ORIGINAL ARTICLE

Effects of Electrical Stimulation on Muscle Trophism in Patients With Hemophilic Arthropathy

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ABSTRACT. Gomis M, González L-M, Querol F, Gallach JE, Toca-Herrera J-L. Effects of electrical stimulation on muscle trophism in patients with hemophilic arthropathy. Arch Phys Med Rehabil 2009;90:1924-30.

Objective: To determine changes occurring in the cross-sectional area, electromyography (EMG) activity, and the strength of the biceps brachii after an 8-week period of bilateral training with surface muscle electrical stimulation in patients with hemophilic arthropathy.

Design: Controlled trial.

Setting: Coagulopathy unit, university hospital.

Participants: Volunteer subjects (N=30) participated in this study: 15 with severe hemophilia A (hemophilic group) and 15 nonhemophilic control subjects (control group).

Interventions: The hemophilic group followed a surface electrical stimulation program (frequency 45Hz, impulse 200μs, 10s on/10s off) over an 8-week period on the biceps brachii of both arms. The control group did no training of any kind.

Main Outcome Measures: The cross-sectional area, maximum voluntary isometric contraction, and EMG activity of the biceps brachii in both arms were determined before and after the 8-week-long task.

Results: The results of the hemophilic group showed significant increases in the diameter (15.8%, $P<.001$), isometric force (4.6%, $P<.05$), and EMG activity (37.6%, $P<.05$) of the biceps brachii muscles in both arms. No significant changes were observed for the control group.

Conclusions: Our findings confirm the efficacy of muscle electrical stimulation in causing muscles to hypertrophy in patients with hemophilia, thereby improving their muscular strength. In addition, these results may also be clinically applicable in the rehabilitation of patients who have similar deficiencies in the locomotor system.

Key Words: Electric stimulation; Exercise; Hemophilia A; Rehabilitation.

HEMOPHILIA A IS A SEVERE X-linked bleeding disorder caused by the absence of functional blood coagulation factor VIII. The hemorrhaging problems that hemophilic patients have usually lead to musculoskeletal lesions, which affect the proper functioning of the locomotor system, particularly the joints and muscles.[1] One of the most common clinical consequences in these patients is hemophilic arthropathy, which may occasionally affect a large number of severe patients. With hemophilic arthropathy, as with osteoarthritis and other chronic musculoskeletal diseases, the muscle-joint system degenerates, leading to a loss of muscle mass and strength. Serious functional limitations can result and, on occasion, invalidity, because the hips and knees are the large joints mainly affected.[2]

With time, hemophilic arthropathy results in weak and unstable joints, The patient is also very vulnerable to stressful locomotor situations, which, in turn, cause greater instability and risk of lesions. This vicious circle of pain, immobility, atrophy, joint instability, and new hemorrhagic episodes may eventually lead to total invalidity.[3]

Accordingly, exercise or sports, or both, would likely be a possible solution to this problem, although these activities were not recommended as a preventive treatment before the 1970s.[4] To date, very few studies of the effects of strength training in hemophilic patients have been published.[4-11] The practical application of strength training is still not widespread, although there appears to be a clear, generalized trend to recommend it as an effective method to recover muscle function in those patients with chronic pathologic conditions in which there are shortfalls in muscle mass and strength.[12]

Nonetheless, there is much controversy about this topic in the hemophilia domain, mainly because of the lack of experimental evidence to support these arguments. More experimental data are necessary to confirm if physical training provides health improvement. For this reason, the main objective of this study was to determine the changes occurring in the CSA, EMG activity, and the strength of the biceps brachii after an 8-week period of bilateral training with surface muscle electrical stimulation.

METHODS

Subjects

Thirty voluntary subjects took part in this study. Fifteen patients with severe hemophilia A (hemophilia group) were

List of Abbreviations

CNS	central nervous system
CSA	cross-section area
EMG	electromyography
MVIC	maximum voluntary isometric contraction
SEM	standard error of the mean
SES	surface electrical stimulation

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Table 1: Age and Anthropometric Data of the Hemophilia and Control Groups

	HG (n=9)	CG (n=14)
Age (y)	34.9±2.1 (23–44)	29.1±2.9 (19–59)
Height (cm)	175.5±2.8 (164.4–187.7)	175.2±1.7 (164–187)
Weight (kg)	78.6±5.5 (56–107.8)	75.1±2.6 (65–104)

NOTE. Data are expressed as mean ± SEM with ranges in parentheses.
Abbreviations: CG, control group; HG, hemophilia group.

selected with a cluster sampling technique according to clinical criteria. They all had hemophilic arthropathy, which was assessed according to Pettersson's radiology score[13] and Gilbert's clinical score.[14] Furthermore, the recommendations of the Orthopaedic Advisory Committee of the World Federation of Hemophilia were followed. Table 1 presents the patients' main anthropometric characteristics. Only those patients with severe hemophilia A (factor VIII $<.01 IU \cdot mL^{-1}$), who had neither developed inhibitors nor had hemorrhaging in the upper limbs in the last 30 years, were considered for the inclusion-exclusion criteria. Those patients who did regular exercise and/or those who had some type of neurologic or sensorial disorder that could affect or prevent them from performing the tests properly were excluded. All of these patients received on-demand treatment (ie, they underwent substitution factor VIII therapy whenever the clinical circumstances merited it). During the training period, no patient had musculoskeletal lesions or needed factor VIII administered. All the patients voluntarily signed an informed consent to participate in this study. The protocols to be used in this study were presented to the University Hospital La Fe Ethical Committee (Valencia) for approval, and these protocols met all the requirements set out in the Declaration of Helsinki of 1975, which was later reviewed in 2008.

Likewise, 15 healthy subjects with a sedentary lifestyle and of similar age, weight, and height (see table 1) were selected to form a control group. Six hemophilic patients and a control subject left the study for personal reasons.

Overall Procedure

All the protocols described in these procedures followed the recommendations by Brown and Weir[15] in 2001. One month before starting the study, clinical and radiology examinations were performed on the participating hemophilic patients to establish the extent of their hemophilic arthropathy.

Having completed these preliminary examinations, MVIC, EMG activity, and the CSA of the biceps brachii of both arms (pretest) were determined. Surface muscle electrical stimulation was then applied over an 8-week period to both patients' arms in the hemophilic group. After the treatment period, the aforementioned measures were determined again for both arms (posttest). The subjects indicated their subjective perception of pain intensity, which may have been caused by the surface electrical stimulation in each working session.

The pretest and posttest measurements were also determined in the control subjects, but they received no type of treatment during the 8 weeks that the experiment lasted. Subjects were requested to continue with their usual activities of daily living and to change them as little as possible.

Clinical and Radiology Assessment Protocol

A study was done before opening patients' records. It entailed recording the assessment scores for joints according to the recommendations of the World Federation of Hemophilia: the Pettersson's radiology score and the Gilbert's clinical score.

Pettersson's score objectifies and scores (0–13 points) the radiologic signs of hemophilic arthropathy, where 0 represents the absence of hemophilic arthropathy. Gilbert's score uses a maximum of 12 points to assess the diagnosis and evolutive control of arthropathy, with 7 items related to poor anatomic structures, biomechanical alterations, and physiopathologic processes. In addition, this scale may have a maximum score of 15 points after assigning between 0 and 3 points for the subjective perception of pain. As with Pettersson's score, a 0 in Gilbert's score means a lack of arthropathy.

Both the hemophilic arthropathy assessment scores by Gilbert and Pettersson are normally used as tools to assess arthropathy in patients with hemophilia.[4,11,16,17] All the patients in our study had hemophilic arthropathy in 1 joint or more.

Maximum Voluntary Isometric Contraction Measurements

A load cell[a] was used to measure the MVIC of the elbow flexions. Before the measuring session, a standard warmup session was done that consisted of 6 series of progressive intensity so that the sixth series coincided with an almost maximum effort.

Throughout all the measuring sessions, the subjects remained in a supine position on a bed, and their waist and trunk were held with nylon bands. The patient's arm formed a flexion and an abduction of 1.57rad, thus taking the anatomic position as 0rad, with the hand grip in a neutral position.[18] The other arm laid out straight and relaxed in line with the body.

In this position, the subjects were asked to make 3 attempts with each arm lasting approximately 4 seconds each, with a 2-minute rest between each attempt. Throughout the sessions, the patients received words of encouragement to accomplish the maximum contraction possible. The order in which the arms were to start was counterbalanced.

All attempts were recorded at a frequency of 2kHz during the approximately 4 seconds that the attempts lasted; the analog signal was converted into a digital signal and was saved on a hard disk for subsequent analyses.

Measuring Electromyography Activity

The surface EMG activity of the biceps and triceps brachii was recorded while each attempt was made and was coordinated with the taking of the MVIC signal. To do this, pregelled Ag/AgCl bipolar electrodes[b] were used. Before placing the electrodes, the skin areas where the electrodes were to be placed were prepared by shaving hair and cleaning the area with alcohol, thereby reducing skin impedance as much as possible. The electrodes were placed on top of the skin on both the biceps and triceps brachii with an interelectrode distance of 20mm, approximately at 50% of the distance between the axis formed by the acromion and the internal lateral epicondyle of the humerus to approximately coincide with the center of the muscle belly and the motor point of the aforementioned muscles.

The reference electrode was placed on the nonactive olecranon tissue of the same arm being measured. The position to

place the electrodes was marked with an indelible pen. The position of the electrodes was noted by measuring with a tape measure the distance at which the electrodes were from the reference axis formed between the acromion and the internal lateral epicondyle of the humerus, with a view to being able to continue in the same way when the electrodes were replaced at a later stage.

The EMG activity was amplified (gain × 5000), and as with MVIC, it was sampled at 2kHz. Once converted from analog to digital, it was saved for subsequent analyses.

Measuring the Diameter of the Biceps Brachii (Cross-Section Area)

A computerized axial tomography (Picker PQ 2000S[c]) was used to measure the diameter of the biceps brachii. An axial cut of 5mm was made at the distal level corresponding to 33% of the distance between the olecranon and the acromion of both arms.[19] To select the point and measurement of the biceps brachii, a "512 pilot" was done. A standard image reconstruction algorithm was used, and the protocol for limbs was used to select the kilovolts and milliamperes.

Later, the equipment's workstation software was used (Picker Voxel Q workstation[c]) to measure the diameter (in centimeters) of the area of interest (the biceps brachii muscle) before adjusting a suitable window to be able to differentiate the anatomic structures correctly. Measurements were taken by determining the distance between the skin's surface and the humerus at a perpendicular point to the largest diameter of the humerus at this level.[20,21]

Surface Electrical Stimulation Treatment

The biceps brachii muscle was chosen to be used with the SES program. The treatment proposed was selected from existing scientific literature by using an electrical stimulation apparatus[d] and pregelled Ag/AgCl bipolar electrodes (10 × 5cm).

Regarding the position of the electrodes, the cathode and anode were placed perpendicularly to the biceps brachii. Specifically, the positive pole was placed distally to approximately coincide with the motor point of the muscle. The negative pole was placed proximally around the point at which the biceps brachii is protected by the deltoids.

Treatment with SES took place over an 8-week period with 3 weekly sessions lasting 35 minutes (ie, a total of 24 sessions). A warmup was done with SES for the first 5 minutes at low frequency. During the next 30 seconds, a force program was run with a frequency of 45Hz, an impulse of 200μs, and a contraction and rest cycle of 10 seconds on and 10 seconds off (a modified protocol for upper limbs of Querol,[11] Pérez,[22] and colleagues). The subjects voluntarily selected the intensity of the impulse, and they were encouraged to gradually increase the intensity while doing the successive sessions (fig 1).

The subjects sat on a chair with their waists and trunks against the chair back. The SES was done in the isometric mode with the elbows at an angle of approximately 1.57rad in each session to enable the anatomic position to be taken as 0rad.

Recording Perceived Pain

The intensity of the pain perceived by the subjects was assessed and recorded immediately after finalizing each SES session. All the subjective comments that the patients made about the session and the feelings they had felt on the days before and after the treatment were noted in a diary of incidences.

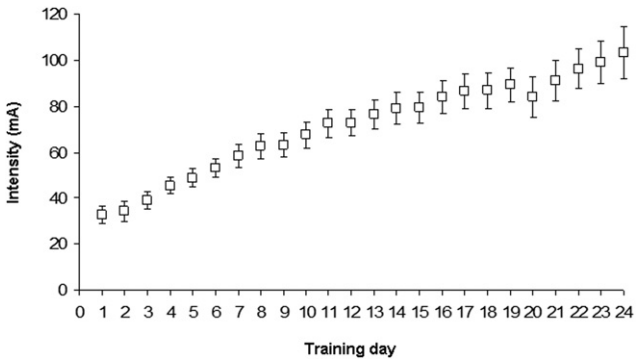

Fig 1. Intensity of the electrical stimulation of both arms during the various work sessions. Squares represent the average value (n=9) of intensity. Bars represent the SEM with regard to the average value. The increase in intensity shows the patients' adaptation to the treatment being applied, with no physiologic harm.

Data Analysis

A program (Matlab version 7.0[e]) that was specially designed for this project was used to analyze the MVIC and EMG signals.

Before the analysis, the EMG signals were filtered with fourth-order Butterworth digital filters at 10 to 400Hz to preserve only those frequencies that were of interest for the study. Signal quantification was carried out by selecting the central second of the 4-second attempt. The maximum force exerted at the central second was used for the pretest and the posttest. In this way, the force signal was quantified as the average force exerted at the central second selected, and was expressed as newtons.

The EMG was recorded in a synchronized fashion with the force signal. Therefore, both signals were analyzed using the same central second. To be able to quantify EMG activity, the amplitude of the signals was quantified by the root mean square and processed in 100-millisecond–sized blocks.

Statistical Analysis

All the data analyses were done with the SPSS 14.0 program for Windows.[f] A descriptive analysis of the variables was done using the mean as the central trend descriptives, and the minimum, maximum, and SEM were used as dispersion statistics. The statistics were calculated with the same sample (n=18 for the hemophilic group and n=28 for the control group). The result of both arms was also taken into account.

Because the sample size was small (n<30), a nonparametric test was chosen for the means differences between the pretest and posttest. Specifically, the Wilcoxon *t* test was used, which compares the central trend of 2 samples with paired data. Nonetheless, the Mann-Whitney *U* test was used to make comparisons between the 2 study groups (control group vs hemophilic group). Those differences whose probability of being random was below 5% ($P<.05$) were considered significant.

RESULTS

Radiologic and Orthopedic Data

According to Gilbert's and Pettersson's scores, all the hemophilic patients in this study had arthropathy (hemophilic group). The mean ± SEM values of all 6 joints as assessed with Gilbert's clinical scale and Pettersson's radiology score

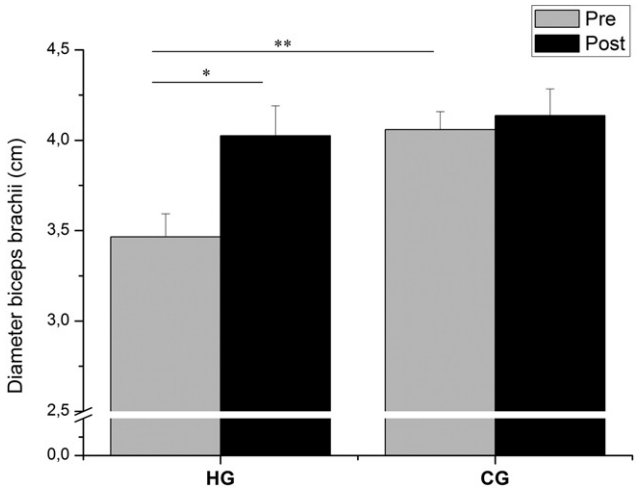

Fig 2. Diameter of the biceps brachii of both groups. The values represent the mean ± SEM expressed as centimeters. *Significant difference between the pretest and the posttest (*P*<.001). **Significant difference (*P*<.001), between the pretest of both groups, hemophilia (HG) and controls (CG).

were 36.1±7.2 and 25.8±4.3 points, respectively. The average scores were 7.0±1.6 and 4.8±0.9, respectively, for the right elbow, and 5.2±1.6 and 3.8±0.9, respectively, for the left elbow.

Diameter of the Biceps Brachii

In the pretest, the diameters of the biceps brachii in the hemophilic group were 17% less than those in the control group ($P<.001$) (fig 2). In the posttest, however, the mean diameter ± SEM of the biceps brachii in the hemophilic group increased significantly after 8 weeks of SES strength training, from 3.5±0.1cm to 4.0±0.2cm ($P<.05$). The change that the patients noted was an average improvement of 0.5cm (15.85%, $P<.001$). In that sense, the differences in the diameters of the hemophilic patients in the posttest disappeared in relation to the control group. Furthermore, no significant increase was noted for the control group between the measurements taken in the pretest and the posttest.

Maximum Voluntary Isometric Contraction

The pretest isometric force values were of a higher percentage in the control group (39.5%, $P<.001$) in relation to the hemophilic group. After the intervention, the hemophilic group accomplished a significant improvement of 4.6% (from 163.8±13.10N to 171.4±14.1N; $P<.05$) in the MVIC of the biceps brachii after 8 weeks of SES treatment. No significant differences were found between the pretest and the posttest for the control group (228.5±8.5N and 225.9±9.0N, respectively).

Intervention of the Nervous System (Electromyography)

The EMG values for each group are presented in table 2. There was a significant difference between the nervous activation of the flexor muscles (agonist) and the extensor muscles (antagonist) for both study groups. Although the hemophilic group achieved a significant improvement of 37.6% ($P<.05$) for the EMG values of the biceps brachii, no statistically significant improvement was noted for the triceps brachii. Finally, no significant differences were found for any of the muscles analyzed in the control group.

DISCUSSION

Our patients noted changes in muscle trophism as a result of the training program carried out. The main aim of the proposed treatment was to increase the diameter of the biceps brachii. The changes that took place as a result of our treatment at the structural level may help reduce the very marked muscle atrophy that limits and often prevents patients from performing activities of daily living.

The data obtained before the SES treatment period revealed 17% less muscle mass in hemophilic patients than in healthy controls. These data are in agreement with other studies that report a loss of muscle mass, typical of hemophilic arthropathy.[10,11] There are 2 basic reasons that account for such muscle loss: (1) inactive joints as the result of long-term immobilization that hemophilic patients are obliged to do because of continuous lesions in muscles and joints, and (2) a decrease in physical exercise by hemophilic patients because of the imminent risk of lesions that they face.[23] In addition, it may be thought that this muscle atrophy can be caused by the appearance of infectious processes (ie, our patients were coinfected with human immunodeficiency virus and hepatitis C virus). Nonetheless, present-day advances with antiretroviral drugs allow us to intuitively believe that this covariable has been controlled in our study subjects.

Once the 8-week SES treatment had concluded, our patients had a significant increase of approximately 15.85% in the diameter of their biceps brachii. These increases noted after the SES treatment are consistent with findings of previous studies done at our coagulopathy unit with both hemophilic patients and healthy subjects. Querol,[11] Pérez,[22] and colleagues used very similar protocols to that used in this study and reported improvements similar to those reported in this study.

Existing literature also includes studies of patients with other pathologic disorders that cause musculoskeletal lesions similar to those seen in patients with hemophilia, in which similar percentages of improvement of muscle trophism were achieved after treatment with various SES protocols. Indeed, there are reports of patients who lost considerable muscle mass because

Table 2: EMG of the Biceps and Triceps Brachii Muscles During Isometric Contractions

	HG (n=18)		CG (n=28)	
	Pretest	Posttest	Pretest	Posttest
Biceps brachii	236.62±24.35	325.67±43.66*	421.39±41.06†	385.05±32.70
Triceps brachii	29.87±3.89	32.25±3.16	48.40±10.70†	31.39±2.53

NOTE. Data are expressed as mean ± SEM for both arms. The EMG values are presented in microvolts during the central second of isometric contraction.
Abbreviations: CG, control group; HG, hemophilia group.
*Significant difference between pretest and the posttest ($P<.05$).
†Significant difference for both groups in the pretest ($P<.05$).

of spinal cord injuries who showed similar percentages of recovery as in this study after being treated with different SES protocols. Dudley et al[24] obtained an improvement in muscle trophism of approximately 20% after an 8-week SES treatment. Likewise, Castro,[25] Mödlin,[26] and colleagues applied SES treatment protocols for a longer duration, 6 months and 1 year, respectively, and found that muscle mass increased by 25% and 30%, respectively. This appears to indicate that if we had maintained our treatment over a longer period, we would have obtained even better results.

Likewise, there are other pathologic disorders with a loss of muscle mass due to intolerance to physical exercise. One example is chronic heart failure, which also shows similar improvements in muscle trophism. The CSA of thigh muscles in patients with refractory heart failure improved by 15.5% after an 8-week treatment with an SES protocol using a frequency of 50Hz.[27] These data are in agreement with results obtained from the hemophilic patients in our study.

Another important objective of our research work was to check the effects of SES treatment on isometric force, because several authors have shown that patients with hemophilia generate significantly lower levels of force when compared with healthy subjects.[4,11,17] Our findings seem to confirm this observation, as the MVIC results before commencing SES treatment showed force values for the hemophilic patients that were lower than those registered for the control group. The values for the hemophilic group revealed an isometric force that was approximately 39% less than that in the control group, and these data are very similar to those found in previous studies. Specifically, Hilberg et al[4] obtained an intergroup difference of approximately 38%.

Some authors have reported that SES is an efficient method to improve muscle strength in patients with chronic pathologic disorders such as osteoarthritis.[28,29] After undergoing 24 SES sessions in our study, hemophilic patients displayed significant improvements as far as the MVIC results were concerned. The maximum isometric force of these patients increased by 4.6% after they had completed the treatment. These results fall below those found by Querol et al,[11] who obtained significant improvements of approximately 13.8% and used a very similar protocol to that used in our study. One explanation may be that the pain felt by some subjects while the measurements were being taken could have limited the application of the MVIC during the 4 seconds that each attempt lasted. Therefore, the potential force values expected were not reached. However, the patients themselves confirmed an improvement in their muscle strength, which enabled them to do their daily living activities in a more comfortable way. Indeed, there are studies in the scientific literature whose aim was to establish the differences in force among populations who complained about pain and those who did not. In that sense, there are scientific references with different populations that show that pain reduces the capacity to apply force.[30-32] O′Reilly et al[30] compared a group of patients with osteoarthritis and pain with control subjects who had no pain. After measuring the MVIC of the quadriceps femoris, the results revealed that the group with pain showed approximately 26% less force than the control group. Therefore, these data reveal, and apparently confirm, that it is possible the lower percentages of force obtained in our study could be related to the pain felt by the patients.

Other authors have used different training protocols to improve the force that hemophilic patients can generate.[4,7] In the study by Pelletier et al,[7] isokinetic training was carried out over a 3-week period with young patients aged 12 years. With this intervention, an improvement in isometric force of between 40% and 70% was achieved. These results are significantly higher than those reported in this study, and may be due to the young age of the subjects, which may mask the maturity process that naturally occurs at this age. In the study by Hilberg,[4] an improvement in isometric force of approximately 34% was achieved. However, the training period in this study lasted 6 months, which is much longer than the 8-week period in our study and could well account for the differences found.

In relation to the results regarding the interventions of the nervous system, a priori, and if we take into account that the means used in this study was SES, improvement in the nervous system may be ruled out. Nonetheless, more noticeable differences were found between the nervous activation of the elbow flexor muscles (agonist) and that of the elbow extensor muscles (antagonist). The agonist muscle, the biceps brachii, significantly improved in terms of the EMG values by 37.6% after an 8-week SES treatment period. However, the antagonist muscle, the triceps brachii, showed no significant improvement over the same study period. A better intermuscle coordination clearly was noted after the SES treatment, which reveals a better agonist-to-antagonist ratio. Therefore, improved muscle efficacy, along with the increases in muscle mass, could corroborate the significant increases obtained in isometric force.

Nonetheless, this significant increase in the nervous activation of the biceps brachii requires further explanation. This activation may lie in the SES protocol used. In our protocol, the subjects were encouraged at all times to withstand intensities with a maximum current in all 24 sessions. In this sense, several studies describe how this high electrical intensity on the muscle at the skin level may have led to a series of increased afferent activity towards the spinal cord in both the muscle and skin receptors.[33,34] Furthermore, these afferences may have become doubly reinforced not only with the high intensity maintained, but also because of the frequency used for the treatment applied (45Hz). This effect is enough to cause a strong muscle contraction, which, in turn, leads to discomfort in the muscle, which may have triggered different reflex actions (eg, a withdrawal reflex to protect the segment involved or a crossed extension reflex to stabilize the system). These reflex actions, as a result of the SES treatment, are supported by studies that have been carried out on this subject.[35,36]

Nonetheless, the "orders" for a muscle to contract come from the electrical stimulation apparatus during the SES treatment rather than from the CNS, which is what would occur in normal muscle contraction. In our study, prolonged stimuli, as in an 8-week SES treatment period, are probably able to permit some form of adaptation to the CNS stimulus at the cortical level, and could lead to possible learning processes of the protocols in response to the stimulus to, in turn, generate efferent activity.[37]

Study Limitations

The main limitation of our study was the small number of patients affected with hemophilia A. Also, 6 patients left the study for personal reasons. Although it would be desirable to extend the study to a larger number of patients, this is not easily done because in our region, the ratio of hemophilic patients to healthy people is 1:5000. In addition, many patients with hemophilia were infected during the 1980s with human immunodeficiency virus and hepatitis C virus. These realities help to explain why we did not have a larger number of patients with hemophilia in our study. However, one solution in the future would be to work together with other health institutions in order to recruit the largest number of hemophilic patients possible.

CONCLUSIONS

We investigated the effects of an 8-week bilateral SES training program on muscle thickness, muscle strength, and activation of the nervous system of the biceps brachii in patients with hemophilia A. Our results suggest that the SES program (45Hz; 200μs; 10s on/10s off; 30min/session; 24 sessions) achieves significant increases in muscle trophism and on the isometric force of the biceps brachii of such patients. Likewise, this training improved the intermuscle coordination of the elbow flexion muscles.

Such evidence corroborates previous experiments done in our laboratory with the same type of patients. Clinically, our patients have adapted extremely well to the electrical stimulation training. Therefore, it seems that this form of treatment may enhance the physical capacities of these subjects without causing lesions to the musculoskeletal system, representing a promising treatment for patient rehabilitation. Additionally, the clinical application of the treatment presented in this study can be extended to other affected areas of the body, after adjusting the electrostimulation program to take into account the specific chronaxy of every muscle group.

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Suppliers

a. CTCS250; Mutronic, C/ Liberación 2, 28033 Madrid, Spain.
b. Blue Sensor M-00-S; Medicotest, Rugmarken 10, 3650 Ølstykke, Denmark.
c. Picker International Inc, 595 Miner Rd, Cleveland, OH 44143.
d. Stim Intelec Advanced; Chattanooga Group, 4717 Adams Rd, Hixson, TN 37343.
e. MathWorks, 3 Apple Hill Dr, Natick, MA 01760-2098.
f. SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.