Original Article

Journal of Geriatric Psychiatry and Neurology
1-9

DOI: 10.1177/0891988720915524
journals.sagepub.com/home/jgp
SAGE

High-Frequency External Muscle Stimulation Reduces Depressive Symptoms in Older Male Veterans: A Pilot Study

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Abstract

Objective: Late-life depression (LLD) is a severe public health problem. Given that pharmacological treatments for LLD are limited by their side effects, development of efficient and tolerable nonpharmacological treatment for LLD is urgently required. This study investigated whether high-frequency external muscle stimulation could reduce depressive symptoms in LLD. **Methods:** Twenty-two older male veterans with major depression were recruited and randomized into a treatment (n = 9) or sham control group (n = 13). The groups received high-frequency external muscle stimulation or sham intervention 3 times per week for 12 weeks. Clinical symptoms and muscle strength were evaluated at baseline and every 2 weeks. **Results:** The 2 groups were homogeneous in age, baseline clinical symptoms, and muscle strength. The treatment group showed significant improvement in depression and anxiety scores and muscle strength (all $P < .01$), whereas the control group showed no significant change after the 12-week follow-up. Compared to the control group, the treatment group showed significant improvements in depression (Geriatric Depression Scale, $P = .009$; Hamilton Depression Rating Scale, $P = .007$) and anxiety scores (HAMA, $P = .008$) and muscle strength (all $P < .001$). Changes in depression and anxiety levels were significantly correlated with changes in muscle strength after the study. In the treatment group, we observed a trend of correlation between the reduction in depression and muscle strength gains. **Conclusion:** High-frequency external muscle stimulation appears to be an effective treatment for older patients with LLD. Large studies with more tests and/or conducted in different populations are warranted to validate these preliminary findings.

Keywords

older people, electric muscle stimulation, major depression, muscle strength

Introduction

Late-life depression (LLD), which increases with age, is the leading cause of geriatric psychiatric problems.[1] Considering its recurrence, chronicity, association with cognitive decline, ischemic white matter lesions, and mortality, LLD is a severe public health problem.[1,2] Late-life depression differs from early-onset major depression with distinctive pattern of cortical excitability,[3] maintenance of treatment response[4] as well as a higher risk of progression into overt dementia.[5] Although effective treatments are available, approximately one-third of patients with depression fail to respond to traditional antidepressant treatment. Moreover, older patients are more vulnerable to antidepressant side effects such as fatigue, drowsiness, fall, dry mouth, blurred vision, constipation as well as interactions with other medicines.[1,6] Pharmacological treatments for LLD are limited by their side effects, while existing non-pharmacological treatments such as repetitive transcranial magnetic stimulation (rTMS) and psychotherapy are costly and

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Received 7/12/2019. Received revised 1/03/2020. Accepted 1/20/2020.

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time-consuming; therefore, development of efficient and tolerable nonpharmacological treatment for LLD is urgently required.

For older adults, epidemiologic studies have shown that low muscle strength is associated with more depressive symptoms.[7,8] Decrease in muscle strength could affect physical independence and autonomy in the elderly individuals, which is linked to geriatric depression.[9] A cross-sectional study on 4298 Korean adults aged 19 to 80 years reported that lower muscle strength was associated with an increased risk of depression in the older population. Moreover, muscle strength was inversely associated with depression severity.[7] Brown et al reported a significant cross-sectional association between depressive symptoms and lower limb muscle fatigability in 1803 older adults aged 70 to 79 years in the United States.[8] Moreover, lower limb muscle mass and strength is negatively associated with depressive symptoms.[10,11] According to a cohort study of Japanese adults aged 40 to 79 years, people with low muscle strength had a high risk of depressive symptoms.[12] Lino et al found that decreased muscle strength was significantly associated with depression in Brazilians aged 60 years and older.[13] Finally, exercise and strength training have the ability to reduce the risk of depression in older adults.[1] These results suggest that increasing muscular strength may potentially reduce LLD.

Studies with TMS indicate that impaired central and peripheral plasticity may underlie the mechanistic pathophysiology of both major depression and cognitive decline in the elderly indiviuals,[14] providing the rationale for innovative neuromodulatory interventions.[15,16] High-frequency external muscle stimulation is the percutaneous electrical stimulation of skeletal muscles using high frequencies to produce a muscle contraction and consequently to increase muscle strength.[17] The most often stimulated muscle group is the femoral muscles.[18,19] The current intensity ($\leq$350 mA) and the frequency (4.096 and 32.768 Hertz) of stimulation are adjusted simultaneously according to the patient's electrosensitivity; the higher the frequency, the more energy can be introduced.[19] This method is widely adopted for orthopedic rehabilitation, sports medicine, and treatment of peripheral nervous system lesions.[17] It is effective in the prevention of muscle atrophy following denervation, regaining muscle strength during rehabilitation to shorten rehabilitation time after injuries,[20] and treatment of symptomatic diabetic polyneuropathy.[21] Previous studies have reported that electrical muscle stimulation (EMS) benefits the muscle strength of older people with prefrailty[22] or knee osteoarthritis,[23] patients with chronic heart failure or chronic obstructive pulmonary disease,[24] and those with critical illness.[25]

To our knowledge, no studies have explored the therapeutic effect of high-frequency EMS on LLD. However, Humpert et al reported that high-frequency EMS could improve sleeping disturbances, a symptom associated with depression, in patients with type 2 diabetes.[26] Moreover, EMS can be viewed as a form of exercise and mobilization that does not require active participation.[20,23] Because older people with depression are prone to fatigue and physical inactivity,[1] high-frequency EMS could be applied in LLD to reduce depressive symptoms through its effect of muscle strength improvement.[17,22,23] Compared to conventional pharmacological and nonpharmacological treatments, high-frequency EMS is a noninvasive intervention with lesser side effects, better accessibility, and higher cost-effectiveness. Therefore, the aim of our study was to investigate whether high-frequency EMS is beneficial in the treatment of depressive symptoms and potentially becomes an alternative or adjunct treatment option in older people with depression.

Methods

Participants

To detect a mean difference of at least 1.5 between the treatment and the control groups with an α level of 0.05 and a power of 80% and with an estimated 20% attrition rate, at least 11 participants per group were required at baseline. Twenty-two older male veterans meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for major depression were recruited by board-certified geriatric psychiatrists from Taipei Veterans General Hospital. Elderly veterans are a distinct minority group in Taiwan who were forced to retreat to Taiwan after the Communists gained control of Mainland China in 1949. Most of them are male, have a minimal education, and live in government-sponsored long-term care institutions called veterans' homes.[27] Participants were required to have the following criteria: fluency in Chinese; provided written consent; aged 60 years or older; and no history of neurological disease, seizures, head injury with loss of consciousness within the past 5 years, stroke or transient ischemic attack, drug or alcohol abuse within the past 5 years, overt dementia, or major psychotic disorders, including schizophrenia or schizoaffective disorder. Patients were required to have been on stable doses of selective serotonin reuptake inhibitors for at least 4 weeks. This study was approved by the Taipei Veterans General Hospital Internal Review Board.

Study Design

Twenty-two older veterans were randomized into 2 groups: high-frequency EMS treatment (n = 9) or sham control group (n = 13). The treatment group received 12 weeks of high-frequency EMS intervention 3 times per week. In the sham group, patients received the same procedure, but the electrodes were not connected to the current source. They were requested to report when they experienced any slightest sensation of tingling under the electrodes. Although no current was applied, all patients in the sham group reported experiencing a tingling sensation, thus justifying the credibility of the control condition. All participants accepted evaluation of their clinical psychiatric symptoms using the Geriatric Depression Scale (GDS),[28] Hamilton Depression Rating Scale (HAMD),[29] Hamilton Anxiety Rating Scale,[30] and University of California, Los Angeles Loneliness Scale[31] and their muscle strength at baseline and every 2 weeks (6 follow-ups).

Manual Muscle Testing

Muscle strength of bilateral ankle dorsiflexors, quadriceps femoris, gluteus maximus, and gluteus medius were assessed by a physical therapist at Taipei Veterans General Hospital. Participants were instructed to lie supine with legs extended, without any pillow underneath their heads. During muscle strength testing, participants were instructed to exert effort using specific muscles according to standard manual muscle testing methods.[32,33] A score was assigned depending on how much the participant was able to resist the pressure applied by the physical therapist.[34] The score for each muscle group was then transformed to a value on a zero to 10-point scale.

High-Frequency External Muscle Stimulation

Patients were treated with a HiToP device (HighTone Power Therapy; GBO Medizintechnik, Rimbach, Germany) to externally stimulate muscle contraction for <60 minutes, 3 times per week for 12 weeks of treatment (36 treatment sessions).[26] The electrodes were placed on the femoral muscles. In the treatment group, external muscle stimulation was performed using a device that generates pulse widths of ≤350 mA at ≤70 V. We used an initial frequency of 4096 Hz which was increased to 32 768 Hz within 3 seconds; the maximum frequency was used for 3 seconds and then modulated down from 32 768 to 4096 Hz. For each patient, the intensity of the electrical therapy was adjusted in the event of pain or uncomfortable sensation.

Statistical Analysis

Descriptive analyses included assessment of the distribution of all variables; data are presented as means ± standard deviation or numbers. Normality of distribution was confirmed through Kolmogorov-Smirnov testing. The unpaired Student t test or Mann-Whitney U test (for non-normal distributions) was used for between-group comparisons. Categorical variables were compared through χ^2 testing.

Repeated measures analysis of variance (ANOVA) was used to compare scores within and between the 2 groups. Within-group comparisons were made by comparing the 7 measurements (baseline and 6 follow-ups) recorded within each group over time during the trial. Between-group comparisons were assessed by fitting an interaction term between changes in score over time and the group variable (treatment and control). Student t tests were also used to compare the scores between the 2 groups at each time point—baseline and the 6 follow-ups. Pearson coefficients (r) were used to analyze the correlation between the changes in depression severity and changes in the levels of muscle strength over the 12 weeks. The SPSS 16.0 software package was used for statistical analysis. A P value of less than .05 was considered statistically significant.

Table 1. Patient Demographics and Primary Baseline Data.[a]

	Total (n = 16)	Control (n = 9)	Treatment (n = 7)	P
Age	84.6 (7.1)	84.3 (8.1)	85.0 (6.2)	.860
Education	6.7 (6.4)	8.8 (6.9)	4.0 (4.9)	.145
Baseline affective status				
GDS	6.9 (2.5)	6.2 (3.0)	7.9 (1.6)	.213
HAMD	11.1 (3.8)	10.4 (4.6)	12.0 (2.6)	.441
HAMA	9.9 (5.0)	9.3 (5.7)	10.7 (4.4)	.605
UCLA-LS	44.6 (9.9)	44.6 (8.2)	44.7 (12.5)	.976
Baseline muscle strength				
Left ankle dorsiflexors	7.56 (0.6)	7.6 (0.5)	7.6 (0.8)	.962
Right ankle dorsiflexors	7.56 (0.6)	7.8 (0.7)	7.3 (0.5)	.124
Left quadriceps femoris	7.13 (0.8)	7.3 (0.7)	6.8 (0.9)	.255
Right quadriceps femoris	7.06 (0.9)	7.3 (0.7)	6.7 (1.0)	.157
Left gluteus maximus	7.00 (0.8)	7.0 (0.9)	7.0 (0.8)	1.000
Right gluteus maximus	7.25 (0.9)	7.1 (0.9)	7.4 (1.0)	.518
Left gluteus medius	5.19 (1.0)	5.1 (0.8)	5.3 (1.4)	.753
Right gluteus medius	5.06 (0.8)	5.0 (0.9)	5.1 (0.9)	.752

Abbreviations: GDS, Geriatric Depression Scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; UCLA-LS, UCLA Loneliness Scale.
[a]Muscle strength assessed with the Manual Muscle Testing scale.

Results

At the 12-week evaluation, 16 participants had completed the treatment and all assessments and were included in the analysis. Two of 9 participants in the treatment group dropped out; one moved to another city and one withdrew because of muscle pain. In the sham control group, 4 of 13 participants withdrew; 3 were lost to follow-up, and 1 had an accidental fall and consequent hip fracture. No participants developed severe adverse effects after completing the course. The 2 groups were homogeneous in terms of age, education, baseline clinical symptoms, and muscle strength (Table 1).

Concerning the change in clinical symptoms before and after intervention (within-group comparisons), treatment group showed significant decreases in severity of depression and anxiety symptoms after the 12-week high-frequency EMS intervention, and scores for these symptoms were reduced by over 50% by the end (58% on the GDS, 55% on the HAMD, and 54% on the HAMA). The reduction in depression and anxiety levels appeared to be gradual and continuous through the end of the study (GDS, $P < .001$; HAMD, $P < .001$; HAMA, $P < .001$ by repeated measures ANOVA; Figure 1A-C, supplemental Table S1). The level of loneliness did not change significantly after the 12-week treatment (UCLA Loneliness Scale, $P = .158$ by repeated measures ANOVA; Figure 1D, supplemental material Table S1). The control group showed no prominent changes in depression, anxiety, or loneliness after the 12-week follow-up. In between-group comparisons, the treatment group showed significant reductions in depression and anxiety symptoms compared to the control group (GDS, $P = .009$; HAMD, $P = .007$; HAMA, $P = .008$ by repeated measures ANOVA; Figure 1A-C). The difference in change of

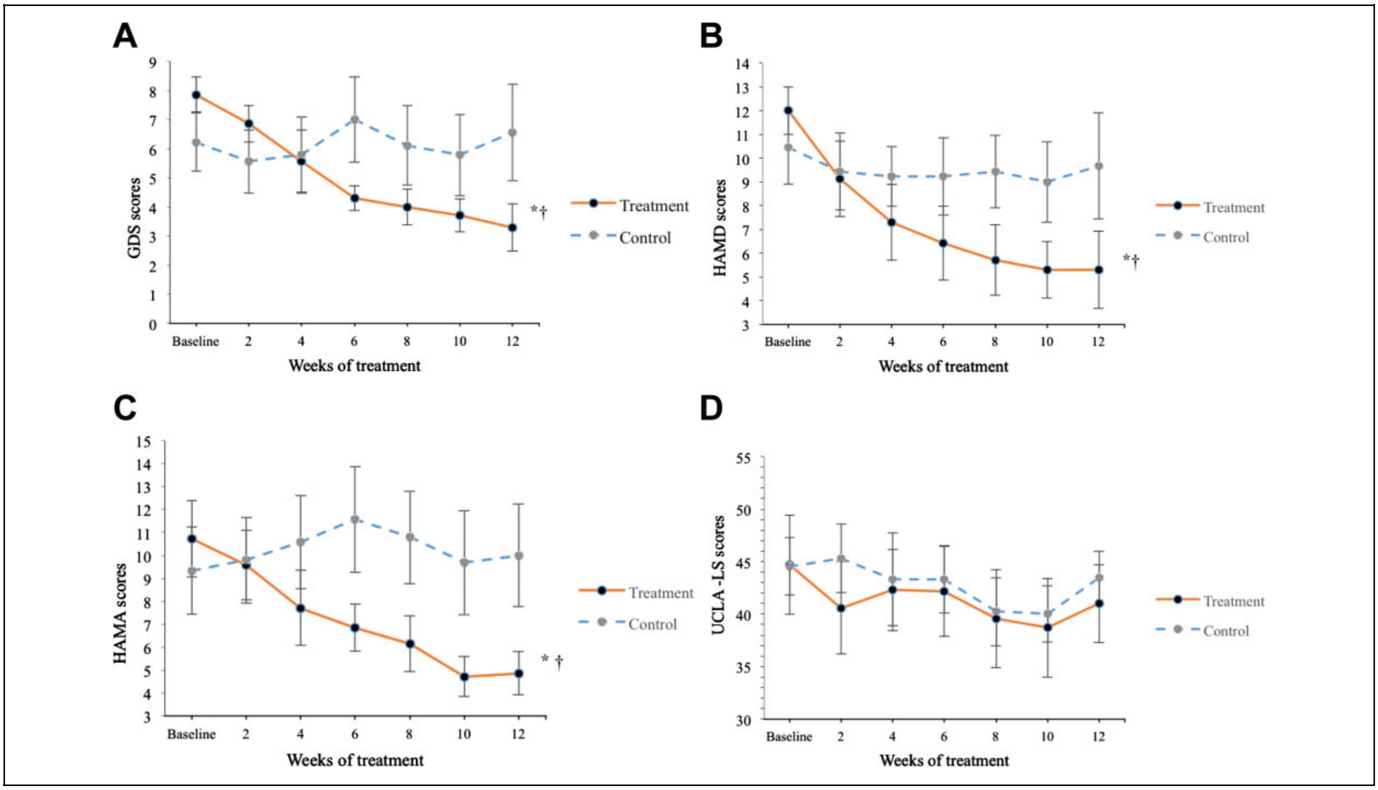

Figure 1. Effects of high-frequency external muscle stimulation (treatment vs control). A, Geriatric Depression Scale score ($^{\dagger}P = .009$). B, Hamilton Depression Rating Scale score ($^{\dagger}P = .007$). C, Hamilton Anxiety Rating Scale score ($^{\dagger}P = .008$). * $P < .001$ by repeated measures analysis of variance (ANOVA) in treatment group. D, UCLA-LS ($P = .762$ by repeated measures ANOVA). Treatment group: solid line (n = 7); sham control group: dashed line (n = 9). Data were represented as means with standard error bars. GDS indicates Geriatric Depression Scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; UCLA-LS, UCLA Loneliness Scale.

loneliness between groups was not significant ($P = .762$ by repeated measures ANOVA; Figure 1D).

In the assessment of muscle strength before and after intervention (within-group comparisons), the treatment group revealed increases in strength in all muscles (left ankle dorsiflexors, $P = .001$; right ankle dorsiflexors, $P < .001$; left quadriceps femoris, $P < .001$; right quadriceps femoris, $P < .001$; left gluteus maximus, $P = .001$; right gluteus maximus, $P = .002$; left gluteus medius, $P = .002$; right gluteus medius, $P < .001$ by repeated measures ANOVA; Figure 2, supplemental Table S2). In the control group, no significant change was observed in any muscle strength at the 12-week follow-up. Between-group comparisons revealed that the treatment group experienced significant increases in the strength of all muscles compared to the control group ($P < .001$ for bilateral ankle dorsiflexors, quadriceps femoris, gluteus maximus, and gluteus medius by repeated measures ANOVA; Figure 2, supplemental Table S2).

Finally, in treatment group, we observed significant correlation between the reduction in depressive severity and muscle strength gains over 12 weeks (GDS scores and left gluteus medius, $r = -.792$, $P = .034$; HADM scores and right ankle dorsiflexors, $r = .818$, $P = .024$). However, such significances disappeared after corrections for multiple testing (Table 2).

Discussion

This prospective clinical pilot study showed that high-frequency EMS can reduce symptoms of depression and anxiety in older male veterans. This nonpharmacological treatment was well tolerated and may offer a new option for treatment of geriatric depression. The therapeutic effects were pronounced, and symptoms were reduced by over 50%. This reduction in symptoms can be considered a strong and clinically relevant improvement.[35] Moreover, high-frequency EMS resulted in increased strength of the quadriceps femoris (to which it was directly applied) and muscle groups of the lower extremities. Finally, reduction in the depression levels correlated with muscle strength gain after the 12-week course of high-frequency EMS treatment.

Late-life depression is generally accepted to be a chronic, relapsing disorder that is frequently not completely responsive to treatment but is prone to treatment-related side effects.[1] Therefore, feasibility, compliance, and adoption of any effective treatment are paramount. In our treatment group, 78% of participants continued the treatment, which is higher than the adherence rate for antidepressants.[36] Consistent with prior high-frequency EMS studies in medical patients,[21,26] our study suggests that EMS is a well-tolerated treatment option for LLD, with potential to enhance compliance.

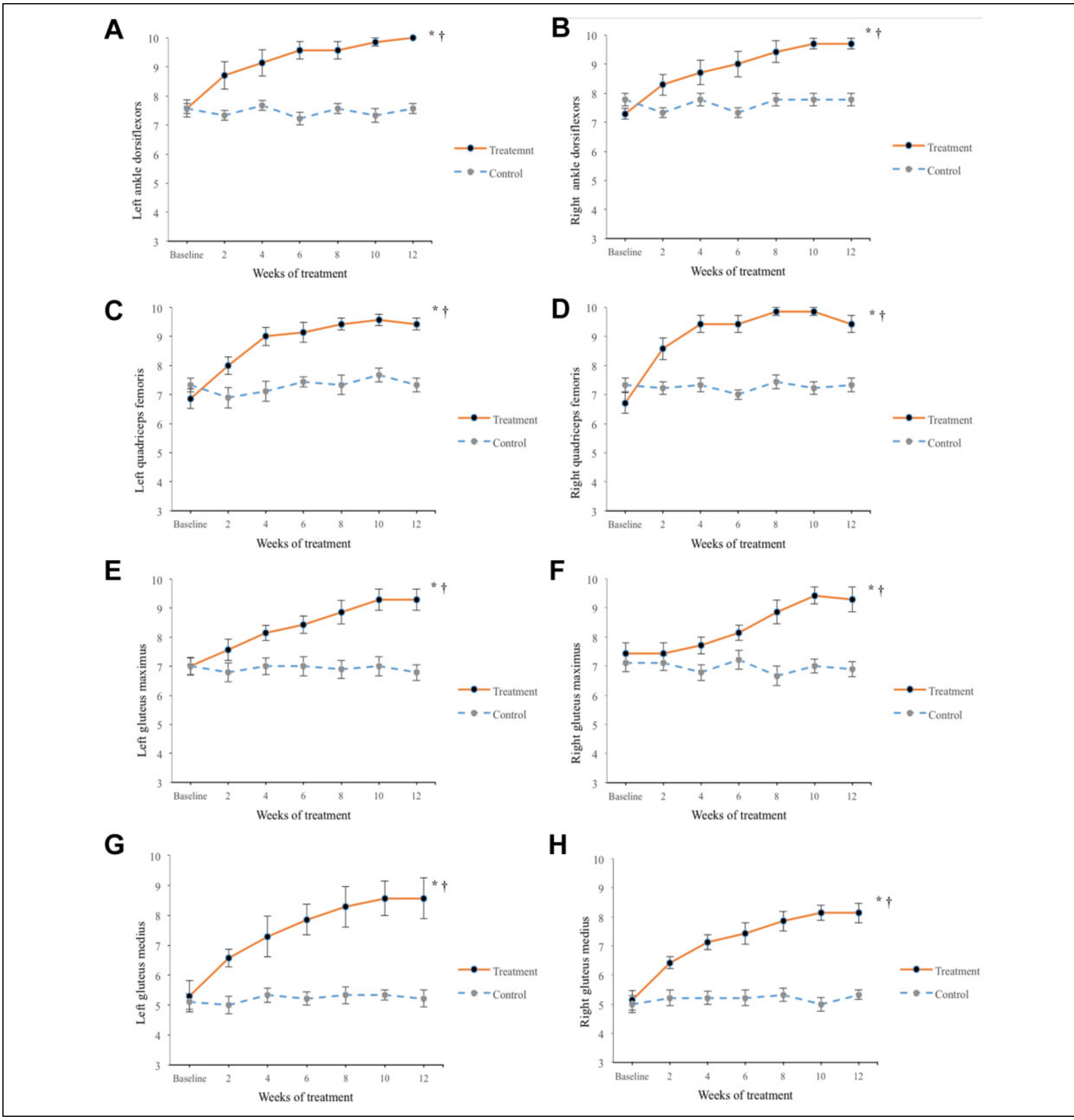

Figure 2. Effects of high-frequency external muscle stimulation treatment on muscle strength. A, Left ankle dorsiflexors. B, Right ankle dorsiflexors. C, Left quadriceps femoris. D, Right quadriceps femoris. E, Left gluteus maximus. F, Right gluteus maximus. G, Left gluteus medius. H, Right gluteus medius. Treatment group: solid line ($n = 7$); sham control group: dashed line ($n = 9$). *$P < .01$ by repeated measures analysis of variance in treatment group; †$P < .001$ versus control. Data represents means with standard error bars.

This is the first investigation of the efficiency of high-frequency EMS treatment for depression and anxiety symptoms in LDD in a population of Chinese descent. However, previous EMS studies have demonstrated the effectiveness of EMS in providing relief from affective symptoms and the improvement in outcome in other patients, such as those with peripheral arterial disease[37] and cardiovascular risk factors[21]; these conditions are highly associated with the risk of LLD.[38] Additionally, EMS can significantly reduce depression-related symptoms, such as fatigue[39]and sleep disturbance, in patients with illnesses.[26] Moreover, evidence supports the use of EMS as an alternative to voluntary exercise, which can already be

Table 2. Correlation Between Changes in Affective Symptoms and Changes in Muscle Strength Over 12 Weeks.

	Affective Status		
Muscle Strength	GDS Score (n = 7)	HAMD Score (n = 7)	HAMA Score (n = 7)
Left ankle dorsiflexors	0.143	−0.445	0.563
Right ankle dorsiflexors	−0.414	−0.818[a]	0.108
Left quadriceps femoris	−0.047	−0.079	−0.494
Right quadriceps femoris	0.197	0.280	0.546
Left gluteus maximus	−0.359	−0.447	−0.224
Right gluteus maximus	−0.445	−0.563	−0.287
Left gluteus medius	0.792[a]	0.510	0.703
Right gluteus medius	0.683	0.382	0.671

Abbreviations: GDS, Geriatric Depression Scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.
[a] $P < .05$.

considered an alternative to antidepressants for treatment of depression in older adults.[1,40]

Finally, other electrical stimulation, such as transcutaneous electrical nerve stimulation, could reduce depression symptoms in older adults.[41] Therefore, high-frequency EMS treatment is potentially helpful for reducing affective symptoms in LLD.

In the current study, EMS increased the strength of the quadriceps femoris to which it was directly applied. It additionally affected other muscle groups of the lower extremities, including the ankle dorsiflexors, gluteus maximus, and gluteus medius. Moreover, a trend of correlation between the reduction in depression level and muscle strength gains were observed. The improvement in muscle strength after EMS application has been a consistent finding in both healthy[18,20] and older[17,22,23,40] populations. Depressive symptom severity was positively associated with muscle weakness in an older population.[8] Muscle weakness and fatigability are treated as synonymous with amotivational or anhedonic states, core symptoms of depression.[42] Muscle weakness crucially affects functional activities, causing dependence and disability in older people; these conditions are associated with vulnerability to depression and anxiety in older populations.[7,8] Moreover, muscle weakness precedes the development of depression and may be of associated pathogenic importance.[12] Because EMS treatment helps preserve muscle strength[40] and muscle strength is closely associated with depression severity in late life,[7,8] EMS treatment may reduce depressive symptoms by increasing muscle strength in patients with LLD and would therefore reduce frailty and inactivity. Further research is required to corroborate the current findings.

Although the mechanisms underlying this therapeutic modality remain unknown, electrical stimulation may reduce peripheral inflammation, improve microcirculation and mitochondrial function, and exert antioxidant properties.[43-47] These mechanisms are all linked to the pathogenesis of depression and may synergize to produce a therapeutic effect in LLD.[48,49] A factor potentially related to the benefits of EMS is inflammation. Evidence from both correlational and experimental studies suggests that inflammation is involved in the pathogenesis of depression, and antidepressant treatments were found to decrease the peripheral levels of inflammatory cytokines in a manner correlated with reductions in depressive symptoms.[49] Electrical muscle stimulation could exert an anti-inflammatory effect,[43] which may help alleviate depressive symptoms in patients with depression. Another factor that could be affected by EMS application and play a role in depression development is microcirculation.[48] Peripheral microvascular changes, endothelial dysfunction, and vascular pathologic conditions contribute to the pathogenesis of depression.[48] Electrical stimulation has been reported to improve microvascular blood flow in limb ischemia[44] and endothelial function in patients with chronic heart failure[43] and promote tissue circulation and wound healing in patients with diabetic ulcers.[45] Therefore, the benefit of EMS in microcirculation could help reduce depressive symptoms. Besides peripheral mechanisms, a portion of EMS effects may arise from central mechanisms, whereby spinal motoneurons are recruited through the evoked sensory volley.[50] Several studies using TMS have suggested that EMS can induce changes in corticospinal excitability[51-53] and interhemispheric inhibition.[54] Finally, other factors of EMS possibly affecting depression include mitochondrial function and release of antioxidant enzymes.[46,47] Electrical muscle stimulation treatment may act through any combination of the aforementioned mechanisms to reduce depressive symptoms in LLD. Future research is required to clarify the underlying mechanism of the therapeutic effect of EMS in LLD.

These results must be interpreted with consideration for the study limitations. The main limitation of the study is the small sample size of patients with LLD and multiple testing; therefore, the results should be considered preliminary because some of the results may be due to chance. Besides, the small sample size and simple randomization method used in this pilot study to randomize study participants has yielded imbalanced groups. Having imbalanced groups reduces the power to detect an effect of the intervention if one exists.[55] Subsequent study should include a larger sample size or use block randomization method to increase the statistical power and to reduce the chances of having imbalanced groups, respectively.[55,56] Another limitation associated with our pilot study is its short duration of follow-up (12 weeks), which may explain the weak effect of EMS treatment. Long-term follow-up studies are required to ascertain the cumulative effects of EMS in older people with depression and assess whether depressive symptoms relapse or worsen after discontinuing treatment. Third, the current study did not record other factors, such as subtype of depressive episodes (eg, atypical or melancholic depression), potentially associated with treatment response. Furthermore, we did not explore other depression-related symptoms such as fatigue, sleep, pain, appetite, and cognition. In future studies, it would be intriguing to correlate the effects of EMS on these symptoms. Fourth, the exclusion of individuals with concomitant medical conditions may have contributed to a selection bias favoring noninflammatory types of depression. Fifth, those in the control group had the electrodes placed, but the stimulator remained inactive. A specific sham device that causes superficial skin stimulation without influencing muscles should be constructed for control groups in a future study. Sixth, not all participants received brain imaging prior to enrollment, and thus the possibility of "vascular dementia" was excluded only by clinical history and physical examination. Finally, the current study enrolled only male veterans and thus should be interpreted with caution. Future studies should include other population, for example, nonveterans and female patients.

Conclusion

In summary, this pilot study suggests that high-frequency EMS maybe a useful and noninvasive nonpharmacological treatment for the management of depressive symptoms in LLD. Findings are to be validated in larger studies. Future research should also explore putative mechanisms underlying the therapeutic effect of high-frequency EMS and aim to develop new therapeutic strategies for geriatric depression.

Authors' Note

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported in part by grants from the Ministry of Science and Technology (105-2314-B-075-024-MY2 and 106-2320-B-182-021), Taipei Veterans General Hospital, (V105E17-002-MY2-1, V106B-004, V108B-009), and Shin Kong Wu Ho-Su Memorial Hospital (SKH-8302-104-DR-16, 2020SKHADR017, 2019SKHADR016)

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Supplemental Material

Supplemental material for this article is available online.

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