

Effects of Intradialytic Neuromuscular Electrical Stimulation Versus Resistance Exercise on Physical Function, Dialysis Adequacy, and Fatigue in Patients Receiving Maintenance Hemodialysis: A Randomized Controlled Trial

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ABSTRACT

Background:

Patients receiving maintenance hemodialysis commonly experience reduced lower-limb muscle strength, impaired walking capacity, fatigue, and reduced physical function. Intradialytic resistance training and neuromuscular electrical stimulation (NMES) are practical rehabilitation strategies, but direct comparisons between these interventions remain limited.

Objective:

To compare the effects of intradialytic NMES, intradialytic resistance training, and usual care on dialysis adequacy, lower-limb muscle strength, functional walking capacity, estimated peak oxygen uptake, and physical fatigue in patients receiving maintenance hemodialysis.

Methods:

This three-arm randomized controlled trial included 90 patients receiving maintenance hemodialysis. Participants were allocated equally to an intradialytic NMES group, an intradialytic resistance-training group, or a usual-care control group. Both active interventions were delivered twice weekly during the first 2 hours of hemodialysis for 16 weeks. Outcomes were assessed at baseline and after the intervention and included urea reduction ratio (URR), bilateral quadriceps and plantar-flexor strength, six-minute walk distance (6MWD), estimated peak oxygen uptake calculated from 6MWD, and physical fatigue. Within-group changes were summarized using paired analyses. Between-group treatment effects were estimated using baseline-adjusted analysis of covariance (ANCOVA) and reported as adjusted mean differences with 95% confidence intervals.

Results:

Both intradialytic NMES and resistance training produced significant baseline-adjusted improvements in URR, bilateral lower-limb muscle strength, 6MWD, estimated peak oxygen uptake, and physical-fatigue scores compared with usual care (all adjusted $p < 0.001$). No statistically significant adjusted differences were observed between the two active interventions for lower-limb strength, 6MWD, estimated peak oxygen uptake, or physical fatigue (all adjusted $p \geq 0.12$); because the trial was not designed as a non-inferiority study, this should not be interpreted as evidence of equivalence. Resistance training produced a significantly higher adjusted post-intervention URR than NMES (adjusted MD 4.12 percentage points, 95% CI 3.21 to 5.02, $p < 0.001$).

Conclusion:

Intradialytic NMES and resistance training were both associated with improved URR, lower-limb muscle performance, functional walking capacity, calculated estimated peak oxygen uptake (a derived measure of 6MWD), and physical fatigue in patients receiving maintenance hemodialysis, relative to usual care. No statistically significant difference was detected between NMES and resistance training for these outcomes other than URR; because the trial was not designed to test non-inferiority, this finding should not be interpreted as demonstrating equivalence between the two interventions. NMES may provide a practical, hypothesis-generating rehabilitation alternative for patients who cannot undertake voluntary resistance training.

Keywords: Renal Dialysis; Electric Stimulation Therapy; Resistance Training; Muscle Strength; Fatigue

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Introduction

Patients receiving maintenance hemodialysis commonly experience physical deconditioning, reduced aerobic capacity, muscle weakness, fatigue, and impaired physical function. These impairments can reduce independence and quality of life and may be compounded by the time and physical constraints of regular dialysis treatment [1].

Hemodialysis also creates practical barriers to physical activity. Regular treatment requires attendance at dialysis sessions several times each week and may contribute to sedentary behavior, frailty, and muscle weakness. Patients may also have limited time, post-dialysis fatigue, and difficulty accessing rehabilitation services outside dialysis units [2].

Muscle weakness in patients receiving maintenance hemodialysis is closely related to the catabolic effects of advanced kidney failure and the progressive loss of skeletal-muscle mass. In end-stage kidney disease, the balance between muscle protein synthesis and degradation is disturbed, resulting in net muscle protein loss. Insulin resistance and impaired insulin-like growth factor-1 (IGF-1)/Akt signaling reduce anabolic signaling and simultaneously promote activation of proteolytic pathways. Increased activity of the ubiquitin-proteasome system, autophagy-lysosomal pathways, and caspase-mediated proteolysis further accelerates skeletal-muscle protein degradation. In addition, chronic inflammation, metabolic acidosis, oxidative stress, mitochondrial dysfunction, uremic toxins, hormonal disturbances, and nutritional abnormalities can amplify these catabolic processes, ultimately contributing to muscle atrophy, reduced muscle strength, and impaired physical performance in patients with kidney failure [3,4].

Muscle wasting in maintenance hemodialysis results from a combination of uremia-related protein catabolism, chronic low-grade inflammation, metabolic acidosis, and physical inactivity imposed by dialysis schedules, processes that preferentially affect the type II (fast-twitch) fibers of postural and antigravity muscles [5].

Intradialytic resistance training provides a practical opportunity to counteract lower-limb muscle weakness by incorporating progressive muscle loading into the time already spent receiving hemodialysis. Evidence from randomized trials and meta-analyses indicates that resistance exercise performed during hemodialysis can improve lower-limb muscle strength and may also contribute to improvements in physical performance and functional capacity. In addition, resistance exercise requires active voluntary participation and adequate exercise tolerance, and adherence may be affected by

fatigue, clinical symptoms, intradialytic complications, or unwillingness to exercise during treatment. These limitations may reduce the feasibility of conventional resistance training for some patients receiving maintenance hemodialysis [6].

Neuromuscular electrical stimulation (NMES) elicits skeletal-muscle contractions through externally applied electrical impulses and may provide a rehabilitation option for patients who have difficulty performing voluntary exercise during hemodialysis. Evidence from randomized trials and meta-analyses indicates that intradialytic NMES can improve lower-limb muscle strength and functional capacity, including six-minute walk distance [7]. Nevertheless, evidence for improvements in muscle mass, habitual physical activity, health-related quality of life, and other clinical outcomes remains less consistent. Furthermore, most published NMES trials have involved relatively small samples, and variations in stimulation parameters and intervention protocols, together with risk-of-bias concerns, limit the certainty and generalizability of the available evidence [8].

Previous studies of intradialytic NMES and exercise, including the pilot trial by McGregor et al. [9] and the trial by Machfer et al. [2], have reported improvements in muscle strength and functional capacity, but have generally been limited by small sample sizes, heterogeneous stimulation or training protocols, in some studies the absence of a usual-care comparator, inconsistent outcome measures, and the lack of a head-to-head comparison between NMES and resistance training using a common set of muscular, functional, fatigue, and dialysis-adequacy outcomes.

Consequently, it remains unclear whether intradialytic NMES produces functional and dialysis-adequacy benefits comparable with intradialytic resistance training, because no trial has directly compared the two interventions against a common usual-care control using the same outcome battery.

Therefore, this study compared the effects of intradialytic NMES, intradialytic resistance exercise, and usual care on URR, quadriceps and plantar-flexor strength, six-minute walk distance, estimated peak oxygen uptake, and physical fatigue in patients receiving maintenance hemodialysis. We hypothesized, a priori, that both intradialytic NMES and intradialytic resistance training would produce significantly greater improvements in these outcomes than usual care, and that the two active interventions would not differ significantly from each other.

Materials and Methods

Study Design, Ethics, and Trial Registration

This prospective, three-arm, parallel-group randomized controlled trial was conducted from October 2023 to July 2024, in accordance with the CONSORT 2025 statement and the ethical principles of the Declaration of Helsinki [10]. Written informed consent was obtained from all participants before enrollment after a detailed explanation of the study objectives, procedures, potential benefits, and possible risks. Ethical approval was granted by the Research Ethics Committee of the Faculty of Physical Therapy, Cairo University (Approval No. P.T.REC/012/003336). The trial was prospectively registered at ClinicalTrials.gov (NCT06079502).

Sample Size

The sample size was calculated a priori using G*Power software (version 3.1.9.7) for a one-way analysis of variance comparing three independent groups (fixed-effects omnibus F test). A large standardized effect size (Cohen's $f = 0.40$) was specified directly, informed by the magnitude of quadriceps-strength improvements reported in prior intradialytic electrical-stimulation and exercise studies [9]. With $\alpha = 0.05$, power = 80%, and three groups (numerator $df = 2$), the required total sample size was 66 participants (22 per group). To allow for an anticipated dropout rate of approximately 30%, the recruitment target was increased to 90 participants (30 per group). This calculation was based on a between-group comparison of a single continuous outcome and therefore approximates, but does not directly correspond to, the power of the baseline-adjusted ANCOVA model subsequently used to estimate treatment effects for the primary outcome (6MWD); a formal a priori power calculation for the ANCOVA model was not performed, and this is acknowledged as a limitation. All 90 randomized participants (30 per group) received the allocated intervention, completed the 16-week study period, and were included in the analysis; there was no loss to follow-up.

Study Setting and Participants

Participants were recruited from the Nephrology and Dialysis Center at Kasr Al-Ainy Hospital, Egypt. Eligible participants were men and women aged 40–55 years who had received regular maintenance hemodialysis for more than 3 years and had a body mass index of 25.0–29.9 kg/m².

Patients were excluded if they had cognitive impairment that prevented completion of the assessments or provision of informed consent; a history of stroke; anemia; diabetes mellitus; coronary artery disease; heart failure; uncontrolled hypertension; infectious or chest disease; disabling osteoarticular or musculoskeletal disorders; or lower-limb peripheral vascular disease. Current smokers were also excluded. Because Group A received NMES, participants with standard contraindications to electrical stimulation

were also excluded: an implanted cardiac electronic device (pacemaker or implantable cardioverter-defibrillator), active malignancy in the region of stimulation, pregnancy, active deep vein thrombosis, epilepsy or a seizure disorder, and skin lesions or infection at the intended electrode-placement sites.

Data Collection Procedures

Data were collected at baseline, before randomization and initiation of the study interventions, and after completion of the 16-week intervention period. Baseline demographic and clinical information, including age, sex, body mass index, and duration of maintenance hemodialysis, was recorded for all participants.

At both assessment points, dialysis adequacy was evaluated using the urea reduction ratio (URR). For each URR assessment, predialysis and postdialysis blood urea nitrogen samples were obtained during the same routine hemodialysis session; baseline sampling occurred before initiation of the study interventions and follow-up sampling occurred after the 16-week intervention period. Physical function was assessed using bilateral quadriceps and plantar-flexor muscle strength, 6MWD, and estimated peak oxygen uptake (VO₂peak). Physical fatigue was assessed using the physical fatigue component of the Chalder Fatigue Questionnaire. The same investigator performed all assessments using the same standardized procedures at baseline and follow-up.

Randomization and Allocation

After completion of baseline assessments, the 90 eligible participants were allocated in a 1:1:1 ratio to intradialytic NMES (Group A), intradialytic resistance training (Group B), or usual care (Group C). The allocation sequence was computer-generated by the principal investigator using the random-number function of Microsoft Excel (Microsoft Corp., Redmond, WA, USA), applying permuted-block randomization with a fixed block size of 9 (3 participants per group per block) to ensure the allocation of exactly 30 participants to each group. Randomization was not stratified by sex or baseline function.

The principal investigator enrolled participants and assigned them according to the generated allocation sequence. Allocation concealment was not implemented because the principal investigator generated the sequence, enrolled participants, and assigned the interventions. Blinding was not feasible because of the nature of the exercise and electrical-stimulation interventions; therefore, participants and the principal investigator were aware of group assignment.

Interventions

All participants continued their prescribed hemodialysis and medical care throughout the study. Groups A and B received supervised intradialytic rehabilitation twice weekly for 16 consecutive weeks

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(32 prescribed sessions). Each session was delivered during the first 2 hours of the routine hemodialysis session. Treatment completion required attendance at a minimum of 80% (≥ 26) of the 32 prescribed sessions. Sessions missed because of acute illness, hospitalization, or dialysis scheduling conflicts were rescheduled within the same week when feasible; sessions that could not be rescheduled were recorded as missed and the participant continued in the program on the standard schedule. Blood pressure and heart rate were monitored before and throughout intervention sessions.

Intradialytic Neuromuscular Electrical Stimulation (Group A)

NMES was delivered using a portable four-channel digital TENS/EMS unit (EV-906; Everyway Medical Instruments Co., Ltd., Shengkeng District, New Taipei City, Taiwan). Stimulation was delivered as an asymmetrical biphasic square-pulsed current. Pulse duration was fixed at 300 μ s, and pulse frequency ranged from 8 to 90 Hz according to the training phase **Table 1. Progression of the intradialytic NMES program.**

Intervention period	Program	Duration	Frequency
Weeks 1–2	Muscle toning	25 min	8 Hz
Weeks 3–4	Aerobic endurance	28 min	60 Hz
Weeks 5–7	Rehabilitation–amyotrophy	30 min	25–40 Hz

Intradialytic Resistance Training (Group B)

Thirty participants received a supervised intradialytic resistance-training program twice weekly for 16 consecutive weeks in addition to their routine medical treatment. The exercise program was performed during the first 2 hours of the hemodialysis session.

The resistance-training program consisted of three parts:

Part 1: Warm-up

The session began with a 5-minute warm-up consisting of active free range-of-motion exercises of the lower limbs performed from the dialysis position.

Part 2: Resistance Training

External resistance was provided using free leg weights in the form of weighted ankle cuffs or sandbags positioned at the distal third of the leg at approximately the level of the malleoli.

Resistance was prescribed at 40%–50% of the individual one-repetition maximum (1RM). Before determining the training load, participants performed familiarization trials without external resistance. The load was then progressively increased in 0.5-kg increments until the participant was unable to complete the required movement, allowing determination of the 1RM. The 1RM was reassessed every 2 weeks, and the

(Table 1). A 1:2 contraction-to-rest duty cycle (5 seconds of stimulation and 10 seconds of rest) was maintained throughout all phases. Stimulation intensity was gradually increased to produce a visible, tolerable muscle contraction according to each participant's tolerance, up to a maximum of 60 mA.

Participants in Group A received bilateral NMES of the quadriceps and calf muscle groups twice weekly, on two non-consecutive dialysis days each week, using a protocol adapted from previously described intradialytic NMES programs [2,7]. Self-adhesive surface electrodes (80 $\times$ 130 mm) were positioned over the motor points of the targeted muscles. For quadriceps stimulation, electrodes were placed approximately 5 cm distal to the inguinal fold and 3 cm proximal to the superior border of the patella. For calf-muscle stimulation, electrodes were placed approximately 2 cm below the knee joint and over the proximal Achilles-tendon region. Participants remained in their usual dialysis position, with the knees supported in slight flexion of approximately 15°.

Intervention period	Program	Duration	Frequency
Weeks 8–10	Rehabilitation–hypertrophy	33 min	55 Hz
Weeks 11–13	Muscle strengthening	35 min	Up to 75 Hz
Weeks 14–16	Strength endurance	38 min	90 Hz

training resistance was adjusted accordingly to maintain the prescribed exercise intensity. Participants remained seated in their dialysis chair with the backrest reclined to approximately 45° and the hip flexed to approximately 90°; the trunk and thigh were stabilized using the chair's standard straps to minimize compensatory trunk movement during weighted knee-extension and calf-raise exercises[11].

For each lower limb, participants performed:

- **3 sets of 15 repetitions** of resisted knee extension for the quadriceps muscles.
- **3 sets of 15 repetitions** of resisted ankle plantar flexion for the calf muscles.
- **1-minute rest intervals** between sets.

Exercises were performed within the participant's tolerated range of motion and under direct supervision of the physical therapist.

Part 3: Cool-down

The session ended with a 5-minute cool-down consisting of active free range-of-motion exercises of both lower limbs performed from the dialysis position. Thus, each resistance-training session lasted approximately **30 minutes** and was performed twice weekly during the first 2 hours of hemodialysis for **16 weeks**. [12]

Usual-Care Control (Group C)

Participants in Group C received routine hemodialysis and standard medical care only. They did not participate in a structured intradialytic NMES or resistance-training program during the 16-week study period.

Outcome Measures

The single primary outcome was six-minute walk distance (6MWD), selected as the primary measure of functional exercise capacity because it is a clinically meaningful, patient-relevant composite of lower-limb strength and cardiorespiratory function and is the outcome on which the sample-size calculation is best aligned. Bilateral quadriceps and plantar-flexor muscle strength, URR, estimated peak oxygen uptake, and physical-fatigue (CFQ-11) scores were prespecified secondary outcomes; because they were not corrected for multiplicity, results for these secondary outcomes should be interpreted as hypothesis-generating rather than confirmatory. All outcomes were assessed at two time points: baseline (within 1 week before randomization) and post-intervention (within 1 week after completion of the 16-week intervention period).

Functional Exercise Capacity

Functional exercise capacity was assessed using the six-minute walk test (6MWT), performed in accordance with the American Thoracic Society guidelines [13]. The test was conducted along a flat, enclosed 30-meter corridor marked at 3-meter intervals. Participants were instructed to walk as far as possible during 6 minutes, were permitted to slow down, stop, and rest as needed without leaving the corridor, and received standardized verbal encouragement at each minute. The total distance covered was recorded in meters. A single trial was performed at each assessment time point. The 6MWT is widely used to assess functional capacity in patients receiving maintenance hemodialysis and has been investigated in relation to peak oxygen uptake in this population [14].

Dialysis Adequacy

Dialysis adequacy was assessed using the urea reduction ratio (URR), calculated from predialysis and postdialysis blood urea nitrogen concentrations as follows: $URR (\%) = [(\text{predialysis blood urea nitrogen} - \text{postdialysis blood urea nitrogen}) / \text{predialysis blood urea nitrogen}] \times 100$. For each participant and assessment time point, the paired predialysis and postdialysis samples were drawn during the same routine dialysis session. Baseline URR was obtained before intervention initiation, and follow-up URR was obtained after 16 weeks. [15]

Lower-Limb Muscle Strength

Bilateral quadriceps and plantar-flexor muscle strength were assessed using a Lafayette Manual Muscle Tester (Model 01163; Lafayette Instrument Company, Lafayette, Indiana, USA), a hand-held dynamometer with a measurement range of 0–1335 N. Isometric peak

force was assessed using a standardized manual break test.

Participants were seated with the back fully supported and the hip and knee flexed to approximately 90°. For quadriceps testing, the knee was fixed at 60° of flexion (0° = full extension); the dynamometer strap was positioned just proximal to the malleoli, with the direction of pull aligned perpendicular to the long axis of the tibia and the examiner providing manual counter-stabilization at the distal thigh. For plantar-flexor testing, the knee was fully extended and the ankle positioned in neutral (0°) dorsiflexion–plantarflexion, with the dynamometer secured against a fixed stable point and the forefoot placed on the sensor pad, the direction of pull again aligned perpendicular to the limb segment. The dynamometer's lever-arm length (distance from the joint axis to the point of force application) was kept constant across all assessments, and only isometric (not dynamic) force was measured. Participants received standardized instructions and a trial assessment before testing. Assessments were performed within the first 2 hours of the dialysis session to minimize complications that may occur later in dialysis. Participants were instructed to exert maximal force for 3 seconds, and the maximum of three attempts was recorded in kilograms-force (kgf). Handheld dynamometry has been used to assess lower-limb muscle strength in patients undergoing hemodialysis [16].

Estimated Peak Oxygen Uptake

Estimated peak oxygen consumption ($VO_{2\text{peak}}$) was derived from the 6MWT using the generalized equation reported by Ross et al. [17]:

$$\text{Mean Peak } VO_2 (\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) = 4.948 + (0.023 \times 6\text{MWD} [\text{meters}]), \text{SEE} = 1.1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$$

This equation estimates mean peak oxygen uptake from mean 6MWD and should not be interpreted as a direct individual measurement of peak VO_2 .

Physical Fatigue

Physical fatigue was evaluated using the physical-fatigue component of the 11-item Chalder Fatigue Questionnaire (CFQ-11). The physical-fatigue subscale comprises 7 items, each scored on a 4-point Likert scale (0–3), yielding a subscale range of 0–21; higher scores indicate greater physical fatigue. The CFQ-11 has been used to assess fatigue in maintenance-hemodialysis populations [18].

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Shapiro–Wilk test, homogeneity of variances using Levene's test, and homogeneity of covariance matrices using Box's M test. Baseline demographic and clinical characteristics were compared among groups using one-way ANOVA for continuous variables and the chi-square test for categorical variables.

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Between-group treatment effects were estimated for each outcome using baseline-adjusted ANCOVA, with the post-intervention value as the dependent variable, group as the fixed factor, and the corresponding baseline value as a covariate. Pairwise comparisons (NMES vs resistance training, NMES vs usual care, and resistance training vs usual care) are reported as adjusted mean differences (MD) with 95% confidence intervals (CI) and p-values. Within-group pre-to-post changes are summarized using paired analyses. Because VO₂peak was estimated mathematically from **Table 2. Baseline characteristics of participants.**

	Group A	Group B	Group C	p-value
	mean ± SD	mean ± SD	mean ± SD	p-value
Age (years)	47.47 ± 4.57	46.63 ± 4.32	48.53 ± 4.70	0.27
Weight (kg)	69.51 ± 6.07	71.69 ± 5.55	70.25 ± 6.36	0.36
Height (cm)	158.97 ± 5.30	161.03 ± 5.22	161.20 ± 5.80	0.21
BMI (kg/m ²)	27.47 ± 1.46	27.62 ± 1.26	27.00 ± 1.44	0.20
Sex distribution, N (%)	Sex distribution, N (%)			
Females	12 (40%)	14 (47%)	15 (50%)	0.73
Males	18 (60%)	16 (53%)	15 (50%)	0.73

SD, standard deviation.

Effects of Treatment

Within-Group Comparisons

Groups A and B showed significant increases in URR, right and left plantar-flexor strength, quadriceps strength, 6MWD, and estimated peak VO₂ (all p<0.001), together with a significant reduction in CFQ-Table 3. Within-group changes in URR and lower-limb muscle strength before and after treatment.

	Group A	Group B	Group C
	mean	mean ± SD	mean ± SD
	± SD		
URR (%)	URR (%)		
Pre treatment	64.30 +/- 1.42	64.67 +/- 1.67	64.57 +/- 1.96
Post	69.47 +/-	73.77 +/-	64.77 +/-

6MWD rather than measured directly, it was treated as a derived, exploratory variable and should be interpreted as a transformation of the 6MWD finding rather than as independent physiological evidence. Statistical significance was set at p<0.05.

Results

Participant Characteristics

There were no statistically significant baseline differences among the groups in age, weight, height, body mass index, or sex distribution (all p>0.05; Table 2).

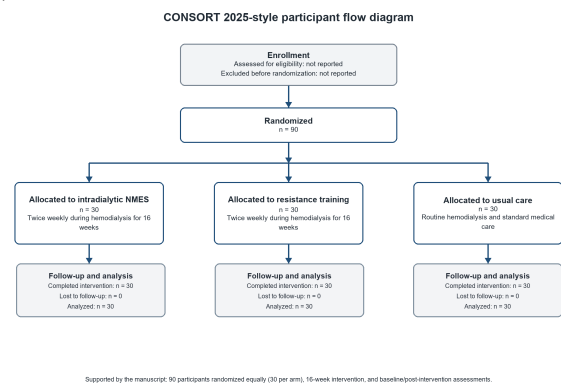


Figure 1. CONSORT 2025-style participant flow diagram for the three-arm randomized controlled trial.

11 physical fatigue scores (p<0.001). Group C showed no significant changes in URR, plantar-flexor strength, quadriceps strength, 6MWD, estimated peak VO₂, or CFQ-11 physical fatigue scores (all p>0.05; Tables 3 and 4).

	Group A	Group B	Group C
treatment	1.78	1.99	1.22
MD (95% CI)	5.17 (4.41, 5.93)	9.10 (8.45, 9.75)	0.20 (-0.40, 0.80)
	p<0.001	p<0.001	p = 0.50
Right plantar-flexor strength (kgf)	Right plantar-flexor strength (kgf)		
Pre	12.88 ± 3.04	14.58 ± 3.70	14.45 ± 3.89

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	Group A	Group B	Group C
treatment			
Post treatment	29.64 ± 3.98	28.62 ± 4.38	14.67 ± 3.96
MD (95% CI)	16.76 (15.43, 18.10)	14.04 (12.70, 15.37)	0.22 (-1.12, 1.55)
	p<0.001	p<0.001	p = 0.75
Left plantar-flexor strength (kgf)	Left plantar-flexor strength (kgf)		
Pre treatment	12.76 ± 2.94	11.61 ± 2.76	11.92 ± 3.21
Post treatment	30.09 ± 2.76	30.21 ± 3.23	12.40 ± 3.21
MD (95% CI)	17.33 (16.31, 18.35)	18.60 (17.59, 19.63)	0.48 (-0.54, 1.50)
	p<0.001	p<0.001	p = 0.35
Right quadriceps strength (kgf)	Right quadriceps strength (kgf)		
Pre treatment	14.47 ± 2.63	14.23 ± 3.07	15.38 ± 3.29
Post treatment	33.83 ± 3.93	34.45 ± 4.81	15.32 ± 3.38
MD (95% CI)	19.36 (18.00, 20.71)	20.22 (18.86, 21.57)	-0.06 (-1.41, 1.30)
	p<0.001	p<0.001	p = 0.93
Left quadriceps strength (kgf)	Left quadriceps strength (kgf)		
Pre treatment	14.25 ± 2.22	13.83 ± 3.11	14.74 ± 2.97
Post treatment	38.97 ± 4.15	38.65 ± 4.12	14.82 ± 3.25
MD (95% CI)	24.72 (23.35, 26.09)	24.82 (23.45, 26.20)	0.08 (-1.29, 1.45)
	p<0.001	p<0.001	p = 0.91

SD, standard deviation; MD, mean difference; CI, confidence interval.

Table 4. Within-group changes in 6MWD, CFQ-11 physical fatigue, and estimated peak VO₂ before and after treatment.

	Group A	Group B	Group C
	mean ± SD	mean ± SD	mean ± SD
6MWD (m)	6MWD (m)		
Pre treatment	269.80 ± 37.33	273.83 ± 38.42	271.87 ± 35.24
Post treatment	350.40 ± 48.97	347.33 ± 58.72	267.37 ± 37.14
MD (95% CI)	80.6 (71.29, 89.91)	73.50 (64.19, 82.81)	-4.50 (-13.81, 4.81)
	p<0.001	p<0.001	p = 0.34
CFQ-11 physical fatigue	CFQ-11 physical fatigue		
Pre treatment	13.97 ± 2.37	13.63 ± 2.28	13.70 ± 2.41
Post treatment	5.23 ± 1.79	5.10 ± 1.81	13.57 ± 2.30
MD (95% CI)	-8.74 (-9.71, -7.76)	-8.53 (-9.51, -7.56)	-0.13 (-1.11, 0.84)
	p<0.001	p<0.001	p = 0.78
Estimated peak VO ₂ (mL/kg/min)	Estimated peak VO ₂ (mL/kg/min)		
Pre treatment	11.15 ± 0.86	11.25 ± 0.88	11.20 ± 0.81
Post treatment	13.01 ± 1.13	12.93 ± 1.35	11.10 ± 0.86
MD (95% CI)	1.86 (1.64, 2.07)	1.68 (1.47, 1.90)	-0.10 (-0.32, 0.11)
	p<0.001	p<0.001	p = 0.34

SD, standard deviation; MD, mean difference; CI, confidence interval.

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Between-Group Comparisons

Baseline-adjusted ANCOVA showed that both Groups A and B had significantly higher post-intervention URR, right and left plantar-flexor strength, right and left quadriceps strength, 6MWD, and estimated peak VO₂, and significantly lower CFQ-11 physical fatigue scores, than Group C (all adjusted $p < 0.001$). Group B also had a significantly higher adjusted post-intervention URR than Group A (adjusted MD 4.12 percentage points, 95% *Table 5. Baseline-adjusted between-group treatment effects (ANCOVA: post-intervention outcome ~ group + baseline outcome).*

Outcome	NMES vs resistance Adjusted MD (95% CI)	p value	NMES vs usual care Adjusted MD (95% CI)	p value	Resistance vs usual care Adjusted MD (95% CI)	p value
URR (%)	-4.12 (-5.02, -3.21)	<0.001	4.79 (4.04, 5.53)	<0.001	8.95 (8.23, 9.68)	<0.001
Right plantar-flexor strength (kgf)	1.68 (-0.46, 3.82)	0.12	15.98 (14.23, 17.74)	<0.001	13.84 (12.40, 15.28)	<0.001
Left plantar-flexor strength (kgf)	-0.60 (-2.07, 0.88)	0.42	17.24 (15.92, 18.56)	<0.001	18.07 (16.96, 19.17)	<0.001
Right quadriceps strength (kgf)	-0.72 (-2.93, 1.49)	0.52	19.12 (17.49, 20.74)	<0.001	20.08 (18.37, 21.78)	<0.001
Left quadriceps strength (kgf)	0.23 (-1.91, 2.37)	0.83	24.50 (22.81, 26.20)	<0.001	24.45 (22.82, 26.08)	<0.001
6MWD (m)	8.04 (-6.14, 22.23)	0.26	85.10 (72.60, 97.60)	<0.001	79.96 (49.75, 110.18)	<0.001

CI 3.21 to 5.02, $p < 0.001$). No significant adjusted differences were observed between Groups A and B in plantar-flexor strength, quadriceps strength, 6MWD, CFQ-11 physical fatigue, or estimated peak VO₂ (all adjusted $p \geq 0.12$; Table 5); because the trial was not designed as a non-inferiority study, these non-significant differences indicate that no difference was detected between NMES and resistance training for these outcomes and should not be interpreted as demonstrating equivalence between the two interventions.

	22.23)		97.60)		110.18)	
CFQ-11 physical fatigue	0.19 (-0.73, 1.11)	0.69	-8.44 (-9.40, -7.48)	<0.001	-8.44 (-9.42, -7.46)	<0.001
Estimated peak VO ₂ (mL/kg/min)	0.19 (-0.14, 0.52)	0.25	1.74 (1.45, 2.02)	<0.001	1.56 (1.28, 1.84)	<0.001

MD, mean difference; CI, confidence interval. MD, 95% CI, and p -values are baseline-adjusted ANCOVA estimates (post-intervention value ~ group + baseline value).

Discussion

This three-arm randomized controlled trial found that 16 weeks of intradialytic NMES and intradialytic resistance training improved URR, bilateral quadriceps and plantar-flexor strength, 6MWD, estimated peak oxygen uptake, and physical fatigue scores compared with usual care. The two active interventions did not differ significantly in post-intervention lower-limb strength, 6MWD, estimated peak VO₂, or fatigue. Resistance training achieved a significantly higher adjusted post-intervention URR than NMES ($73.77 \pm 1.99\%$ vs $69.47 \pm 1.78\%$; adjusted mean difference, 4.12 percentage points; 95% CI, 3.21 to 5.02; $p < 0.001$).

The improvement after NMES is consistent with a small randomized trial by Machfer et al., in which 12 weeks of intradialytic quadriceps NMES improved maximal voluntary contraction, 6-minute walk distance, sit-to-stand performance, mobility, and postural-balance measures, whereas no significant changes occurred in the control group [2].

Both active groups demonstrated improved walking capacity, whereas the usual-care group did not show meaningful improvement. This finding is consistent with evidence that intradialytic exercise, including resistance exercise, can improve walking capacity in patients receiving maintenance hemodialysis [19,20].

An updated systematic review and meta-analysis also found that NMES improved lower-limb muscle strength and 6MWD in patients undergoing hemodialysis [8]. These findings support NMES as a practical rehabilitation option for patients who are unable or unwilling to perform voluntary exercise during dialysis.

The improvement in 6MWD in the resistance-training group is also biologically plausible because repeated voluntary lower-limb loading may improve muscle strength, endurance, and walking performance. Large-scale intradialytic exercise evidence has shown improved physical function and 6MWD compared with usual care [1]. In addition, intradialytic resistance exercise has been associated with improved lower-limb strength and functional capacity in hemodialysis patients [11]. Although resistance training produced a significantly higher adjusted post-intervention URR than NMES in the present study, no statistically significant difference was detected between resistance training and NMES for 6MWD; this should not be interpreted as evidence of equivalence because the study was not designed as a non-inferiority trial.

Estimated peak VO₂ increased in both active-intervention groups. However, this result should be interpreted as a derived indicator of improved walking capacity because peak VO₂ was calculated from 6MWD rather than measured directly with cardiopulmonary exercise testing. In patients undergoing hemodialysis, the 6MWT has shown good reliability for estimating peak VO₂ [14]. Ross et al.

also demonstrated that 6MWD can estimate mean peak VO₂ at the group level, although it is less accurate for interpreting individual values [17]. Therefore, the estimated peak VO₂ findings support the observed improvement in functional exercise performance but do not independently establish a physiological improvement in directly measured aerobic capacity.

The improvement in functional capacity and physical fatigue observed after intradialytic NMES is consistent with emerging evidence that electrically induced lower-limb muscle contraction can improve exercise performance in patients receiving hemodialysis. Machfer et al. reported that 12 weeks of intradialytic NMES improved muscle strength, functional capacity, and postural-balance measures compared with usual care [2]. In addition, an updated systematic review and meta-analysis found that NMES improved lower-limb muscle strength and 6MWD in hemodialysis patients [8]. A further randomized trial demonstrated improved exercise tolerance, muscle oxygenation, and peripheral fatigue tolerance following intradialytic NMES [22]. These findings provide a plausible basis for the reduced physical-fatigue scores and improved walking capacity observed in the NMES group in the present study.

Physical fatigue decreased in both active-intervention groups without a significant difference between NMES and resistance training. This pattern is consistent with the systematic review and network meta-analysis by Lu et al. [21], who found, across 23 studies (1,867 participants), that exercise reduces fatigue in maintenance-hemodialysis patients, with intradialytic combined aerobic-resistance exercise ranked most effective versus routine care. In addition, a 12-week pilot randomized controlled trial found that intradialytic NMES improved peripheral-fatigue tolerance and exercise capacity in patients with end-stage renal disease [22].

Park et al. reported that intradialytic NMES, with or without protein supplementation, improved aspects of functional capacity, while higher-intensity NMES was associated with improvements in leg muscle strength and mobility [23]. Selection of intradialytic rehabilitation should consider functional ability, fatigue, tolerance, patient preference, and unit resources. The present findings therefore suggest that both intradialytic NMES and intradialytic resistance training may be useful strategies for improving functional performance and reducing the physical-fatigue burden of hemodialysis.

The improvement in URR observed in the present study is consistent with findings by Rohmah et al., who reported that 12 weeks of intradialytic aerobic exercise significantly improved URR and Kt/V compared with usual care in patients receiving maintenance hemodialysis [24].

In the present study, both intradialytic NMES and resistance training were associated with significant

improvements in URR compared with usual care; however, resistance training produced a significantly higher adjusted post-intervention URR than NMES. This finding suggests that voluntary resistance exercise may provide an additional dialysis-adequacy benefit beyond electrically induced muscle contraction in this sample. A plausible explanation is that repeated active contraction of large lower-limb muscle groups during resistance exercise may increase regional skeletal-muscle blood flow and capillary recruitment, thereby facilitating transfer of urea from peripheral tissues into the vascular compartment for subsequent removal by the dialyzer. In contrast, NMES may recruit muscle fibers differently and may produce a lower overall metabolic and circulatory demand, depending on stimulation intensity, the muscle mass activated, and participant tolerance.

This interpretation should remain cautious. URR is influenced not only by intradialytic activity but also by dialysis prescription, treatment duration, blood-flow and dialysate-flow rates, ultrafiltration, vascular access function, nutritional status, and the timing and technique of blood sampling. These factors were not measured in the present study. Therefore, the higher URR observed with resistance training should be interpreted as an association rather than definitive evidence that resistance exercise directly improves dialysis clearance. The finding is hypothesis-generating and should be confirmed in larger trials that measure Kt/V and dialysis-prescription parameters while directly comparing resistance exercise with NMES [24,25].

Although prior intradialytic NMES studies have shown improvements in muscle strength, functional capacity, and exercise tolerance, evidence regarding its effect on URR remains limited [25].

Beyond the physical outcomes, the concurrent improvements in lower-limb strength, functional walking capacity, estimated peak VO₂, and physical fatigue may have important implications for health-related quality of life and psychological well-being in patients receiving maintenance hemodialysis. Improved walking ability and reduced fatigue may increase independence in daily activities, confidence in physical functioning, and participation in social roles. In a large multicenter trial, intradialytic combined endurance and resistance exercise improved physical function, the physical health summary score, and vitality compared with usual care [1].

Evidence from recent systematic reviews indicates that structured exercise therapy can improve fatigue, general health, and the physical component of health-related quality of life in patients receiving maintenance hemodialysis; reductions in depressive symptoms have been observed in programs lasting longer than 3 months [26,27].

Limitations

This study has several limitations. Allocation concealment was not implemented, because the same principal investigator generated the randomization sequence, enrolled participants, and assigned interventions; this is a substantive weakness that could not be corrected retrospectively and may have increased the risk of selection bias, even though the sequence itself was computer-generated. Detailed dialysis-prescription parameters (Kt/V, blood-flow rate, dialysate flow, ultrafiltration volume, vascular access type) and additional clinical/nutritional characteristics (hemoglobin, albumin, dialysis vintage, residual kidney function) were not collected, which limits our ability to confirm that dialysis conditions remained stable across groups and to fully characterize the study population; this is particularly relevant to interpretation of the URR findings. Secondary outcomes were not corrected for multiplicity and should be considered hypothesis-generating. The trial was not designed or powered as a non-inferiority study, so the absence of a statistically significant difference between NMES and resistance training does not establish that the two interventions are equivalent. The single-center design may limit generalizability. The restricted age range (40-55 years), body-mass-index range, and exclusion of diabetes, cardiovascular disease, and anemia further limit extrapolation to the broader, typically older and more comorbid, hemodialysis population that often has the greatest rehabilitation needs. Adherence to prescribed sessions and adverse events during the intervention period were not systematically reported in this manuscript. Finally, the absence of post-intervention follow-up precluded evaluation of the durability of treatment effects.

Conclusion

Intradialytic NMES and intradialytic resistance training were associated with improved URR, lower-limb muscle strength, functional walking capacity, calculated estimated peak VO₂ (a derived measure of 6MWD), and physical fatigue compared with usual care. Resistance training achieved a higher adjusted post-intervention URR than NMES, and no statistically significant difference was detected between the two active interventions for the remaining measured outcomes; because this trial was not designed as a non-inferiority study, this absence of a detected difference should not be interpreted as evidence that NMES and resistance training are equivalent. The URR finding should be interpreted cautiously because detailed dialysis-prescription data were not collected. NMES may provide a reasonable hypothesis-generating candidate for a clinically useful intradialytic rehabilitation option for patients who cannot perform conventional resistance exercise, pending confirmation in trials with allocation concealment, blinded assessment, and a formal non-inferiority design.

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