". The questions address the previous 7 d and assess the following 3 domains: function (9 questions), overall impact (2 questions), and symptoms (10 questions). The sum of the score for function (range, 0–90) is divided by 3, the sum for overall impact (range, 0–20) is not changed, and the sum for symptoms (range, 0–100) is divided by 2. The total FIQR score is the sum of these 3 domain scores, with a maximum total score of 100.

The SF-36v2 Health Survey is a widely used scale to evaluate health issues related to QOL. Developed to obtain subjective estimates of functional status regarding patients' health, it contains 36 items on how daily activities (*e.g.*, walking, shopping, going up some steps) have been limited by health problems. It provides a classification in 8 domains that correspond to the dimensions most related to a health indication: role physical health, physical functioning, bodily pain, vitality, social functioning, role emotional, mental health, and general health. These dimensions are evaluated in a standardized 0-to-100 scale, in which the higher the score, the better the representation of health status.

The QOL analog scale assesses the frequency and severity of 6 symptoms associated with fibromyalgia — migraines, headaches, leg cramps, fatigue, joint pain, and muscle pain — on the basis of an 11-point rating scale of 0 to 10, with 10 being "worst".

2.5 Statistical analysis

The demographic characteristics of the participants were summarized using descriptive statistics of mean (standard deviation, SD) for continuous variables and frequency (percentage) for categorical variables. FIQR scores, SF-36v2 scores, and QOL analog scale scores were compared at baseline and at 2 and 4 weeks using paired *t* test. Intention-to-treat and per-protocol analyses were done. All statistical analyses were performed with statistical software (SAS version 9.3; SAS Institute Inc). Bonferroni adjustment was used to account for multiple comparisons. Therefore, $P<0.017$ was considered statistically significant.

3 Results

A total of 40 patients enrolled in the study. The Consolidated Standards of Reporting Trials flow chart, outlining study enrollment and completion rates, is shown in Figure 1.

3.1 Descriptive statistics

Of women enrolled in the study, 24 completed and returned all follow-up measures (at week 2 and week 4). The total dropout rate was 40%, with 22.5% being due to skin irritation caused by the $MgCl_2$ product. Five patients were unable to finish the first 2 weeks of the protocol because of skin problems, and 4 participated for more than 2 weeks but were unable to finish the 4-week study course because of skin irritation.

Descriptive statistics of the population are reported in Table 1. Participants had a mean (SD) age of 57.2 (7.6) years and a mean body mass index of 31.3 kg/m^2, and 95% were white.

3.2 Intention-to-treat analysis

To account for the dropout in participation, we conducted an intention-to-treat analysis by replacing missing values due to participation dropout with each patient's previous score. This method showed that, compared with baseline scores, FIQR subscale and total scores were significantly improved at week 2 and week 4 (all $P<0.01$) (Table 2 and Figure 2). Significant differences were also noted in SF-36v2 scores for physical function, role physical, and physical composite (Table 2 and Figure 3). Bodily pain, vitality, social function, role emotional, mental health, and mental composite scores were not significantly different from baseline at either week 2 or week 4.

Patients also reported decreased cramp severity, decreased fatigue, and decreased joint and muscle pain at study completion. The overall QOL score, or the mean of 12 item scores (Table 2 and Figure 4), had significantly improved at week 2 and week 4.

3.3 Per-protocol analysis

The results of the per-protocol analyses are summarized in Table 3. All subscales of the FIQR had improved significantly at week 2 and week 4 compared with baseline. Although significant improvements were found in physical function, role physical, and physical composite scores from baseline to week 2 with the per-protocol analysis, none of the SF-36v2 domain scores were significantly different from baseline scores at week 4. However, significant decreases in cramps and fatigue were found at both week 2 and week 4. The overall QOL score had improved

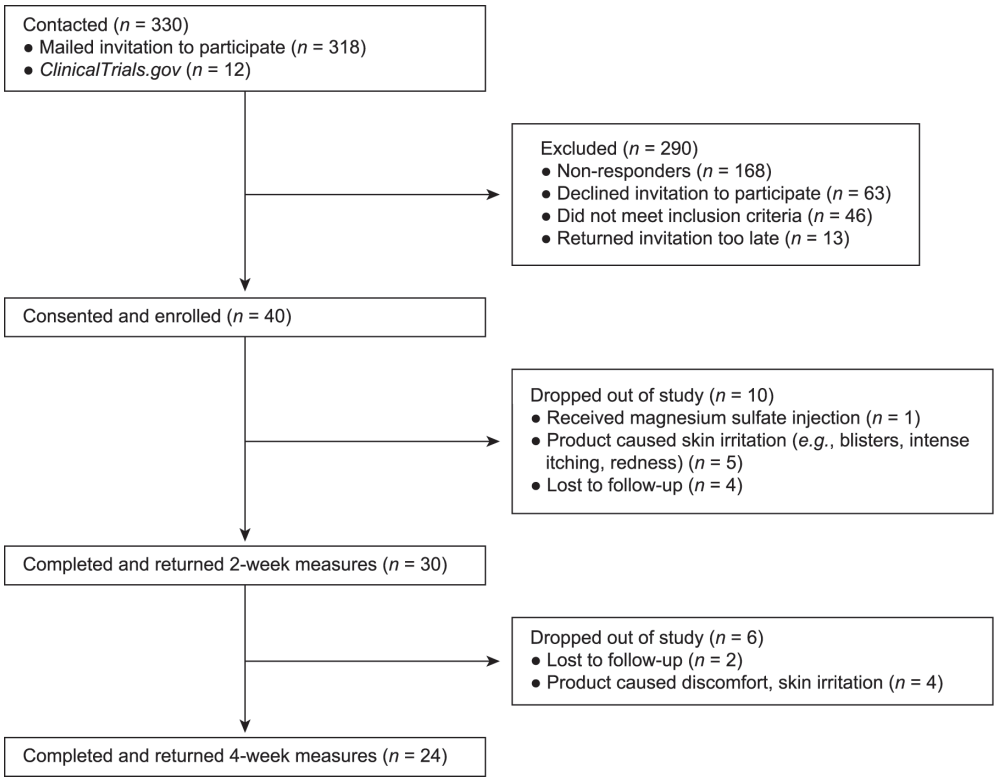

Figure 1 Flow chart of study enrollment and completion

Table 1 Demographic characteristics of the 40 study patients

Demographic characteristic	Value[a]	Demographic characteristic	Value[a]
Age (years)	57.2 (7.6)	Education level	
BMI (kg/m^2)	31.3 (8.5)	High school diploma or GED	7 (18.4)
Race		Some college or 2-year college degree	18 (47.4)
White	38 (95.0)	Four-year college degree	7 (18.4)
Black	1 (2.5)	Postgraduate studies	6 (15.8)
Unknown	1 (2.5)	Unknown	2 (5.3)
Ethnicity		Relationship status	
Non-Hispanic or Non-Latino	36 (90.0)	Married	24 (60.0)
Hispanic or Latino	1 (2.5)	Divorced	7 (17.5)
Unknown	3 (7.5)	Separated	1 (2.5)
Work status		Single	2 (5.0)
Employed	23 (60.5)	Widowed	3 (7.5)
Unemployed	2 (5.3)	Committed	3 (7.5)
Work-disabled	4 (10.5)		
Retired	7 (18.4)		
Full-time homemaker	1 (2.6)		
Other	1 (2.6)		
Unknown	2 (5.3)		

[a]Values are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables.
BMI: body mass index; GED: graduate equivalency degree.

Table 2 Intention-to-treat comparison of baseline, week 2, and week 4 questionnaire scores

Variable[a]	Baseline	Week 2	Baseline *vs* week 2[b] *P* value	Week 4	Week 2 *vs* week 4[b] *P* value	Baseline *vs* week 4[b] *P* value
FIQR score						
Function	12.68 (7.82)	9.79 (7.93)	<0.001	8.78 (7.45)	0.05	<0.001
Overall	11.10 (6.41)	7.93 (6.67)	<0.001	7.45 (6.44)	0.21	<0.001
Symptoms	28.31 (9.52)	24.86 (10.69)	0.009	24.05 (11.12)	0.13	0.002
Total	52.10 (21.62)	41.82 (23.94)	<0.001	39.52 (24.02)	0.01	<0.001
SF-36v2 score						
Physical function	33.94 (9.97)	35.94 (10.10)	0.003	36.72 (10.45)	0.15	0.003
Role physical	32.49 (10.65)	35.30 (11.91)	0.008	36.22 (12.14)	0.20	0.005
Bodily pain	33.85 (7.55)	35.11 (8.09)	0.10	35.92 (8.92)	0.25	0.05
General health	38.90 (9.42)	39.28 (10.85)	0.67	39.48 (10.76)	0.85	0.59
Vitality	37.42 (6.29)	38.51 (7.30)	0.24	39.45 (7.41)	0.14	0.04
Social function	36.67 (13.54)	38.85 (14.36)	0.08	38.85 (14.31)	>0.99	0.17
Role emotional	36.64 (14.96)	37.41 (15.72)	0.64	38.48 (16.04)	0.32	0.34
Mental health	43.95 (12.28)	44.52 (12.61)	0.58	45.36 (12.83)	0.24	0.31
Physical composite	32.78 (8.48)	34.85 (8.12)	0.006	35.56 (8.53)	0.18	0.003
Mental composite	42.32 (12.73)	42.84 (13.06)	0.64	43.85 (12.66)	0.19	0.31
QOL score						
Often migraines	2.55 (2.52)	2.60 (3.00)	0.89	2.75 (2.89)	0.41	0.51
Level of migraines	3.35 (3.10)	2.55 (2.61)	0.01	2.75 (2.90)	0.43	0.03
Often headaches	5.25 (3.23)	4.60 (3.14)	0.15	4.83 (3.16)	0.49	0.25
Level of headaches	5.00 (2.90)	4.15 (2.83)	0.02	4.45 (2.84)	0.23	0.10
Often cramps	5.03 (3.21)	3.88 (2.70)	0.02	4.30 (3.01)	0.15	0.18
Level of cramps	5.48 (2.94)	4.13 (2.65)	0.004	4.15 (2.67)	0.91	0.005
Often fatigue	9.53 (1.81)	7.48 (3.23)	<0.001	7.95 (3.16)	0.09	0.001
Level of fatigue	8.60 (2.15)	6.88 (2.76)	<0.001	7.05 (2.80)	0.24	<0.001
Often joint pain	9.08 (2.49)	7.48 (3.20)	<0.001	7.88 (3.07)	0.17	0.01
Level of joint pain	7.83 (2.57)	6.50 (2.80)	0.001	6.63 (2.88)	0.61	0.003
Often muscle pain	9.50 (1.78)	8.10 (2.48)	0.003	8.10 (2.75)	>0.99	0.008
Level of muscle pain	8.43 (2.42)	6.95 (2.54)	<0.001	7.08 (2.73)	0.55	0.002
Mean of all 12 QOL items	6.63 (1.41)	5.44 (1.88)	<0.001	5.66 (2.05)	0.08	<0.001

[a]Values are presented as mean (standard deviation); [b]all comparisons were made with paired *t* tests.
FIQR: Revised Fibromyalgia Impact Questionnaire; QOL: quality of life.

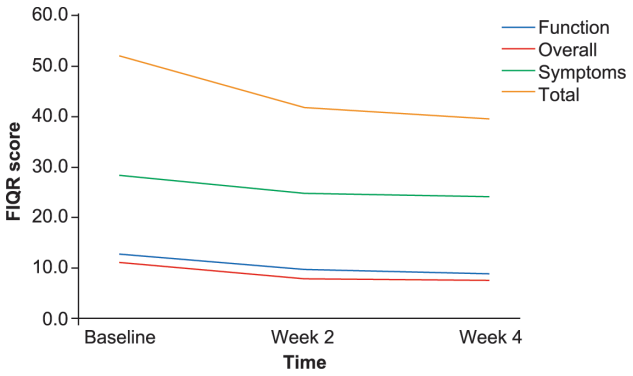

Figure 2 Changes in Revised Fibromyalgia Impact Questionnaire (FIQR) subscale and total scores over time

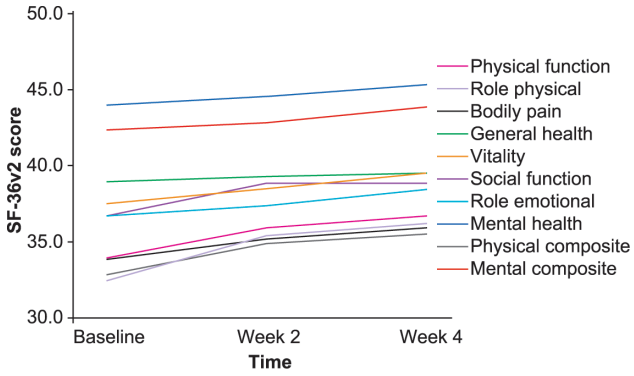

Figure 3 Changes in SF-36v2 Health Survey subscale and total scores over time

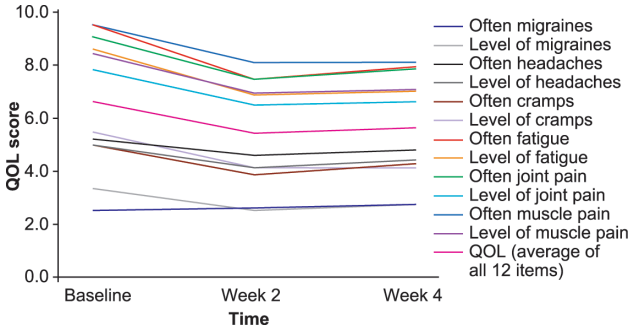

Figure 4 Changes in selected quality of life (QOL) symptoms over time

significantly by week 2, but no significant improvement was seen from baseline to week 4.

4 Discussion

The results of this pilot study suggest that transdermal $MgCl_2$ applied twice daily on the upper and lower limbs may be beneficial for patients with fibromyalgia. To our knowledge, this is the first study evaluating the effectiveness and feasibility of transdermal $MgCl_2$ for treatment of fibromyalgia symptoms, although several studies have evaluated the effect of oral magnesium supplements. Oral magnesium in the form of magnesium citrate (300 mg/d)

Table 3 Per-protocol comparison of baseline, week 2, and week 4 questionnaire scores

Variable[a]	Baseline (*n*=40)	Week 2 (*n*=32)	Baseline *vs* week 2[b] *P* value	Week 4 (*n*=24)	Week 2 *vs* week 4[b] *P* value	Baseline *vs* week 4[b] *P* value
FIQR score						
Function	12.68 (7.82)	8.53 (7.25)	<0.001	7.78 (7.02)	0.04	<0.001
Overall	11.10 (6.41)	7.03 (6.35)	<0.001	6.83 (5.78)	0.21	0.001
Symptoms	28.31 (9.52)	22.71 (10.34)	0.009	21.23 (11.22)	0.13	0.01
Total	52.10 (21.62)	37.56 (22.12)	<0.001	35.84 (22.56)	0.01	0.001
SF-36v2 score						
Physical function	33.94 (9.97)	37.14 (10.26)	0.003	37.13 (10.82)	0.15	0.03
Role physical	32.49 (10.65)	36.63 (12.37)	0.008	35.83 (12.32)	0.20	0.08
Bodily pain	33.85 (7.55)	36.38 (7.68)	0.10	37.06 (9.22)	0.25	0.15
General health	38.90 (9.42)	38.76 (11.33)	0.67	38.47 (11.49)	0.85	0.63
Vitality	37.42 (6.29)	38.90 (7.20)	0.24	39.33 (7.76)	0.14	0.16
Social function	36.67 (13.54)	40.49 (14.01)	0.08	40.26 (13.97)	>0.99	0.26
Role emotional	36.64 (14.96)	39.45 (15.44)	0.65	39.68 (16.91)	0.32	0.42
Mental health	43.95 (12.28)	45.83 (11.90)	0.58	48.05 (9.95)	0.24	0.37
Physical composite	32.78 (8.48)	35.42 (8.78)	0.006	35.55 (8.92)	0.18	0.03
Mental composite	42.32 (12.73)	44.33 (12.71)	0.64	46.18 (11.17)	0.20	0.36
QOL score						
Often migraines	2.55 (2.52)	2.25 (2.46)	0.89	2.63 (2.50)	0.42	0.55
Level of migraines	3.35 (3.10)	2.25 (2.13)	0.01	2.71 (2.82)	0.44	0.07
Often headaches	5.25 (3.23)	4.09 (3.02)	0.15	4.42 (3.26)	0.49	0.26
Level of headaches	5.00 (2.90)	3.59 (2.43)	0.01	4.04 (2.74)	0.23	0.14
Often cramps	5.03 (3.21)	3.47 (2.33)	0.02	3.52 (2.78)	0.15	0.08
Level of cramps	5.48 (2.94)	3.69 (2.31)	0.004	3.50 (2.34)	0.91	0.008
Often fatigue	9.53 (1.81)	6.91 (3.33)	<0.001	7.33 (3.46)	0.09	0.004
Level of fatigue	8.60 (2.15)	6.44 (2.73)	<0.001	6.54 (3.01)	0.24	0.001
Often joint pain	9.08 (2.49)	7.22 (3.17)	<0.001	7.67 (3.21)	0.17	0.05
Level of joint pain	2.55 (2.52)	2.25 (2.46)	0.89	2.63 (2.50)	0.42	0.55
Often muscle pain	3.35 (3.10)	2.25 (2.13)	0.01	2.71 (2.82)	0.44	0.07
Level of muscle pain	5.25 (3.23)	4.09 (3.02)	0.15	4.42 (3.26)	0.49	0.26
Mean of all 12 QOL items	5.00 (2.90)	3.59 (2.43)	0.01	4.04 (2.74)	0.23	0.15

[a]Values are presented as mean (standard deviation); [b]all comparisons were made with paired *t* tests.
FIQR: Revised Fibromyalgia Impact Questionnaire; QOL: quality of life.

has been shown to decrease the number of tender points, tender point index, FIQ scores, and Beck Depression Inventory scores in patients with fibromyalgia[28]. Abraham and Flechas[27] used a combination of magnesium (300–600 mg) and malate (1 200–2 400 mg) in 15 patients during an 8-week period. They reported a statistically significant improvement in the treatment group *vs* the placebo group in regard to pain and tenderness. Russell *et al*[30] studied the effect of Super Malic tablets, which contained 200 mg of malic acid and 50 mg of magnesium hydroxide, on patients with fibromyalgia. Although no positive effect was noted in that blinded low-dose trial, the authors reported a significant reduction of pain and tenderness with dose escalation and longer treatment duration in an open-label trial. Our results indicate that the effects of transdermal $MgCl_2$ may be similar to those observed in trials of oral magnesium supplements.

Since inconsistencies in bioavailability from one form of magnesium to the next have been a concern and since nearly all magnesium supplements share a common tendency to create a laxative effect, we believed that transdermal application may be a sensible alternative. Since patients with fibromyalgia are usually taking a multitude of oral medications, we believed that transdermal application may be better accepted than oral application in this patient population. Transdermal $MgCl_2$ solution is ideal for use in transdermal applications because it is rapidly absorbed through the skin and, therefore, can rapidly increase low or depleted levels of magnesium in the body[31]. We empirically advised 16 sprays of $MgCl_2$ twice daily, which equals 400 mg of magnesium. However, magnesium blood levels before and after therapy were not measured.

There are no known adverse effects to dermally applied $MgCl_2$ other than possible skin irritation. The frequency of skin irritation leading to discontinuation of the use of transdermal $MgCl_2$ was high in the present study, with 22.5% of patients citing skin irritation as the reason for discontinuing study participation. These skin irritations were not documented by a provider but reported by the patient, and the severity was not graded. The lack of information available regarding the symptoms of patients who experienced skin irritation and thus withdrew from the study is a limitation of this study. To conduct an intention-to-treat analysis, we carried forward the last observation, which could have resulted in inflated symptom scores. The consistency of the intention-to-treat analysis with the per-protocol analysis is reassuring, but further studies will need to consider the potential implications of problems such as skin irritation on outcomes. The high incidence of reported skin irritation is surprising since it is well documented that bathing in magnesium salts, the prevalent minerals in Dead Sea water, produces favorable effects on inflammatory skin diseases by improving skin barrier function and reducing skin roughness and inflammation[32].

Since the mechanisms responsible for symptom expression in fibromyalgia are complex and multifactorial, no single treatment is available for this condition, and a multitude of therapies — from pharmacologic to nonpharmacologic managements — have been applied. We are encouraged by the significant improvement in all 3 domains of the FIQR, which was developed specifically for evaluation of fibromyalgia, with the use of transdermal $MgCl_2$. We plan to proceed with further dose-finding studies using transdermal $MgCl_2$, which should include intracellular magnesium measurements and detailed documentation of skin irritation.

5 Conclusion

The results of this pilot study suggest that transdermal $MgCl_2$ applied twice daily on upper and lower limbs may be beneficial for patients with fibromyalgia. To our knowledge, this is the first study evaluating the effectiveness and feasibility of transdermal $MgCl_2$ for treatment of fibromyalgia symptoms. Further dose-finding studies with a larger sample size and including intracellular magnesium measurements in the setting of a randomized control trial seem indicated.

6 Competing interests

The authors declare no competing interests.

REFERENCES

1 Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA*. 2004; 292(19): 2388–2395.

2 Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Scheon RP. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia: report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990; 33(2): 160–172.

3 Wolfe F, Cathey MA. Prevalence of primary and secondary fibrositis. *J Rheumatol*. 1983; 10(6): 965–968.

4 Wolfe F, Cathey MA. The epidemiology of tender points: a prospective study of 1520 patients. *J Rheumatol*. 1985; 12(6): 1164–1168.

5 Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain*. 2001; 91(1–2): 165–175.

6 Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, Curatolo M. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. *Pain*. 2004; 107(1–2): 7–15.

7 Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, Lopez Y, MacKillip F. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis Rheum*. 1994; 37(11): 1593–1601.

8 Mountz JM, Bradley LA, Modell JG, Alexander RW, Triana-Alexander M, Aaron LA, Stewart KE, Alarcón GS, Mountz JD. Fibromyalgia in women: abnormalities of regional

cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. *Arthritis Rheum*. 1995; 38(7): 926–938.
9 Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med*. 1996; 156(10): 1047–1052.
10 Crofford LJ, Demitrack MA. Evidence that abnormalities of central neurohormonal systems are key to understanding fibromyalgia and chronic fatigue syndrome. *Rheum Dis Clin North Am*. 1996; 22(2): 267–284.
11 Holdcraft LC, Assefi N, Buchwald D. Complementary and alternative medicine in fibromyalgia and related syndromes. *Best Pract Res Clin Rheumatol*. 2003; 17(4): 667–683.
12 Rao JK, Mihaliak K, Kroenke K, Bradley J, Tierney WM, Weinberger M. Use of complementary therapies for arthritis among patients of rheumatologists. *Ann Intern Med*. 1999; 131(6): 409–416.
13 Herman CJ, Allen P, Hunt WC, Prasad A, Brady TJ. Use of complementary therapies among primary care clinic patients with arthritis. *Prev Chronic Dis*. 2004; 1(4): A12.
14 Wahner-Roedler DL, Elkin PL, Vincent A, Thompson JM, Oh TH, Loehrer LL, Mandrekar JN, Bauer BA. Use of complementary and alternative medical therapies by patients referred to a fibromyalgia treatment program at a tertiary care center. *Mayo Clin Proc*. 2005; 80(1): 55–60.
15 Ali M, Ali O. Fibromyalgia: An oxidative-dysoxygenative disorder (ODD). *J Integr Med*. 1999; 3: 17–37.
16 Bagis S, Tamer L, Sahin G, Bilgin R, Guler H, Ercan B, Erdogan C. Free radicals and antioxidants in primary fibromyalgia: an oxidative stress disorder? *Rheumatol Int*. 2005; 25(3): 188–190.
17 Chung CP, Titova D, Oeser A, Randels M, Avalos I, Milne GL, Morrow JD, Stein CM. Oxidative stress in fibromyalgia and its relationship to symptoms. *Clin Rheumatol*. 2009; 28(4): 435–438.
18 Iqbal R, Mughal MS, Arshad N, Arshad M. Pathophysiology and antioxidant status of patients with fibromyalgia. *Rheumatol Int*. 2011; 31(2): 149–152.
19 Cordero MD, Cotán D, del-Pozo-Martín Y, Carrión AM, de Miguel M, Bullón P, Sánchez-Alcazar JA. Oral coenzyme Q_{10} supplementation improves clinical symptoms and recovers pathologic alterations in blood mononuclear cells in a fibromyalgia patient. *Nutrition*. 2012; 28(11–12): 1200–1203.
20 Milne DB. Burtis CA, Ashwood ER. *Trace elements: Tietz textbook of clinical chemistry*. 3rd ed. Philadelphia: WB Saunders Company. 1999: 1280.
21 London M. *The role of magnesium in fibromyalgia*. (1994) [2015-01-02]. http://web.mit.edu/london/www/magnesium.html.
22 Magaldi M, Moltoni L, Biasi G, Marcolongo R. Changes in intracellular calcium and magnesium ions in the physiopathology of the fibromyalgia syndrome. *Minerva Med*. 2000; 91(7–8): 137–140. Italian with abstract in English.
23 Eisinger J, Zakarian H, Pouly E, Plantamura A, Ayavou T. Protein peroxidation, magnesium deficiency and fibromyalgia. *Magnes Res*. 1996; 9(4): 313–316.
24 Clauw D, Katz KWP, Rajan S. Muscle intracellular magnesium levels correlate with pain tolerance in fibromyalgia. *Arthritis Rheumat*. 1994; 37(9 Suppl): S213.
25 Eisinger J, Plantamura A, Marie PA, Ayavou T. Selenium and magnesium status in fibromyalgia. *Magnes Res*. 1994; 7(3–4): 285–288.
26 Romano TJ, Stiller JW. Magnesium deficiency in fibromyalgia syndrome. *J Nutr Med*. 1994; 4(2): 165–167.
27 Abraham GE, Flechas JD. Management of fibromyalgia: rationale for the use of magnesium and malic acid. *J Nutr Med*. 1992; 3(1): 49–59.
28 Bagis S, Karabiber M, As I, Tamer L, Erdogan C, Atalay A. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? *Rheumatol Int*. 2013; 33(1): 167–172.
29 Sendur OF, Tastaban E, Turan Y, Ulman C. The relationship between serum trace element levels and clinical parameters in patients with fibromyalgia. *Rheumatol Int*. 2008; 28(11): 1117–1121.
30 Russell IJ, Michalek JE, Flechas JD, Abraham GE. Treatment of fibromyalgia syndrome with Super Malic: a randomized, double blind, placebo controlled, crossover pilot study. *J Rheumatol*. 1995; 22(5): 953–958.
31 Watkins K, Josling PD. *A pilot study to determine the impact of transdermal magnesium treatment on serum levels and whole body CaMg ratios*. [2015-05-22]. http://www.aucoeurdestraditions.com/COEUR/HUILE_DE_MAGNESIUM_files/ETUDE.pdf.
32 Proksch E, Nissen HP, Bremgartner M, Urquhart C. Bathing in a magnesium-rich Dead Sea salt solution improves skin barrier function, enhances skin hydration, and reduces inflammation in atopic dry skin. *Int J Dermatol*. 2005; 44(2): 151–157.