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Treadmill with Transcutaneous Electrical Nerve Stimulation Impact on Peak Velocity in Peripheral Arterial Disease: a Randomized Controlled Trial

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ABSTRACT

INTRODUCTION. Patients' functional ability and quality of life are negatively impacted by peripheral arterial disease, which presents as incapacitating leg discomfort that affects walking. Although there are numerous methods for treating these symptoms, as treadmill training, individuals stopped because of their persistent pain. Transcutaneous electrical nerve stimulation (TENS) is a suggested treatment for pain relief.

AIM. This study aimed to determine how combined treadmill training and TENS affect walking distance, pain, and peak velocity in patients with peripheral artery disease.

MATERIALS AND METHODS. The study included 50 people with peripheral arterial disease (PAD), stage II Fontaine, and an ankle-brachial index of 0.90 or lower at rest or 0.73 or lower after exercise. Participants were randomly assigned to either supervised treadmill training (control group, $n = 25$) or supervised treadmill training combined with TENS (experimental group, $n = 25$) for 3 months. Doppler ultrasonography, and skeletal muscle oxygen saturation (SmO_2) were evaluated at baseline and after the study's completion.

RESULTS AND DISCUSSION. The experimental group significantly improved all parameters being assessed more than the control group (< 0.05), except total hemoglobin, which did not differ statistically between groups.

CONCLUSION. This trial is the first to use treadmill training in conjunction with TENS as an adjuvant method to improve vascular function in people with PAD. Patients may use this strategy over time to improve their walking abilities, and it might be introduced into normal care in cardiovascular retraining**.**

REGISTRATION: Clinicaltrials.gov identifier No. NCT06061211, registered 28.09.2023.

KEYWORDS: vascular function, pain, exercise test, ankle-brachial index, oxygen saturation

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Эффективность беговой дорожки с использованием транскутанной электрической нервной стимуляции при заболеваниях периферических артерий: рандомизированное контролируемое исследование

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РЕЗЮМЕ

ВВЕДЕНИЕ. Заболевания периферических артерий негативно сказываются на функциональной способности и качестве жизни пациентов, что проявляется в виде дискомфорта в ногах, который приводит к потере трудоспособности и влияет на ходьбу. Несмотря на то, что существует множество методов лечения этих симптомов, таких как тренировки на беговой дорожке, люди отказываются от них из-за постоянной боли. Для облегчения боли рекомендуется использовать транскутанную электрическую нервную стимуляцию (ТЭНС).

ЦЕЛЬ. Определить, как комбинированные тренировки на беговой дорожке и ТЭНС влияют на дистанцию ходьбы, боль и максимальную скорость у пациентов с заболеваниями периферических артерий.

МАТЕРИАЛЫ И МЕТОДЫ. В исследование было включено 50 человек с заболеваниями периферических артерий, II стадией по классификации Фонтейна и лодыжечно-плечевым индексом, равным 0,90 или ниже в состоянии покоя или 0,73 или ниже после физической нагрузки. Пациенты были случайным образом распределены на две группы для занятий под наблюдением врача на беговой дорожке (контрольная группа, $n = 25$) или на беговой дорожке в сочетании с ТЭНС (основная группа, $n = 25$) в течение 3 месяцев. Ультразвуковая допплерография и насыщение кислородом скелетных мышц (SMO_2) оценивались в начале исследования и после его завершения.

РЕЗУЛЬТАТЫ И ОБСУЖДЕНИЕ. Основная группа значительно улучшила все оцениваемые показатели по сравнению с контрольной группой ($p < 0,05$), за исключением общего уровня гемоглобина, который статистически не отличался между группами.

ЗАКЛЮЧЕНИЕ. В этом исследовании впервые используются тренировки на беговой дорожке в сочетании с ТЭНС в качестве вспомогательного метода для улучшения функции сосудов у людей с заболеваниями периферических артерий. Пациенты могут со временем использовать эту стратегию для улучшения своих способностей к ходьбе, и она может быть внедрена в обычную практику при переподготовке сердечно-сосудистых специалистов.

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INTRODUCTION

Peripheral arterial disease (PAD) is thought to affect at least 113 million people worldwide and possibly as many as 236 million, even though prevalence estimates vary greatly [1]. Due to the prevalence of conventional risk factors, specifically smoking, hyperlipidemia, and a high incidence of diabetes mellitus (DM), lower limb ischemia and peripheral atherosclerotic occlusive disease (PAOD) are common in the Egyptian population [2]. Although the prevalence is higher in men, as in several other parts of the world, both men and women are equally affected [3, 4].

Despite being a major worldwide health burden, PAD remains mostly untreated and mistreated. Individuals may already be experiencing stenotic or occlusive illness that begins at the aortoiliac bifurcation and ends in the crural arteries [3]. Initially, intermittent claudication (IC), defined as "fatigue, discomfort, cramping, or pain in the muscles of the lower limbs that is regularly provoked by movement and always resolved by rest in 10 minutes," is the most common clinical presentation of PAD [5]. As PAD progresses, symptoms such as critical limb ischemia emerge [6]. It increases the risk of serious cardiovascular problems, premature death, and a lower quality of life [7, 8]. Exploring techniques that can alleviate pain and minimize ischemia in people with PAD is thus particularly important.

The National Institute for Health and Care Excellence (NICE) recommends supervised exercise therapy (SET) as the primary treatment for IC [9]. It has been found to improve quality of life, walking distance, and physical activity (PA), as well as assist in reducing major adverse cardiovascular events (MACE) [10].

Individuals with IC should exercise above the threshold that causes discomfort to benefit from secondary prevention through PA. This is an additional barrier to participation in physical training [11]. However, many claudication patients may struggle to keep walking, as seen by the comparatively high dropout rate of approximately 30 % from walking programs [10]. Despite the evident benefits of exercise therapy, about 45 % of patients do not follow medical professionals' advice to exercise frequently and walk "through" IC discomfort. A variety of other therapeutic strategies have been proposed [12].

Despite this, a systematic review [13] found that there has been little research on using pain management to motivate exercise and physical activity. Transcutaneous electrical nerve stimulation (TENS) applied to the lower leg while walking on a treadmill may improve absolute claudication distance over placebo [14]. TENS therapy for PAD patients would increase walking distance by addressing two aspects of vascular claudication: pain and reduced vascular flow [15]. TENS may help IC patients improve their walking abilities and walking-based physical activity [14, 16].

According to earlier studies, increasing patient awareness about the disease and the need for exercise is necessary to prevent consequences from poorer adherence to treadmill training owing to pain [12]. This pain forces patients to stop exercising until the pain subsides by vasodilation and increasing blood supply to exercising muscle; repeated ischemic reperfusion events increase damage to the artery and increase the risk of cardiovascular events. from here arises the concept of increasing adherence by using additional modalities such as TENS [13]. Therefore, the purpose of this study was to assess the impact of treadmill TENS on patients with PAD, which has not been studied before. We hypothesized that TENS combined with aerobic exercise improves walking distance, pain, and peak velocity in PAD patients more effectively than aerobic exercise alone.

MATERIALS AND METHODS

Study design

This three-month intervention is a prospective randomized controlled experiment. TENS with a treadmill (experimental group, $n = 25$) and treadmill exercise alone (control group, $n = 25$) were the two groups into which study participants were randomly assigned.

Ethical approval

The study was conducted from 1 October 2023 to 30 November 2024. This study was carried out in compliance with the Declaration of Helsinki [17], and all procedures involving human participants were authorized by Cairo University's Faculty of Physical Therapy's Research Ethics Committee (ethics reference No P.T.REC/012/004528). This trial was registered in ClinicalTrials.gov (NCT06061211) and was reported following CONSORT criteria.

Data collection procedure

An independent nurse contacted participants for eligibility at screening (at least 4 months before baseline from May 2023 to September 2023) by acquiring phone call data on their age and health status.

Interviews for the study: At baseline and three months following exercise rehabilitation, patients were assessed during study visits. Patients took tests in the following order during each research visit: (1) history and physical examination; (2) health, physical function, and physical activity questionnaires; (3) peripheral hemodynamic testing; (4) exercise and physical function tests; and (5) medical history and current medication review. Following a physical examination and review of their medical histories, all patients were diagnosed with Fontaine stage II PAD at the initial baseline visit. To start the evaluation, a medical history interview was conducted to gather information on the patient's demographics, cardiovascular risk factors, comorbidities, self-reported claudication history, site of claudication, and current medications. Throughout the trial, each patient's medication schedule remained unchanged.

Participants

Patients with peripheral arterial disease were sourced from Cairo University's Kasr el Ainy (Medical Faculty) in Giza, Egypt. Every participant was fully aware of the study's goals and procedures, which adhered to ethical guidelines. Each subject provided written informed permission. Participants were chosen based on the following standards. Ankle-brachial index (ABI) of 0.90 or less at rest or 0.73 or less after exercise, 50 patients with intermittent claudication secondary to PAD, and ambulation during a graded treadmill test limited by leg pain consistent with intermittent claudication (stage II of the Fontaine classification of PAD) They were between the ages of 40 and 75, had a body mass index (BMI) between 18.5 and 40 kg/m^2, were clinically stable, smoked, had a verified clinical diagnosis of peripheral arterial disease, and were sedentary in their activity level as measured by the Global Physical Activity Questionnaire (GPAQ).

Exclusion criteria were the absence of PAD and the inability to acquire an ABI measure due to non-compressible vessels. Asymptomatic PAD was identified from the medical history and confirmed on the graded treadmill test. The use of cilostazol and pentoxifylline began within three months before the investigation. Factors other than leg pain that limit exercise tolerance include active cancer, renal disease, or liver disease; the presence of a contraindication to TENS use, such as a pacemaker or skin lesion; walking disorders related to orthopedic or neuromuscular disease; myopathy; associated progressive disease causing deterioration in general health; an implanted pacemaker or defibrillator; and uncontrolled diabetes.

Randomization

Participants were divided into the experimental and control groups at random and in equal measure. A masked centralized randomized technique with allocation concealment was carried out by a statistician who was not a member of the research team. The assignment was kept a secret from the participants and the research team, except for the physiotherapists who were participating in the intervention. Separated by gender, age (40–75 years), and BMI, the randomization sequence was made using R Software (version 2.11). Block sizes ranged randomly from four to eight to maintain an even number of participants in each group. Additionally, the control group members received their exercise on a different day than the experimental group members.

Training and testing

Supervised treadmill training

Three times a week for 12 weeks, the experimental and control groups engaged in an aerobic exercise regimen on different days using the SIDEA-Germany treadmill. Every participant worked out under the guidance of a doctor and research physiotherapists, who kept an eye on their blood pressure, heart rate, and degree of exhaustion during the training. 25 patients completed a total of 36 training sessions of supervised treadmill training for 45 minutes per session. Treadmill walking started with a warm-up period for 5 minutes at a speed of 1.5 km/h at a 0 % grade, then the speed increased during the exercise phase (30 minutes) gradually till reaching maximum heart rate calculated for each patient and the degree of claudication pain on the claudication pain scale (4 of 5) to avoid the risk of ischemic reperfusion [14]. A participant was able to walk for 8 minutes at the starting workload without needing to stop because of fairly severe claudication. The treadmill grade was increased by increments of 0.5%, and the exercise intensity was increased throughout training sessions by raising the treadmill speed by increments of 0.1–0.2 mph (0.2–0.3 km/h) as tolerated, then the walking finished with a cooling down time of 5 minutes [18].

TENS

In the experimental group, TENS (Electric stimulator MH8001, China) was applied to the pain site according to the diseased artery and the muscle that is supplied by this artery while walking on a treadmill with a starting frequency of 2 Hz, then gradually increased the frequency of TENS up to 120 Hz, pulse width of 200 microseconds, and patient-determined intensity of "strong but comfortable and slight muscle twitch" [19]. All sessions took place at Egypt's Faculty of Physical Therapy outpatient clinic.

Outcome measures

Primary measures

Doppler ultrasonography

Pathology is detected and assessed directly using duplex ultrasound (US) (a General Electric Logic P6 machine equipped with a linear probe with 7.5–12 MHz frequency and a curvilinear probe with 2.5–7.5 MHz frequency), which uses color, grayscale, and spectral Doppler ultrasound [20]. Color Doppler pinpoints the degree of illness more accurately and efficiently, whereas spectral Doppler is quantitative. Experienced vascular scientists examined an individual in a horizontal position with a portable US system equipped with a 5–10 MHz linear array, using imaging, color, and pulsed Doppler modes. The aortoiliac, femoral, popliteal, and pedal parts were all scanned throughout the assessment [21] as seen in Figure 1.

To confirm a PAD case, one of the following requirements must be met: (1) at least one narrowing of more than 50 %. (2) a blockage, or (3) extensive stenosis to the point where circulation was impeded and the waveform was reduced in the popliteal area. A typical Doppler waveform contains three distinct triphasic features: a visible upward systolic peak, a little negative early diastolic wave, and a slightly positive late diastolic wave. When PAD is present, Doppler waves might be biphasic or monophasic [20].

Ankle peak systolic velocity (APSV) is a new alternative metric for assessing the degree of peripheral ischemia. The APSV is the mean peak systolic velocity of the anterior and posterior tibial arteries (PTAs) recorded at the ankle. A 5- to 12-MHz linear transducer is used for the infrainguinal arteries. The Doppler angle of insonation was adjusted to 60 µ. Prior to imaging, each patient was given one hour of rest and a lying-down assessment. The ambient temperature was set to 22 °C for recording purposes [21]. APSV is unaffected by vascular stiffness and was assessed when toe gangrene or amputation occurred; it was effective in some cases. It was also evaluated when the lower limbs were submitted to arterial duplex scanning [22].

Secondary measures

Skeletal muscle oxygen saturation (SmO_2)

SmO_2 was measured noninvasively using near-infrared spectroscopy (NIRS) by Moxy (Fortiori Design LLC, Minnesota). SmO_2, a tissue oxygenation marker, was measured in the muscle vasculature. Muscle oxygen saturation was measured at each participant's medial gastrocnemius on the diseased leg while conducting the treadmill activity test using continuous-wave spectroscopy with greater precision in the muscle layer and less precision in the fat layer [23].

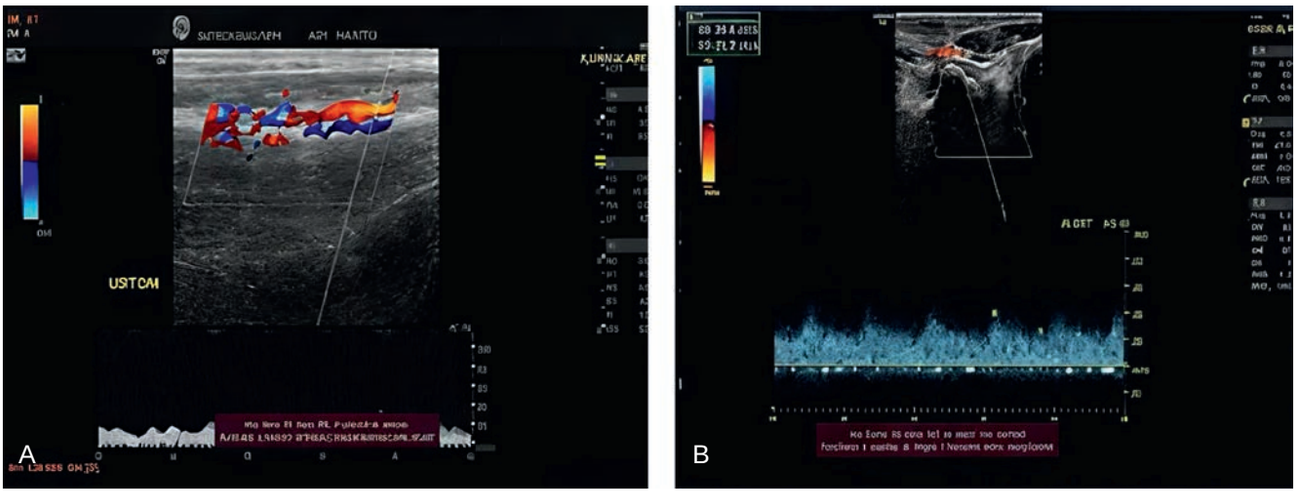

Fig.1. A — depicts Doppler scanning of the dorsalis pedis artery in a peripheral arterial disease patient with intermittent claudication prior to intervention; B — indicates an improvement in both peak systolic velocity and acceleration time following 12 weeks of supervised treadmill training with TENS

Eligibility

Sixty-five patients were evaluated for participation; 15 were rejected ($n = 6$ did not fulfill the inclusion criteria, $n = 4$ declined to take part, and $n = 5$ had other reasons). Out of the 50 patients who completed the trial, 25 were randomly allocated to the experimental group and 25 to the control group. These patients were the only ones included in the data analysis, as seen in Figure 2.

The necessary sample size was estimated. Using data from a prior study [24], the sample size was determined using G* Power software, version 3.1.9.4, based on the anticipated change in the primary outcome, Doppler Flow Velocity in the right dorsalis pedis artery (RDP). The control group's mean RDP was 10.896 ± 3.976 cm/s, while the exercise groups was 14.568 ± 4.002 cm/s. The effect size was 0.92, with the anticipated mean difference in RDP between the two groups being 3.672 cm/s. To attain a power of 80 % and a significance level of 5 % (two-tailed level), a sample size of 20 patients per group, or 40 patients with peripheral arterial disease, was determined. There were 25 patients in the final needed sample size of 50, with 25 patients in each group, allowing for an expected 20 % attrition/dropout rate.

Statistical analysis

SPSS statistics software version 25 was used to analyze the data. Categorical variables were reported in frequency counts and percentages. The categorical variables were compared using the chi-square (χ^2) test. The Shapiro — Wilk test was used to determine whether continuous variables were normal. Normal continuous variables were expressed using mean and standard deviation (SD), while non-normally distributed data were expressed using median (25th percentile [Q1] — 75th percentile [Q3]). For data that was not normally distributed, a paired t-test was used, and a rank was signed by Wilcoxon. Differences between groups were found using an independent sample t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data, respectively. Each group's mean change between baseline and post-intervention was calculated, along with a 95% confidence interval (CI). A mixed repeated measures ANOVA was used to investigate the impact of time and group interaction. Partial eta squared ($\eta 2$) was utilized to measure the difference between the two groups. The magnitude of the treatment effects within and across the groups was also analyzed using Cohen's d-test, and they were classed as high (d = 0.8), medium (d = 0.5), and small (d = 0.2). P-values less than 0.05 ($p < 0.05$) were considered statistically significant.

RESULTS AND DISCUSSION

This study comprised 50 individuals with PAD, with a mean age of 55.80 ± 9.78, ranging from 40 to 75 years old. The majority of participants were male (72.0 %) (Table 1).

Table 1 shows that there was no significant difference between groups in terms of all baseline variables ($p > 0.05$).

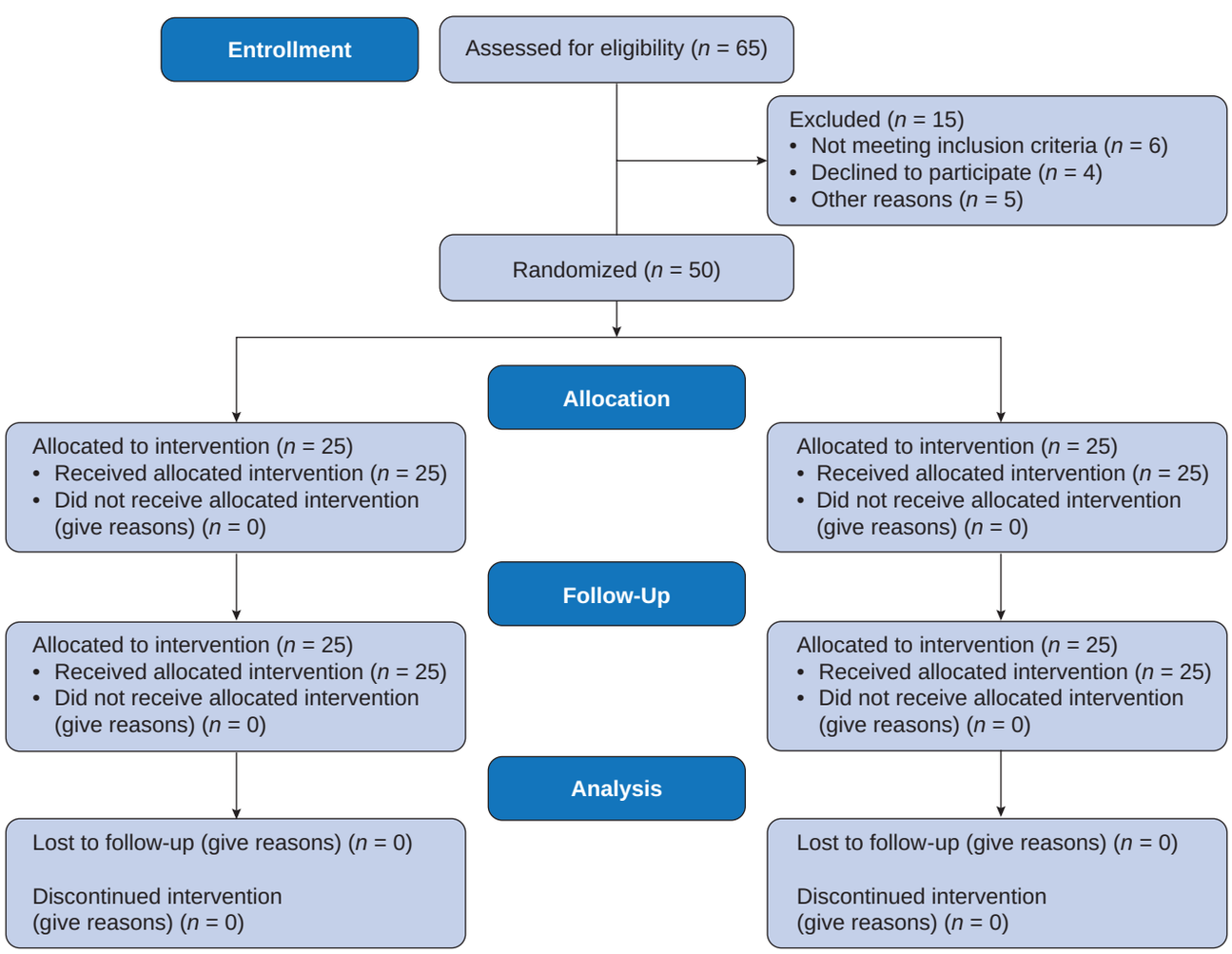

Fig. 2. Consort flow chart of this study

Table 1. Baseline characteristics of studied patients

Variables	Total (*n* = 50)	Experimental group (*n* = 25)	Control group (*n* = 25)	Test of Significance	P-value
Age (Years)	55.80 ± 9.78 (40.00–75.00)	54.96 ± 0.95 (40.00–65.00)	56.64 ± 10.56 (40.00–75.00)	*t* = –0.603	0.549
Sex, *n* (%) Male Female	36 (72.0 %) 14 (28.0 %)	18(72.0 %) 7(28.0 %)	18(72.0 %) 7(28.0 %)	$\chi 2 = 0.000$	1.000
BMI (kg/m²)	28.02 ± 3.40 (20.40–35.00)	27.93 ± 3.82 (20.40–35.00)	28.11 ± 3.00 (23.60–34.00)	*t* = –0.185	0.854
Artery sides Right Left	26 (52.0 %) 24 (48.0 %)	13 (52.0 %) 12 (48.0 %)	13 (52.0 %) 12 (48.0 %)	$\chi 2 = 0.000$	1.000
No. of sessions	32.62 ± 5.77 (15.0–36.00)	32.32 ± 6.02 (18.00–36.00)	32.92 ± 5.60 (15.00–36.00)	*t* = –0.365	0.717
PSV CFA	44.26 ± 22.89 0.00–80.00	46.12 ± 23.66 0.00–80.00	42.40 ± 22.43 0.00–80.00	*t* = 0.571	0.571
PSV SFA	33.82 ± 25.93 0.00–82.00	34.04 ± 23.05 0.00–82.00	33.60 ± 29.02 0.00–81.00	*t* = 0.059	0.953
PSV POP A	29.44 ± 20.77 0.00–80.00	29.40 ± 22.44 0.00 v 80.00	29.48 ± 19.43 0.00–80.00	*t* = –0.013	0.989
PSV ATA	21.50 ± 15.18 0.00–60.00	20.38 ± 14.14 0.00–60.00	22.62 ± 16.38 0.00–60.00	*t* = –0.518	0.607
PSV PTA	26.92 ± 18.03 0.00–80.00	27.04 ± 20.24 0.00–70.00	26.80 ± 15.95 0.00–80.00	*t* = 0.047	0.963
SmO_2 max	39.29 ± 20.64 8.60–92.30	39.10 ± 19.64 8.60–86.00	39.48 ± 21.99 8.80–92.30	*t* = –0.064	0.949
SmO_2 min	14.52 ± 9.59 0.10–40.70	14.38 ± 9.49 0.10–40.70	14.65 ± 9.88 0.10–40.50	*t* = –0.099	0.921
SmO_2 AV	27.04 ± 12.57 6.30–63.35	27.18 ± 12.95 6.70–63.35	26.8912.45 6.30–57.45	*t* = 0.082	0.935
THB MAX	12.33 ± 0.49 11.37–13.16	12.44 ± 0.53 11.37–13.16	12.23 ± 0.42 11.45–13.05	*t* = 1.492	0.142
THB MIN	12.06 ± 0.58 10.83–13.12	12.16 ± 0.62 10.94–13.12	11.96 ± 0.52 10.83–12.91	*t* = 1.223	0.227
THB AV	12.15 ± 0.56 10.97–13.15	12.24 ± 0.59 11.12–13.15	12.06 ± 0.51 10.97–12.99	*t* = 1.140	0.260

Note: *BMI — Body mass index; PSV CFA — Peak systolic velocity common femoral artery; PSV SFA — Peak systolic velocity Superficial femoral artery; PSV POP A — Peak systolic velocity Popliteal artery; PSV PTA — Peak systolic velocity Posterior tibial artery; PSV ATA — Peak systolic velocity Anterior tibial artery; APSV — Ankle peak systolic velocity; SmO_2 Max — Skeletal muscle oxygen saturation maximum; SmO_2 Min — Skeletal muscle oxygen saturation minimum; SmO_2 AV — Skeletal muscle oxygen saturation average; THB Max — Total hemoglobin maximum; THB Min — Total hemoglobin minimum; THB AV— Total hemoglobin average; χ2 — Chi square test; t — Independent t-test.*

Categorical variables are presented as number (%). Continuous variables are presented as Mean ± SD (Min-Max) or Median (Q1-Q3) and range.

Table 2 demonstrates that APSV scores increased statistically significantly from pre-intervention to post-intervention during three months. The experimental group showed significantly larger improvements (86.89 % for APSV) compared to the control group (32.41 %) ($p < 0.003$). Time and therapy had statistically significant impacts on APS ($F = 91.182$; $\eta 2 = 0.655$; $p < 0.001$ and $F = 4.618$; $\eta 2 = 0.088$; $p = 0.037$). There was a significant interaction effect between time and treatment for APSV ($F = 21.469$; $\eta 2 = 0.309$; $p < 0.001$).

Figure 3 shows that the waveform patterns of the CFA, SFA, POP A, ATA, and PTA in the experimental group changed significantly after the intervention (p = 0.014, 0.002, 0.007, 0.007, 0.031, respectively).

Table 2. Comparison of ankle peak systolic velocity pre-and post-intervention between the two groups

Variables	Experimental group (n = 25)				Control group (n = 25)							
	Pre	Post	MD (95%CI)	p-value[b]	Pre	Post	MD (95 %CI)	p-value[a]	p-value[b]	p-value[c] Within time	p-value[c] between Group	p-value[c] Time X Group
APSV (cm/s)	22.58 ± 13.14	42.20 ± 20.60	+ 19.62 (14.74, 24.49)	< 0.001**	20.98 ± 9.35	27.78 ± 10.28	+ 6.80 (3.83, 9.77)	< 0.001**	0.003*	< 0.001**	0.037*	< 0.001**

Note: *APSV — Ankle peak systolic velocity; MD — Mean difference; CI — Confidence interval; Test of significance a — Paired t-test; b — Independent t-test; C — Mixed repeated measure ANOVA; * — Statistically significant at p-value < 0.05; ** — Statistically significant at p-value < 0.01). Data presented as Mean ± SD and range.*

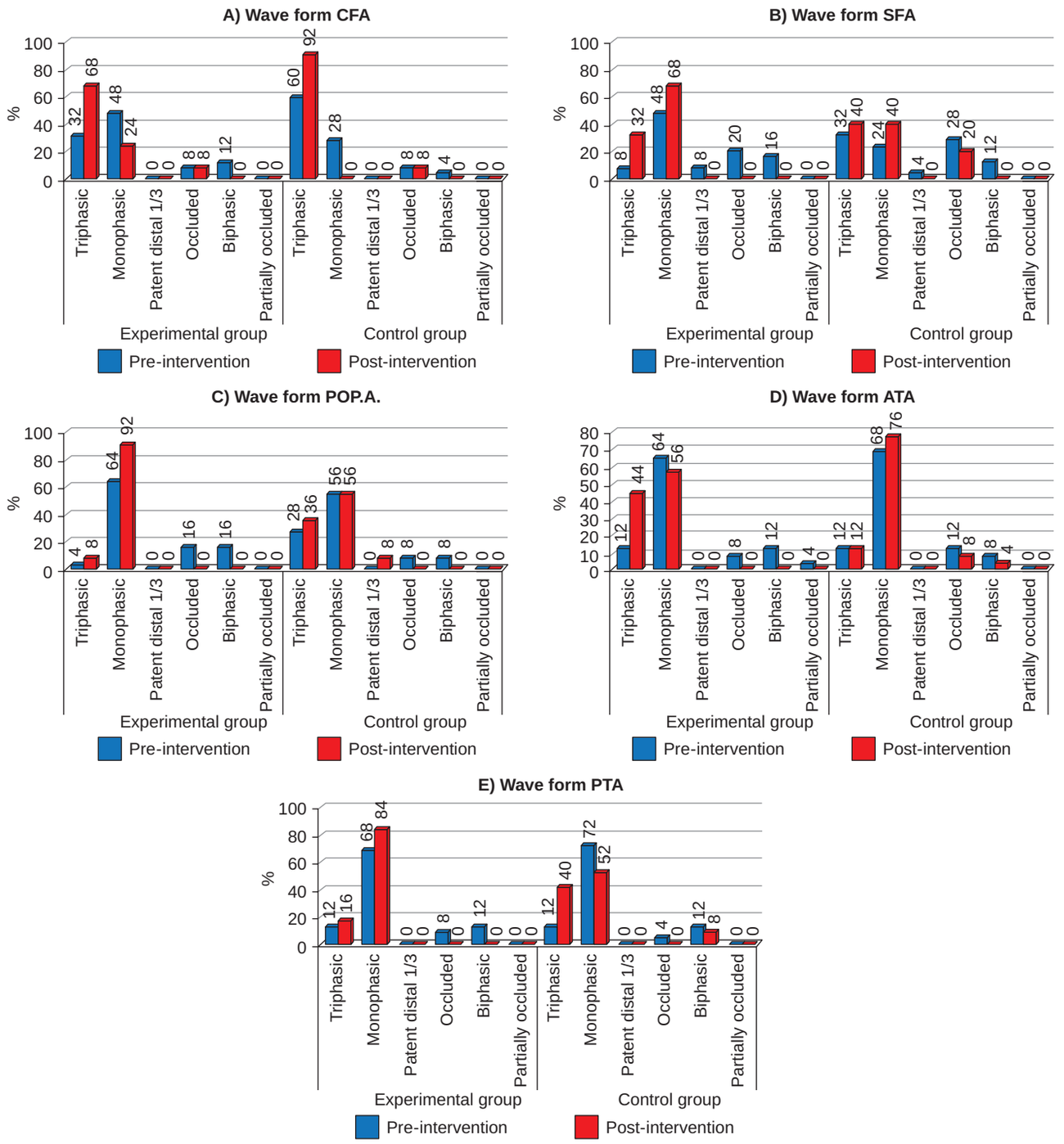

Fig. 3. Comparison of Doppler waveform distribution pre- and post-intervention between the two studied groups

Note: *CFA — Common Femoral Artery; SFA — Superficial femoral artery; POP.A — Popliteal artery; PTA — Posterior tibial artery; ATA — Anterior tibial artery.*

Pre-intervention, most patients in the experimental group had a monophasic (12 (48.0 %)), followed by triphasic (8 (32.0 %)), biphasic (3 (12.0 %)), and occluded (2 (8.0 %)) regarding waveform CFA. Post-intervention, 6 (24.0 %) patients reported monophasic and 17 (68.0 %) triphasic in the experimental group. In contrast, in the control group, the majority were triphasic (15 (60.0 %), followed by monophasic (7 (28.0 %)), occluded (2 (8.0 %)), and biphasic (1 (4.0 %)), pre-intervention, but post-intervention, the majority of patients reported triphasic (23 (92.0 %)).

Regarding waveform SFA, 12 patients (48.0 %) had a monophasic waveform, 4 (16.0 %) were biphasic, 2 (8.0 %) were triphasic, 5 (20.0 %) were occluded, and 2 (8.0 %) had patent distal 1/3 in the experimental group pre-intervention. Post-intervention, the experimental group reported 17 (68.0 %) triphasic and 8 (32.0 %) monophasic.

In terms of waveform POP A, the majority of patients in the experimental group (16 (64.0 %)) had a monophasic waveform, followed by biphasic (4 (16.0 %)), occluded (4 (16.0 %)), and triphasic (1 (4.0 %)) waveforms prior to intervention. Post-intervention, 6 (24.0 %) patients in the experimental group reported monophasic patterns, while 2 (8.0 %) reported triphasic patterns.

For the ATA, the experimental group showed 16 (64.0 %) patients had monophasic waveforms, followed by 3 (12.0 %) who had triphasic, 3 (12.0 %) who had biphasic, and 2 (8.0 %) who had occluded waveforms pre-intervention. Post-intervention, it was found that 14 (56.0 %) had monophasic and 11 (44.0 %) triphasic.

In the PTA, the experimental group had a higher frequency of patients with monophasic waveforms (17 (68.0 %), followed by 3 (12.0 %) triphasic, 3 (12.0 %) biphasic, and 2 (8.0 %) excluded pre-intervention, while 21 (84.0 %) were monophasic and 4 (16.0 %) triphasic.

Additionally, there was a statistically significant difference between the experimental and control groups regarding the distribution of waveforms, including CFA, SFA, POP A, ATA, and PTA ($p = 0.032$, 0.030, 0.013, 0.040, and 0.040, respectively).

In terms of Doppler PSV, the experimental group showed a statistically significant rise from pre- to post-intervention across 3 months, whereas the control group showed a statistically significant increase in CFA only from pre- to post-intervention (Table 3). The experimental group improved significantly more than the control group in the following areas after intervention: CFA (80.83 % vs. 29.25 %), SFA (101.058 % vs. 20.24 %), POP A (123.40 % vs. 19.27 %), ATA (171.84 % vs. 43.24 %), and PTA (96.59 % vs. 18.96 %).

There were statistically significant effects of time and treatment for all Doppler PSV, including CFA ($F = 46.420$; $\eta2 = 0.492$; $p < 0.001$ and $F = 4.618$; $\eta2 = 0.088$; $p = 0.046$, respectively), SFA ($F = 70.884$; $\eta2 = 0.596$; $p < 0.001$ and $F = 4.815$; $\eta2 = 0.091$; $p = 0.033$), POP A ($F = 29.926$; $\eta2 = 0.384$; $p < 0.001$ and $F = 4.592$; $\eta2 = 0.087$; $p = 0.037$), ATA ($F = 28.004$; $\eta2 = 0.368$; $p < 0.001$ and $F = 4.430$; $\eta2 = 0.084$; $p = 0.041$, respectively), and PTA ($F = 23.952$; $\eta2 = 0.333$; $p < 0.001$ and $F = 4.983$; $\eta2 = 0.094$; $p = 0.030$), respectively). Furthermore, time X treatment interaction effects were significant for all PSV measures, as in CFA ($F = 11.643$; $\eta2 = 0.195$; $p = 0.001$), SFA ($F = 31.811$; $\eta2 = 0.309$; $p < 0.001$), POP A ($F = 15.915$; $\eta2 = 0.249$; $p < 0.001$), ATA ($F = 8.889$; $\eta2 = 0.156$; $p = 0.004$), and PTA ($F = 10.893$; $\eta2 = 0.185$; $p = 0.002$).

Table 3. Comparison of Doppler peak systolic velocity (PSV) pre- and post-intervention between the two studied groups

Doppler PSV	Experimental group ($n = 25$)				Control group ($n = 25$)							
	Pre	Post	MD (95% CI)	*p*-value[a]	Pre	Post	MD (95% CI)	*p*-value[a]	*p*-value[b]	*p*-value[c Within time]	*p*-value[between c Group]	*p*-value[Time X Group]
CFA	46.12 ± 23.66	83.40 ± 46.92	+ 37.28 (23.82, 50.74)	< 0.001**	42.40 ± 22.43	54.80 ± 22.75	+ 12.40 (5.66, 19.14)	0.001*	0.009*	< 0.001**	0.046*	0.001**
SFA	34.04 ± 23.05	68.44 ± 22.84	34.40 (28.48, 40.32)	< 0.001**	33.60 ± 29.02	40.40 ± 22.59	6.80 (–1.38, 14.98)	0.099	< 0.001**	< 0.001**	0.033*	< 0.001**
POP A	29.40 ± 22.44	65.68 ± 46.19	36.28 (21.66, 50.90)	< 0.001**	29.48 ± 19.43	35.16 ± 15.59	5.68 (–0.39, 11.75)	0.065	0.003*	< 0.001**	0.037*	< 0.001**
ATA	20.38 ± 14.14	55.40 ± 30.95	35.02 (23.43, 46.61)	< 0.001**	22.62 ± 16.38	32.40 ± 26.19	9.780 (–3.29, 22.86)	0.136	0.007*	< 0.001**	0.041*	0.004**
PTA	27.04 ± 20.24	53.16 ± 26.78	26.12 (16.73, 35.5)	< 0.001**	26.80 ± 15.95	31.88 ± 16.99	5.080 (–4.13, 14.29)	0.266	0.002*	< 0.001**	0.030*	0.002**

Note: *PSV — Peak systolic velocity; CFA — Common femoral artery; SFA — Superficial femoral artery; POP.A — Popliteal artery; PTA — Posterior tibial artery; ATA — Anterior tibial artery; MD — Mean difference; CI — Confidence interval; Test of significance a — Paired t-test; b — Independent t-test; c — Mixed repeated measure ANOVA; * — Statistically significant at p-value < 0.05; ** — Statistically significant at p-value < 0.01. Data presented as Mean ± SD and range.*

Table 4 reveals that the experimental group experienced a statistically significant rise in SmO_2 Max, Min, and AV from baseline to 3 months post-intervention. However, the control group only experienced a large increase in SmO_2 AV, with no changes in Max or Min. The experimental group improved significantly more after three months of intervention, by 76.65 % (Max), 128.65 % (Min), and 73.77 % (AV), than the control group, which improved by 21.94 %, 24.51 %, and 23.50 %, respectively.

There were no statistically significant changes in THB Max, Min, or AV between baseline and 3 months post-intervention in either group. After three months of intervention, no statistically significant differences were seen between the two groups. THB Max did not show statistically significant impacts from time, treatment, or time × treatment interaction.

Adverse events of applied intervention

According to weekly interviews conducted to document any adverse events encountered by the participants, no adverse events related to the use of TENS or aerobic exercise were noted during this study.

To the best of our knowledge, this is the first randomized controlled clinical trial that examined the effects of treadmill training in conjunction with TENS on the following parameters: muscle oxygenation, Peak velocities and waveform response to treatment in patients with intermittent claudication (stage II Fontaine). The experimental group outperformed the control group in both primary and secondary outcomes, including Doppler examination, APSV, and SmO_2 as we had predicted. However, there was no statistical difference between the groups in THB.

Our findings were consistent with a study showing that TENS can increase resting coronary blood flow velocity. The findings indicate that the site of action is at the microcirculatory level and that the effects could be mediated by brain mechanisms [25]. A study found that TENS resulted in a slight increase in middle cerebral artery (MCA) blood flow velocity (0.78 cm/s) [26].

Furthermore, Castro-Sánchez A.M. et al. discovered that exercise enhanced the blood flow velocity in the dorsalis pedis and posterior tibial arteries [24]. Using the Doppler probe, we were able to measure the pulse volumes of the dorsalis pedis and posterior tibial arteries bilaterally; this method works extremely well for determining the distal flow, blood flow velocity in the stenosis area, and distal flow [27].

Table 4. Comparison of SmO_2 and THB pre- and post-intervention between the two studied groups

Variables	Experimental group (n = 25)				Control group (n = 25)				*p*-value[b]	*p*-value Within time	*p*-value between Group	*p*-value[c] Time X Group
	Pre	Post	MD (95% CI)	*p*-valuea	Pre	Post	MD (95% CI)	*p*-value[a]				
SmO_2												
Max.	39.10 ± 19.64	69.07 ± 21.27	29.96 (21.26, 38.67)	< 0.001**	39.48 ± 21.99	48.14 ± 12.37	8.65 (–0.56, 17.86)	0.064	< 0.001**	< 0.001**	0.026*	0.001**
Min.	14.38 ± 9.49	32.88 ± 17.69	18.49 (12.13, 24.86)	< 0.001**	14.65 ± 9.88	18.24 ± 15.04	3.59 (–1.54, 8.7)	0.161	0.003**	< 0.001**	0.032*	< 0.001**
AV.	27.18 ± 12.94	47.23 ± 16.69	20.05 (14.34, 25.76)	< 0.001**	26.89 ± 12.45	33.21 ± 11.16	6.32 (0.94, 11.71)	0.023*	0.001*	< 0.001**	0.035*	0.001**
THB												
Max.	12.44 ± 0.53	12.35 ± 0.56	–0.08 (–0.43, 0.27)	0.626	12.23 ± 0.42	12.36 ± 0.29	0.13 (–0.05, 0.31)	0.148	0.940	0.814	0.295	0.270
Min.	12.16 ± 0.62	12.13 ± 0.33	–0.09 (–0.11, –0.06)	0.832	11.96 ± 0.52	11.90 ± 0.64	–0.01 (–0.16, –0.09)	0.608	0.123	0.617	0.115	0.858
AV.	12.24 ± 0.59	12.22 ± 0.32	–0.02 (–0.26, 0.22)	0.868	12.06 ± 0.51	12.03 ± 0.61	–0.03 (–0.24, 0.18)	0.771	0.173	0.751	0.150	0.946

Note: *SmO_2 — Skeletal muscle oxygen saturation; Max — Maximum; Min — Minimum; AV — Average; THB — Total hemoglobin; MD — Mean difference; CI — Confidence interval; Test of significance a — Paired t-test; b — Independent t-test; c — Mixed repeated measure ANOVA; * — Statistically significant at P-value < 0.05; ** — Statistically significant at p-value < 0.01. Data presented as Mean ± SD and range.*

Another study contradicted our findings, finding that the time-average-mean velocity and flow volume of the posterior and anterior tibial arteries in both legs did not vary substantially between or between groups across the 6-month intervention. This could be due to mixing resistive exercises with treadmill walking, which is different from our intervention [28].

Our work was the first to show favorable alterations in blood flow waveforms, with fewer monophasic waves and more triphasic waves. That indicates a considerable improvement. Electrical stimulation causes two physiological changes: increased blood flow and an impact on peripheral circulation [29]. As a result, electrical stimulation has an impact on blood flow regulation, and careful modulation of this electrical excitation is required to avoid tissue injury [30].

This finding was consistent with Chauhan A. et al. research, which indicates that TENS may affect the sympathetic nervous system of the heart. They found TENS was associated with a significant increase in mean coronary artery blood flow in 34 patients with chest pain [31]. Moreover, Kaada B. et al. reported that TENS promoted vasodilatation in people with diabetic neuropathy and Raynaud's phenomenon [32].

Furthermore, this was a novel research feature about the effect of combined supervised treadmill training with TENS on SmO_2, which showed a beneficial effect because TENS promoted vasodilation, boosting perfusion and oxygen extraction. Our findings were consistent with those of Baker W.B. et al. study, which found that exercise training increased the vasculature's ability to increase oxygen extraction and delivery during physical activity. These improvements in oxygen extraction and delivery result in improved oxidative metabolism in muscles [33].

Manfredini F. et al. discovered that the medial gastrocnemius muscle's oxygenated hemoglobin levels increased. The subcategory that received planned training at a predetermined intensity saw significant gains in dynamic muscle perfusion. This group displayed enhanced walking performance, as well as a higher ability to receive oxygen from the calf [34].

Baker W.B. et al. found that treadmill activity increased peak leg muscle blood supply and oxygen consumption by 29 % (13 %, 50 %) and 8 % (1 %, 12 %), respectively, during monitored training sessions [$p < 0.001$; median (25th percentile, 75th percentile)]. Compared to the control group, the exercise group's overall benefits were significantly greater [33]. However, Beckitt T.A. et al. showed that angioplasty, but not supervised exercise training, modestly enhanced gastrocnemius muscle oxygenation during submaximal activity in claudicants, which contradicts our findings and could be related to differing treatment procedures followed in the study [35].

Regarding THB, there were no statistically significant changes in our result, which concurred with Baker's study. Even though increased capillary circulation expansion suggests that exercise training may have a significant impact on total hemoglobin/myoglobin concentration (i. e., micromole per volume of tissue), no obvious increases in THC were observed [33].

Muscle contraction and capillary blood volume expansion are two opposing variables that may impact THC during exercise. THC is lowered when muscular contraction compresses the venous component of the vascular tree, causing the muscle to expel venous blood volume. THC, on the other hand, increases with increased capillary blood volume [33]. Capillary blood volume expansion affects hemoglobin in the blood, but it has no effect on myoglobin in muscle. As a result, the unknown but approximate 20 % myoglobin contribution to the THC signal [28] may reduce the sensitivity of the THC measurement to changes in capillary blood volume [35].

CONCLUSION

This trial is the first to use treadmill training in conjunction with TENS as an adjuvant method to improve vascular function in people with PAD. This strategy may be used by patients over time to improve their walking abilities and might be introduced into normal care in cardiovascular retraining.

ADDITIONAL INFORMATION

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Ethical Approval. The authors declare that all procedures used in this article are in accordance with the ethical standards of the institutions that conducted the study and are consistent with the 2013 Declaration of Helsinki. The study was approved by the study was approved by the Local Ethics Committee of faculty of physical therapy Cairo University, Egypt, ethics reference No. P.T.REC/012/004528 dated 05.04.2023.
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