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High Tone External Muscle Stimulation versus Aerobic Exercise on Endothelial Dysfunction and Walking Parameters in Peripheral Arterial Disease

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Abstract: Peripheral arterial disorder (PAD) is a common vascular disorder caused primarily by atherosclerosis, it leads to a decrease in blood flow in the legs. The theory of high tone external muscle stimulation (HTEMS) first in transmitting possibly the highest dose of energy into tissues by high frequency, and second by the resonance effect inducing oscillation of cellular and tissue structures improves cell metabolism, leading to analgesic, circulatory effects. The aim of the study was to investigate the effect of HTEMS on endothelial dysfunction and walking parameters in PAD. **Methods:** 60 diabetic patients with moderate stage PAD based on their ankle brachial pressure index (ABPI) which ranged from 0.4 to 0.7 with IC and their age ranged from 40 to 70 years, selected from an outpatient clinic of Vascular Medicine Department, Cairo University Hospitals, were assigned randomly into two groups A&B. Group (A) (HTEMS group) included 30 patients who received high tone external muscle stimulation performed for 60 minutes per session, 3 times per week, for 12 weeks, in addition to their medical treatment. Group (B) (Exercise group) included 30 patients who participated in supervised regular aerobic exercise training program on treadmill with moderate intensity, (score 12-14 on Borg scale for rate of perceived exertion) 40 minutes per session, 3 times per week, for 12 weeks in addition to their medical treatment. The endpoints of this study were nitric oxide (NO) and walking parameters which are claudication Pain distance (CPD), claudication pain time (CPT), Peak walking distance (PWD), Peak walking time (PWT). **Results:** comparing both groups post treatment revealed statically significant improvement in group A and B with no significant difference between them in all parameters, as the percent increase in CPD value in groups A and B was 108.46% and 112.78%, respectively, while it was 95.30% and 102.18% in CPT in group A and B respectively. The percent increase in PWD value in groups A and B was 90.36% and 91.31%, respectively, while it was 96.29% and 99.03%, in PDT in group A and B respectively. The percent increase in the NO mean value in groups A and B was 17.94% and 17.36%, respectively. **Conclusion:** HTEMS had positive influence in the improvement of walking capacity and endothelial function in patients with PAD. It might also be employed as an alternative modality to exercise training, especially for patients with PAD who cannot adhere to exercise training or where the exercise is contraindicated

Keywords: High tone external muscle stimulation, peripheral arterial disease, walking capacity, intermittent claudication.

1 Introduction

Peripheral arterial disease (PAD) is decreased lower extremity arterial perfusion which is commonly referred to as "poor circulation". Reduced blood flow can cause Thigh or calf pain with walking due to temporary ischemia. [1]. peripheral arterial disease affects nearly 200 million people worldwide. The prevalence of PAD is 3 to 4 times higher and severe in diabetic individuals compared with

non- diabetics individuals. Almost two-thirds of diabetic patients with foot ulcers have PAD, which is associated with a high amputation rate and mortality. [2].

Supervised exercise therapy (SET) is particularly effective in improving symptoms in PAD. Several research studies have shown that supervised exercise, when conducted according to best practices, is equally or more effective in improving walking ability as compared to a balloon and stent procedure [3].

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A special stimulation system (HiTop 191) is used for external muscle contraction. With application of 1-s frequencies of 4,096–32,768 Hz, introducing up to 5,000 mW into the muscles. High-frequency electrical muscle stimulation has previously been shown to be effective in the relief of chronic diabetic neuropathic pain and several other chronic painful conditions, including back pain, phantom-limb pain, and severe angina [4].

The beneficial action of HTEMS could be firstly attributed to an improvement of circulatory disturbance, it enhanced peripheral microcirculation in the intact skin of healthy patient, and improving healing of diabetic ulcers, it also induced circulatory effect and enhanced bioavailability of NO [5].

2 Experimental Sections

2.1 Materials

2.1.1 Evaluation Instruments

- Recording data sheet: All data and information of each patient in this study including name, age, height, weight and BMI were recorded in a recording sheet.
- Handheld Doppler ultrasound for ABPI measuring.
- Claudication Pain Scale [6]. Discussed in procedure
- Walking Impairment Questionnaire [7]
- Electronic Treadmill

Disposable plastic syringes were used for drawing venous blood sample. Polypropylene tubes with EDTA for keeping blood samples. Centrifuge. Analyzing chemical and commercial kits. Spectrophotometer, were used for measuring nitric oxide (NO).

2.1.2 Therapeutic Instruments

- HiTop 191 appliance, (gbo Medizintechnik AG, Rimbach, Germany) Device HiToP® with Frequencies continuously scanned from 4096 Hz to 31768 Hz, allowing for a much higher power of up to 5000 m W. It was be introduced to group “A” 3 times per week, for 12 weeks plus their medical treatment.
- Electrical treadmill with a digital screen and multiple set buttons to control speed, time, and inclination. It had extra-long safety handles and wide side rails for easy on and off. Digital screen showing time, distance, calories and speed. It had speed adjusts in increment of 1/10 mph to a maximum 4 mph, also the inclination could be adjusted. It also had sensors in their hands that measure the pulse regularly. It was used in group

“B” 3 times per week, for 12 weeks plus their medical treatment.

2.2 Deposition Method of High Tone External Muscle Stimulation

2.2.1 Evaluation Procedure

- 11 patients were referred by the vascular physician after diagnosed as PAD patient with ABPI ranged from 0.4 to .07
- The procedure of the study was explained for all patients.
- Claudication pain severity is assessed by claudication pain scale [6].

graded treadmill exercise testing: Patients started walking on treadmill with 2 mph, 0 grade. With gradually increasing the inclination (2% increase every 2 minutes) until maximal claudication pain force cessation of the exercise. The perception of claudication pain severity was ascertained using a perceived pain scale from 1 to 5. 1= no pain and the longest possible walking distance reached by the patient before the appearance of intolerable pain is the absolute claudication distance. The walking time at which ambulation could not continue due to maximum pain was defined as Peak walking time

Walking variables that were measured using graded treadmill exercise testing

- 1- Claudication pain time (CPT) and distance (CPT)
- 2- Peak walking time (PWT) and peak walking distance (PWT)

Measuring serum Nitric Oxide, the chemical analysis was performed in medical biochemistry lab. Three millimeters of venous blood were drawn from the antecubital vein of each patient before conduction and after completion of the study. Blood sample were drawn for NO measurement.

2.2.2 Therapeutic Procedure

Participants were assigned randomly into two groups: Thirty patients (12 female, and 18 male) with PAD with previous criteria were incorporated in this study. They participated in physical therapy program in form of (HTEMS), Voltage: 230-V Pulse widths: ≤ 350 mA. Electrical Frequency: An initial frequency of 4,096 Hz will be used first, which was increased up to 32,768 Hz within 3 s; the maximum frequency was used for 3 s and then downmodulated from 32,768 to 4,096 Hz. Intensity: the electrical stimulation was adjusted to a pleasant level that did not produce any pain or discomfortable paraesthesia, Duration 60 minutes per session plus their medical treatment.

Thirty patients (13 female, 17male) with PAD with same criteria participated in a supervised regular aerobic exercise program on treadmill with moderate intensity, (score 12-14 on Borg scale for rate of perceived exertion) 40 minutes per session plus their medical treatment.

Both groups were received 3 sessions per week, for 12 weeks. The assessments were done before and after the study.

2 Results and Discussion

In the current study, a total of 60 patients participated and they were randomly assigned into 2 groups (30 patients/group). No significant difference in demographic data for age (P =0.616), weight (P= 0.485), height (P= 0.515) and BMI (P=0.817) between group A and group B (**table 1**)

3.1 Inter – and Intra Groups Comparison for Nitric Oxide (NO)

The statistical analysis using ANCOVA within each group for nitric oxide (**table 2**) indicated that there was significant increase in the mean value of NO measured at post-treatment when compared with its corresponding value measured at pre-treatment in group A and B with p value = 0.001 for both groups, and the percent increase in groups A and B was 17.94% and 17.36%, respectively.

The statistical analysis using ANCOVA between both groups indicated that there were no statistically significant difference between the two groups pretreatment p= 0.371 and post treatment p = 0.871

Table 1: Demographic characteristics of group A and B.

| Item | Groups | | p- value |
|-------------|-----------------|------------------|-----------|
| | Group A (n =30) | group B (n = 30) | |
| Age (year) | 56.37 ± 6.38 | 57.17 ± 5.91 | 0.616(NS) |
| Weight (Kg) | 83.40 ± 4.05 | 84.40 ± 6.66 | 0.485(NS) |
| Height (cm) | 1.72 ± 0.03 | 1.73 ± 0.05 | 0.515(NS) |
| BMI (Kg/m2) | 28.13 ± 1.08 | 28.19 ± 1.16 | 0.817(NS) |

Data are expressed as mean ± SD NS= p> 0.05= not significant.

Table 2: Inter – and intra groups comparison for nitric oxide (NO).

| Variable | Item | groups (Mean± SD) | | F value | p- value |
|--------------|-----------------|-------------------|------------------|---------|------------|
| | | Group A (n =30) | group B (n = 30) | | |
| Nitric oxide | Pre-treatment | 64.00 ± 6.29 | 65.37 ± 5.51 | 0.814 | 0.371 (NS) |
| | Post-treatment | 75.48 ± 5.49 | 76.72 ± 5.27 | 0.027 | 0.871 (NS) |
| | Mean difference | -11.48 | -11.35 | | |
| | % improvement | 17.94 ↑↑ | 17.36 ↑↑ | | |
| | t value | -23.422 | -33.214 | | |
| | p- Value | 0.001 (S) | 0.001 (S) | | |

Data are expressed as mean ± SD; F value= ANCOVA test; t value= paired t test.

NS= p> 0.05= not significant; S= p≤ 0.05= significant.

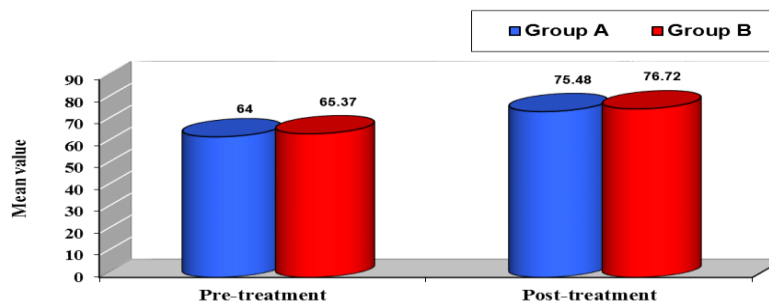


Fig. 1: Mean values of mean NO in the two studied groups measured pre- and post-treatment.

3.1 Inter – and Intra Groups Comparison for Walking Parameters

The statistical analysis using ANCOVA within each group for walking parameters (**table 3**) indicated that there were significant increase in the mean value of all walking parameters CPD, CPT, PWD and PWT measured at post-treatment when compared with its corresponding value measured at pre-treatment in group A and B with p value = 0.001 for both groups. The

percent of increase in CPD in groups A and B was 108.46% and 112.78%, respectively, in CPT 95.30% and 102.18%, respectively, in PWD 90.36% and 91.31%, respectively, and in PWT 96.29% and 99.03%, respectively.

In addition, there were no statistically significant difference ($p > 0.05$) between the two groups in all walking parameters table 3.

Table 3: Inter – and intra groups comparison for walking parameters.

| Variable | Item | Groups (Mean± SD) | | F value | p- value |
|---------------------------|-----------------|-------------------|------------------|---------|------------|
| | | Group A (n =30) | group B (n = 30) | | |
| Walking parameters | | | | | |
| | CPD | 132.67 ± 29.53 | 133.92 ± 29.32 | 0.027 | 0.870 (NS) |
| | (NS) | 276.56 ± 60.85 | 284.96 ± 66.14 | 0.770 | 0.384 |
| | | 143.89 | 151.04 | | |
| | | 108.46 ↑↑ | 112.78 ↑↑ | | |
| | | -22.148 | -19.963 | | |
| | p- Value | 0.001 (S) | 0.001 (S) | | |
| CPT | Pre-treatment | 4.04 ± 1.23 | 4.12 ± 1.26 | 0.075 | 0.785 (NS) |
| | Post-treatment | 7.89 ± 2.38 | 8.33 ± 2.00 | 1.542 | 0.219 (NS) |
| | Mean difference | -3.85 | -4.21 | | |
| | % improvement | 95.30 ↑↑ | 102.18 ↑↑ | | |
| | t value | -16.026 | -21.877 | | |
| | p- Value | 0.001 (S) | 0.001 (S) | | |
| PWD | Pre-treatment | 389.77 ± 79.57 | 390.10 ± 87.19 | 0.001 | 0.988 (NS) |
| | Post-treatment | 741.97 ± 105.34 | 746.29 ± 114.94 | 0.063 | 0.803 (NS) |
| | Mean difference | -352.20 | -356.19 | | |
| | % improvement | 90.36 ↑↑ | 91.31 ↑↑ | | |
| | t value | -37.116 | -28.220 | | |
| | p- Value | 0.001 (S) | 0.001 (S) | | |
| PWT | Pre-treatment | 7.28 ± 1.20 | 7.20 ± 1.15 | 0.074 | 0.786 (NS) |
| | Post-treatment | 14.29 ± 1.93 | 14.33 ± 2.17 | 0.327 | 0.570 (NS) |
| | Mean difference | -7.01 | -7.13 | | |
| | % improvement | 96.29 ↑↑ | 99.03 ↑↑ | | |
| | t value | -35.649 | -28.569 | | |
| | p- Value | 0.001 (S) | 0.001 (S) | | |

Data are expressed as mean ± SD. F value= ANCOVA test; t value= paired t test.

NS= $p > 0.05$ = not significant; S= $p \leq 0.05$ = significant.

The purpose of this study was to investigate the effect of (HTEMS) on endothelial dysfunction and walking parameters in Peripheral arterial disease.

The result of this study showed that there is significant improvement in NO levels and walking parameters by HTEMS in PAD patients, with no significant difference with exercise group so we could use HTEMS as alternative method in PAD patients who have issues preventing them from adhere to the exercise program and may further

The previous results of this study come in agreement with Szymańska et al., 2011 [8] who stated that HiToP makes it possible to improve lower limb function, as evidenced primarily by improved claudication distance, maximum walking distance and improved blood flow parameters in cutaneous microcirculation.

Our results are in line with Hak et al., 2004. [9] who reported that High tone external muscle stimulation therapy has been found highly effective in circulation disorders and pain syndromes which in a way justifies its inclusion in the

treatment of patients with chronic lower limb ischaemia, the most important finding of which is that HiToP therapy has an impact on functional walking ability in chronic patients with chronic lower limb ischaemia.

The results of this study re confirmed with Di et al., 2014 [5] who reported that HTEMS increases vasodilatation (enhanced bioavailability of nitric oxide) leading to improved microcirculation and endoneural blood flow (locally and systemically).

This improvement was supported also by Damásdi et al., 2013 [10] who found in a small, open-label, self-controlled intervention study that HTEMS therapy of the thighs in patients with severe erectile dysfunction (ED) and vascular dysfunction resulted in an acute improvement in penile blood flow and acute rise of penile peak systolic velocity (PSV) in the semi-rigid state. Within the following 4 weeks of HTEMS treatment (3 times per week), basal penile blood flow and ED were not significantly improved. It is an open question whether a more frequent therapy (daily sessions) in patients with less severe ED might be more successful, and this study was done over 12 weeks to examine if longer duration produces better results.

The analgesic effectiveness of the HTEMS encourages further uses in the treatment of low back pain syndrome, sciatica, diabetic polyneuropathy and other conditions, it stated that this modality seem to be an effective method of increasing the pain threshold, and thus reducing pain p over TENS [11-17].

All previous studies that confirmed the effect of HTEMS in reduce pain in even many different cases support our result in the role of HTEMS in improve walking parameters as shown previously.

The NO improvement results in our study also agreed with Peckova et al., 2012, [18] whom study confirmed that activated striated muscles could release vasoactive substances that might induce distant effects of HTEM, and observed an increased diuresis and natriuresis during HTEMS therapy as in study of healthy volunteers, HTEMS treatment resulted in a significant transient increase of creatinine clearance and fractional sodium excretion. This finding suggests that HTEMS can transiently increase glomerular filtration rate and decrease the tubular sodium transport. Changes of glomerular filtration rate are very likely caused by an increase of renal blood flow and might be explained by the influence of vasodilating factors including an enhanced NO formation.

Biagio et al., 2014 [5] was a line with our results and showed that in acute kidney injury (AKI) patients, application of HTEMS is associated with a faster normalization of lowered NOx and elevated Asymmetric dimethylarginine (ADMA) endothelial 1 (ET-1) plasma levels, the more rapid amelioration of these parameters in the HTEMS group contributed to the accelerated recovery of AKI. With regard to the small study groups with

different causes of AKI, investigations in a greater number of AKI patients is required.

Treatment with HTEMS or (high-tone therapy) seems a promising approach in the therapy of Chemotherapy-induced peripheral neuropathy (CIPN) and showed good results. It provided important evidence about the therapeutic effects HTEMS in CIPN, which is a worldwide concern in oncologic patients. Since HTEMS has hardly any side effects, it seems to be a promising approach in the therapy of CIPN [19].

Furthermore, HTEMS demonstrated improvement in pain, discomfort, sleep disturbance, and quality of life in patients with end-stage renal disease due to uremic peripheral neuropathy [20].

Klassen et al., 2013 [21] stated that the study demonstrated for the first time that subjective amelioration of uremic peripheral neuropathy by HTEMS treatment is associated with significant improvement in an objective electrophysiological parameter, motor nerve conduction velocity.

In obese diabetic patients, application of high frequency external muscle stimulation also called HTEMS ameliorated the Hb A1C level and homeostatic model assessment (HOMA) index, indicating improved insulin sensitivity [22].

HTEMS has beneficial effect on the functional status of patients with multiple sclerosis. Obtaining results in terms of number of tested parameters allows for the use of this therapy in the comprehensive improvement of patients with multiple sclerosis [23].

3 Conclusion

In summary both HTEMS and supervised treadmill training are successful in improving treadmill walking ability and NO in patients with moderate stage of PAD patients. The HTEMS could be a feasible, effective noninvasive physiotherapeutic modality with a better acceptance that may be employed as an alternative modality to exercise training, especially for patients with PAD who cannot adhere to exercise training or where the exercise is contraindicated.

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