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CLINICAL EVALUATION OF S-ADENOSYL-L-METHIONINE VERSUS TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION IN PRIMARY FIBROMYALGIA

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ABSTRACT

The effects of S-adenosyl-L-methionine (SAMe) and transcutaneous electrical nerve stimulation (TENS) were evaluated in a 6-week controlled trial of 30 patients with primary fibromyalgia. Unlike TENS, SAMe significantly decreased the total number of tender points, had a significant beneficial effect on the subjective symptoms of pain and fatigue, and significantly reduced the scores on the Hamilton Depression and Anxiety Rating Scales and Zung's Self-Rating Scale for Depression. At the end of treatment, patients in the TENS group exhibited significantly reduced scores on the Hamilton Anxiety Scale only.

INTRODUCTION

Primary fibromyalgia is a nonarticular rheumatism characterized by general and chronic pain in the skeletal muscle, stiffness, and well-defined pressure-sensitive areas or tender points. Up to 15% of the general population suffer from this disorder. The pathologic cause is still unknown, although it may result from an endocrine disorder (latent spasmophilia with blood calcium instability and subsequent neuromuscular hyperexcitability) or a pain modulation disorder, as postulated by Smythe.[1]

The aim of this study was to outline the most prominent clinical features of primary fibromyalgia and to compare two therapeutic approaches: S-adenosyl-L-methionine (SAMe), a pharmaceutic approach, and transcutaneous electrical nerve stimulation (TENS), a physiotherapeutic approach. SAMe was chosen as the pharmacologic therapy because it is a physiologic methyl donor that has been reported to be effective in primary fibromyalgia.[2–5]

PATIENTS AND METHODS

After giving informed consent, 30 patients (29 women and one man) ages 31 to 75 years (mean age, 51 ± 9.5 years) with primary fibromyalgia entered

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the study. Diagnoses were made using the criteria described by Goldenberg[6] (table). A questionnaire was used for preliminary evaluation.

Patients were excluded from the study if they had an associated pathologic condition, such as rheumatoid arthritis, other rheumatic diseases, or hypothyroidism, that would complicate the diagnosis of primary fibromyalgia. Patients with severe renal, liver, or cardiovascular diseases; those receiving typical and atypical antidepressant agents, nonsteroidal antiinflammatory drugs (NSAIDs), or systemic or topical corticosteroids during the preceding 4 weeks; and patients who were not compliant were also excluded.

The study included a preliminary washout period of 7 days during which NSAIDs and neuropsychoactive drugs were not permitted; analgesic agents such as paracetamol were allowed only occasionally. After completing the washout period, the patients were randomly assigned to receive 6 weeks of treatment with either SAMe or TENS. Patients in the SAMe group (n = 15) received one 200-mg vial intramuscularly at 8 AM and two 200-mg tablets, one at 12 noon and one at 6 PM. Patients in the TENS group (n = 15) completed five morning sessions a week (Monday to Friday), as usual. At each session, four tender points were treated for 20 minutes each; the tender points were chosen by the investigator after consultation with the patient. A rectangular, continuous, 70-microsecond current at a frequency of 80 to 100 cps was used during the TENS sessions. The minimum intensity capable of causing a "pleasant tingling" sensation in the patient was used.

Clinical evaluations were made at enrollment (T −7); at baseline after the 7-day washout period (T0); and after 2 weeks (T14), 4 weeks (T28), and 6 weeks (T42) of treatment. The evaluations included manual and instrumental assessment of tender points, assessment of anxiety and depression, evaluation of subjective parameters, and laboratory tests.

Pain during manual assessment of tender points was graded on a scale of 0 (no tenderness) to 4 (maximum tenderness) for each point. Investigators palpated the unilateral sites at the interspinous ligaments of C4-C5 and L4-L5, the bilateral sites (right and left) at the upper borders of the

Table. Diagnostic criteria for primary fibromyalgia.*[6]

Major criteria:	1. Diffuse chronic pain or stiffness at three or more anatomic sites for more than 3 months 2. Tender points at characteristic sites 3. No further conditions accounting for skeletal muscle symptoms
Minor criteria:	1. Chronic headache 2. Sleep disorders 3. Pain at neck, shoulders, or upper back 4. General fatigue or malaise 5. Subjective swelling, paresthesias, and morning stiffness

* Primary fibromyalgia diagnosis = 3 major + 3 minor criteria.

trapezius, the second costochondral junctions, the lateral epicondyles, the supraspinatus origins (at the medial border of the scapula), the upper outer quadrants of the buttocks, and the medial fat pads of the knees. The total number of tender points and the total tender point score (sum of all 14 individual tender point scores) were computed at each time and for each patient.

The instrumental assessment of tender points at the trapezius muscle, elbow, and knee was made using a digital dolorimeter (NIM, S.r.L., Verona, Italy). The mean of two measures was expressed in kg/cm^2.

The following psychiatric rating scales were used: the 21-item Hamilton Rating Scale for Depression (HRSD); the Hamilton Rating Scale for Anxiety (HRSA); Zung's Self-Rating Scale for Depression; and the face scale, which was scored from 1 (very happy) to 20 (very sad). Subjective evaluations of pain, fatigue, sleep, and well-being were made using a 10-cm visual analog scale. Laboratory tests (complete blood picture, including platelet count, erythrocyte sedimentation rate, creatinine phosphokinase, transaminases, and alkaline phosphatase; bilirubinemia; gamma-GT; creatininemia; and urinalysis) were performed at T −7 and T42.

The overall evaluation of efficacy was performed at the end of the treatment (T42). The severity of illness was rated on a scale of 1 (normal) to 7 (very serious); global improvement, from 1 (considerably improved) to 7 (considerably worsened); and efficacy index, from 1 (very good therapeutic effect/no adverse effects) to 16 (unchanged or worsened/predominant adverse effects). The pharmacologic or physiotherapeutic treatments and rating scales were administered by different investigators.

Statistical Analysis

The total tender point score, all four visual analog scales, and the HRSD, HRSA, and Zung psychiatric rating scales, which are parameters that are usually normally distributed, were analyzed by split-plot analysis of variance. Tukey's test was used for multiple individual comparisons. All other parameters were analyzed by nonparametric tests. Two-way Friedman's test within each treatment group was used for each tender point score, the total number of tender points, and the face scale. Multiple comparisons were performed using Newman-Keuls tests. The Mann-Whitney nonparametric test between groups was used for comparisons of groups before and after treatment, each tender point score and the total number of tender points, the face scale, and the overall evaluation of efficacy.

RESULTS

Of the 30 patients studied, 14 women and 1 man were treated with SAMe and 15 women were treated with TENS. There were no significant differ-

ences between treatment groups with regard to demographic data. The mean duration of symptoms before the study was 64.8 ± 57.7 months. Two (6.7%) patients reported that their pain was localized; the remaining 28 (93.3%) patients reported diffuse pain. Pain was described as continuous by 18 (60%) patients and as intermittent by 12 (40%) patients. A physical or psychic trauma was observed before the onset of symptoms in 19 (63.3%) patients; paresthesias occurred in 26 (86.7%). Nineteen (63.3%) patients had family histories of disorders similar to primary fibromyalgia, while only four (13.3%) patients had family histories of rheumatic or autoimmune diseases.

Twenty-nine (96.7%) patients complained of weakness, and 24 (80%) reported morning stiffness. Sixteen (53.3%) patients complained of headache, which was migrainous in three (10%) patients. A total of 19 (63.3%) patients reported irritable bowel syndromes. Twenty-five (83.3%) patients took psychotropic drugs or reported symptoms of anxiety or depression.

Examination of tender points under pressure and by digital dolorimeter, and assessment of analog scales for pain, fatigue, and sleep both at T −7 and T0 (baseline) showed that the two groups of patients were homogeneous and comparable. The individual tender point analysis within groups showed a significant difference with SAMe treatment on the right and left gluteus maximus only ($P < 0.05$). No significant effects were observed for this parameter with TENS treatment. Groups significantly differed at the end of treatment (T42) for tenderness at the right gluteus maximus ($P < 0.05$).

The total number of tender points decreased significantly only in the SAMe group ($P < 0.01$). The two groups differed significantly at the end of treatment ($P = 0.05$) in the total number of tender points ($P < 0.05$) (Figure 1).

The total tender point score improved significantly ($P < 0.01$) during SAMe treatment (Figure 1). There was a significant treatment-to-time interaction ($P < 0.05$) and a significant time effect in the SAMe group only ($P < 0.01$, T0 versus T42). At the end of treatment, there was a significant difference ($P < 0.05$) between groups in the total tender point score. The instrumental evaluation of tender points between groups revealed no relevant differences.

In the subjective evaluation, significant time effects were observed only in the SAMe group for pain and fatigue; in this group, significant differences in these two parameters were also seen at the end of treatment ($P < 0.05$) (Figure 2). The SAMe treatment had no effect on sleep or well-being, and no significant effects of TENS treatment on any of the subjective parameters were recorded.

On the psychiatric rating scales, the SAMe group showed a significant decrease in the HRSD and HRSA as early as day 14 of treatment (Figure 3). A significant decrease on the Zung scale was seen in the last 2 weeks

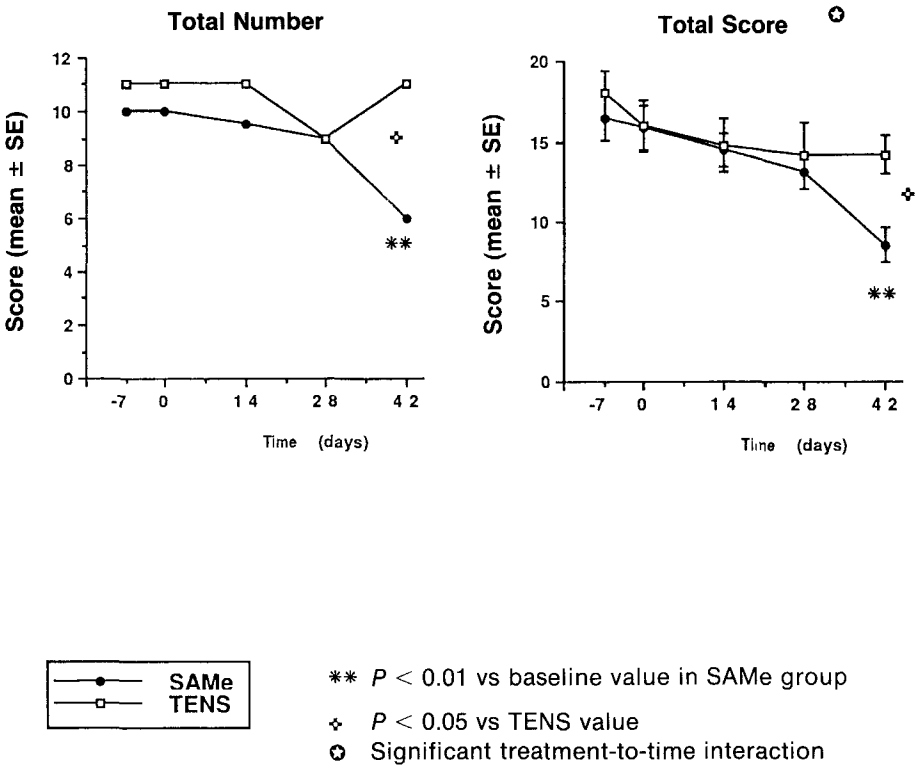

Figure 1. Effects of treatment with S-adenosyl-L-methionine (SAMe) and transcutaneous electrical nerve stimulation (TENS) on the total tender point number and score.

of treatment only (Figure 3). In addition, the treatment-to-time interaction was significant for the HRSD ($P < 0.01$). No significant effects on the face scale were noted. During TENS therapy, significant effects on the HRSA were observed at the end of treatment only (Figure 3).

On the overall evaluation of efficacy, no significant differences were noted between groups. Similarly, no changes were found in the laboratory tests performed. Both treatments were well tolerated and no side effects were reported.

After concluding the study, we reexamined the group of patients who did not respond to TENS therapy (10 of 15). Six of these patients agreed to undergo a treatment course with SAMe. Surprisingly, five of these patients showed a decrease in tender point number and score, as well as in the HRSD and HRSA scores; an improvement in the sleep pattern was also found. Only two patients exhibited a reduction in Zung's scale score and well-being.

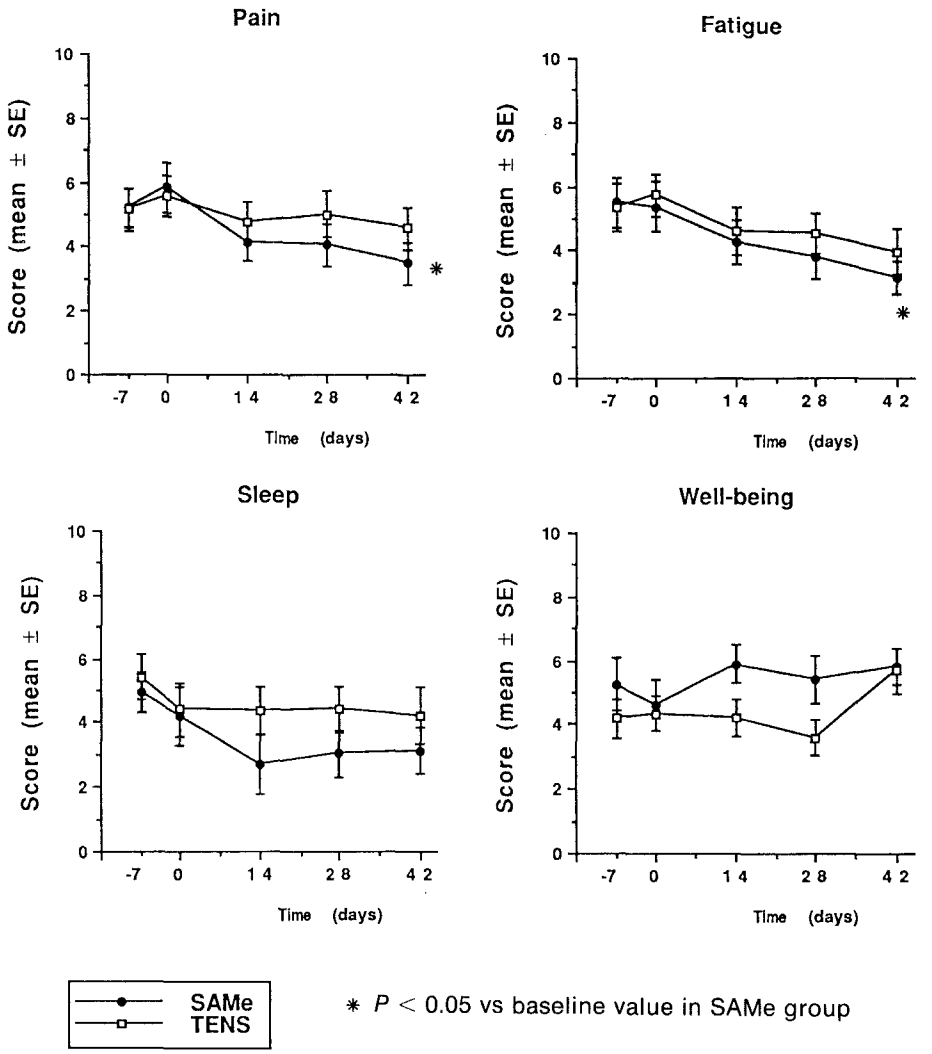

Figure 2. Effects of treatment with S-adenosyl-L-methionine (SAMe) and transcutaneous electrical nerve stimulation (TENS) on subjective parameters measured by a visual analog scale.

DISCUSSION

The results of our controlled clinical trial indicate that SAMe is effective in relieving the signs and symptoms of primary fibromyalgia. In addition, it can significantly improve the overlying depressive mood. The importance of psychological discomfort in the pathogenesis of primary fibromyalgia is well-known,[7,8] and it accounts for the pronounced beneficial effects

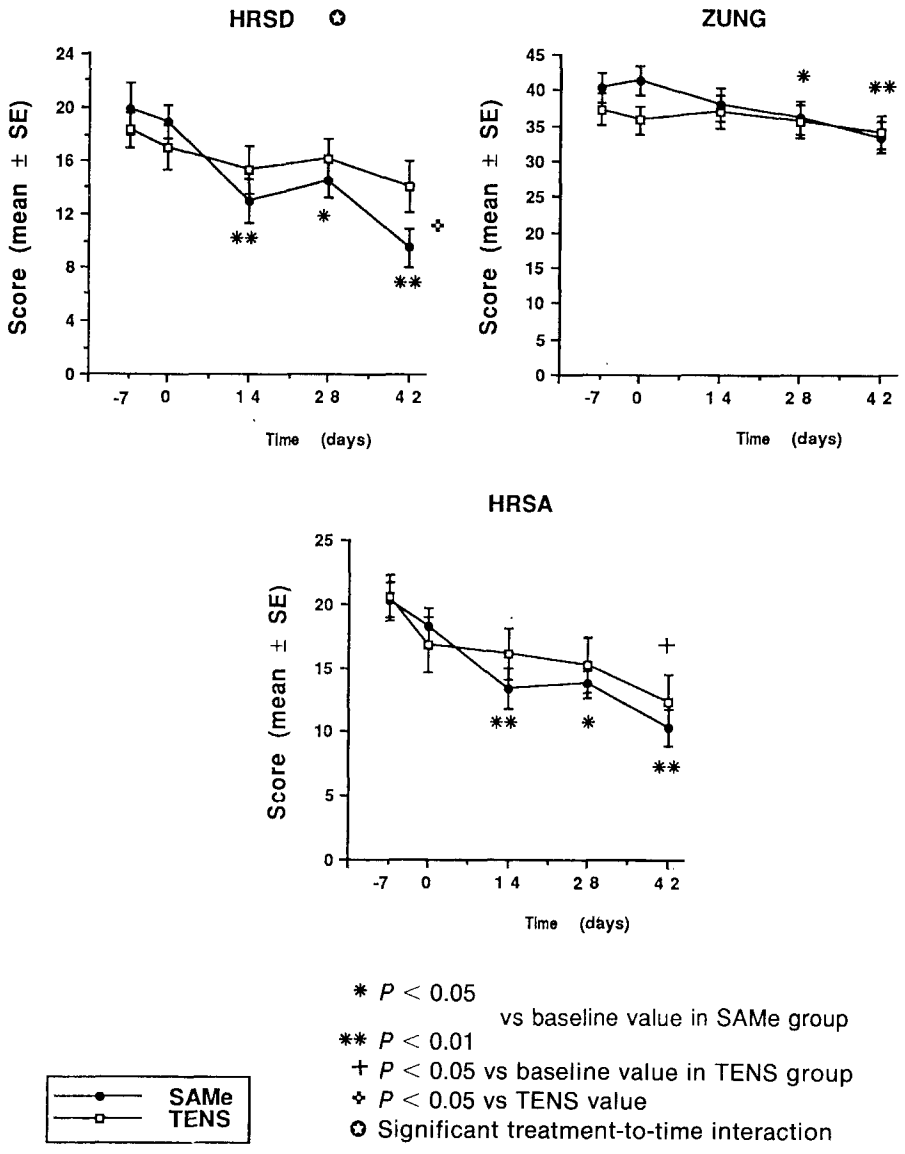

Figure 3. Effects of treatment with S-adenosyl-L-methionine (SAMe) and transcutaneous electrical nerve stimulation (TENS) as measured by the Hamilton Rating Scale for Depression (HRSD), Zung's Self-Rating Scale for Depression, and the Hamilton Rating Scale for Anxiety (HRSA).

of placebo observed in up to 50% of patients with this disorder.[8,9] In this respect, the response to TENS as measured by the HRSA could be ascribed to the increased attention given to the patients by the investigators. On the other hand, primary fibromyalgia has proved to be responsive to standard antidepressant agents, such as amitriptyline,[10,11] maprotiline,[12] and clomipramine,[12] whereas it is usually unresponsive to steroidal and non-steroidal anti-inflammatory drugs.

Unlike standard antidepressants, SAMe is devoid of adverse effects. Our study shows that SAMe has some beneficial effects in patients with primary fibromyalgia and could be useful in the treatment of this condition. However, further investigations are needed to validate the effectiveness of this drug in a larger number of patients treated for longer periods of time.

Acknowledgment

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