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Effects of very early exercise on inflammatory markers and clinical outcomes in patients with ischaemic stroke- a randomized controlled trial

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Abstract

Background Apart from the limited evidence of the effects of very early exercise (VEE) on clinical outcomes (COs) in stroke, better knowledge is required to understand the cellular action induced by VEE. This study investigated the effects of VEE on inflammatory markers (IMs) and COs. It further evaluated the association between acute changes in IMs and COs at follow-up in individuals with first-ever mild-to-moderate ischaemic stroke.

Methods A prospective, single-center, single-blind, randomized controlled trial **(**retrospectively registered: PACTR202406755848901; 10–06-2024) was conducted. Forty-eight patients randomized (1:1) into the VEE group (VEEG) and usual care group (UCG) completed the follow-up. Within 24 h of stroke onset, patients in VEEG underwent 45 min of VEE twice daily, amounting to 1.5 h/d, for seven days while patients in UCG received regular turning and positioning. The levels of IMs including interleukin-6 (IL-6), fibrinogen, leucocytes, neutrophils, lymphocytes, and monocytes were assessed at baseline, 4th, and 7th day for both groups. Thereafter, each patient received 90-min follow-up physiotherapy twice weekly for three months. Motor impairment, physical disability, functional independence, anxiety, depression, and cognition were evaluated at 1st and 3rd month of follow-up.

Results On the 4th and 7th day, patients in VEEG show trends of lower levels of IL-6, leucocytes, neutrophils, and monocytes and higher levels of lymphocytes. However, a non-linear effect of VEE on plasma fibrinogen was observed compared to UC. Furthermore, better improvement in motor impairment, physical disability, functional independence, anxiety, depression, and cognition were observed in VEEG. The positive modulation of IMs by VEE was associated with COs over time, including associations between changes in IL-6 at days 4 and 7 and 3-month functional independence (r_s = -0.33; p = 0.019; r_s = -0.33; p = 0.021), and at day 7 and 3-month motor impairment (r_s = 0.30; p = 0.039).

Conclusions Initiating moderate-intensity exercise within 24 h appears beneficial in positively modulating IMs, including IL-6, at the acute stage and improving the physical, motor, cognitive, and affective functions at 1-and 3-month follow-up. The association between exercise-induced acute changes in IMs and improved COs over time

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highlights the potential role of moderate-intensity VEE in enhancing stroke recovery through positive inflammatory modulation.

Keywords Very early rehabilitation, Disability, Cognition, Interleukin-6, Fibrinogen

Introduction

The occlusion of cerebral arteries gives rise to ischaemic stroke. This leads to the formation of an ischemic core, causing neuronal damage and the formation of glial scars [1, 2]. Ischaemic stroke, among all stroke subtypes, comprises about 90% of stroke cases and is often associated with high mortality rates and the development of enduring stroke-related sequelae [1, 2]. Consequently, individuals with ischaemic stroke may have sensorimotor, physical, and psychosocial impairments [3]. Meanwhile, evidence has shown that the time for optimum recovery of brain tissue following stroke is limited. Previous research conducted using animal models has shown that the window of opportunity for brain plasticity, functional and structural rearrangement, and neuronal recovery after a stroke is restricted and typically occurs in the early stages after the stroke event [4, 5]. The process of regenerating damaged brain tissue after a stroke peaks one week after [6, 7]. Subsequently, this process gradually declines and reaches a plateau a few weeks after the stroke. With cortical sensory maps, Krakauer et al. showed that neuroplasticity is more enhanced during the first few days after a stroke than at any other time [4]. Therefore, intervention during the very early stage of stroke has been recommended to facilitate both ischaemic and clinical recovery [8].

A previous study found that physical inactivity was associated with a higher risk of stroke (OR = 1.17; 95% CI = 1.12–1.21; $p < 0.001$) [9], which may also worsen positive stroke outcomes [10, 11]. One of the main non-pharmacological interventions in early stroke management is exercise prescription. Thus, the introduction of physical exercise very early after stroke onset can help with neuroplasticity and enhance clinical recovery [10–13]. While Wei et al. [14] in their recent systematic review and meta-analysis showed a positive clinical efficacy of early exercise intervention in patients with ischaemic stroke; however, their review centers majorly on studies that started exercise intervention two weeks after the onset of stroke. They concluded that the results of their systematic review and meta-analysis cannot be generalized to exercise intervention undertaken less than 48 h after stroke onset (i,e., very early exercise intervention) [14].

Meanwhile, the evidence of significant clinical recovery of stroke patients who started very early exercise (VEE) intervention compared to delayed exercise intervention is inconclusive [10, 11, 13, 15, 16]. The AVERT II study conducted among 71 stroke patients showed no significant difference in the primary outcome (death within 3 months) between very early mobilization (8/38) and usual care (3/33) [11]. There were also no significant differences in harmful events or neurological deterioration between the two groups [11]. In the AVERT III study, 2014 patients with acute stroke (90.7% ischaemic stroke) were randomized from five countries into very early mobilisation and standard care groups [17]. The findings revealed that the frequency of patients who had favourable outcomes at 3 months (score of 0–2 on modified Rankin Scale [mRS]) was significantly lower among patients who started mobilization within 24 h of stroke onset (46%) than those with just usual care (50%) [17]. In another Early Sitting in Ischemic Stroke Patients (SEVEL) study, 138 ischaemic stroke patients were randomized into very early sitting (within 24 h) or progressive sitting (sitting on day 3) group [18]. Their findings showed no significant difference in the frequency of good outcomes (0–2 mRS scores) at 3 months (76.2% vs. 77.3%) [18]. Furthermore, a study by Anjos et al. among patients with ischaemic stroke showed no significant benefits of very early mobilisation after thrombolysis on primary (functional independence) and secondary (mobility, balance, and complications) outcomes at 90 days when compared with usual care [19].

Conversely, a study by Morreale and colleagues in 340 patients with ischaemic stroke showed that patients who started proprioceptive neuromuscular facilitation or cognitive therapeutic exercise intervention within 24 h of stroke onset had better outcomes than those who started the same intervention later (after 24 h) at 12 months follow-up [20]. The results of a pooled analysis of nine randomized clinical trials indicated that very early mobilization showed no significant difference in mortality or complications but contributed significant improvement to activities of daily living and length of hospital stay [21]. These contradictory effects have sparked debate on the safety, efficacy, and optimum dose of VEE in stroke management [8, 17, 18]. Studies have shown that a high dose of mobilization exercise within 24 h may be counterproductive to good outcomes [22] and promote neural cell apoptosis [23]. Meanwhile, Marzolini et al. [8] cautioned against VEE in acute stroke without evidence to justify its safety and efficacy concerning its influence on early stroke inflammatory processes, which are important

in stroke recovery. Stroke disrupts the integrity of the blood–brain barrier (BBB), thus, VEE in the presence of BBB dysfunction makes the brain parenchyma susceptible to infiltrating peripheral molecular cells or biomarkers [8]. Therefore, at the acute stage when BBB is very dysfunctional, VEE may theoretically promote pro- or anti-inflammatory mechanisms and potentially harm or enhance brain tissue recovery and worsen or improve the eventual stroke outcome. In stroke rehabilitation, biomarkers have proved useful in the choice of therapy and in knowing the therapy's course of action [24], and are reliable in defining therapy that is beneficial, futile, or harmful [25].

Meanwhile, because favourable recovery after a stroke incident is contingent on immediate intervention; VEE is still recommended in stroke rehabilitation guidelines [23, 26, 27], despite little understanding of the cellular action induced by VEE on ischaemic tissue. This knowledge is essential to provide a biological rationale in determining the safety, efficacy, and dose–response association of VEE in patients with stroke. Thus, this study provides empirical data on the effects of initiating moderate-intensity exercise intervention within 24 h of stroke on acute inflammatory mechanisms and the link between acute modulation of inflammatory markers following exercise and clinical outcomes over time. Building on the previous evidence that ischaemic stroke mechanisms and clinical outcomes are defined by certain biomarkers involved in inflammation and blood clotting, such as cytokines, inflammatory cells, and haemostasis markers (e.g., Interleukin-6 [IL-6], leucocytes, fibrinogen, etc.) [24, 25, 28], the specific objectives of the present study are to: (1) quantify the acute changes in IL-6, fibrinogen, leucocytes, neutrophils, lymphocytes, and monocytes following VEE interventions, (2) evaluate the impact of VEE interventions on clinical outcomes, including motor, functional, cognitive, and affective functioning at follow-up, and (3) analyse the association between VEE-induced acute regulation of inflammatory markers and clinical outcomes at follow-up in individuals with acute ischaemic stroke.

Materials and methods

Participants

Participants for this study were patients with acute ischaemic stroke admitted to the emergency room and stroke wards at the Osun State University Teaching Hospital, Osogbo, Nigeria. Patients with clinical and radiological diagnosis (Computed Tomography or Magnetic Resonance Imaging Scans) of acute ischaemic stroke, who were 40 years and older, who were admitted to the hospital within 24 h of the stroke incident, who presented with mild to moderate stroke severity (with National Institute of Health Stroke Scale (NIHSS) scores ≤ 15), and those without any major communication problems preventing them from understanding the protocol were included. However, patients admitted into the intensive care unit or with a problem of consciousness (≥ 2 score on item one of NIHSS), with recurrent stroke, with a score more than 0 on the modified Ranking Scale (mRS) before stroke or with any apparent physical disability before stroke onset, on treatment with recombinant tissue plasminogen activator, and with other stroke type were excluded from the study. Out of 101 patients assessed for eligibility, 51 patients were excluded on account of major communication problems ($n=8$), recurrent stroke ($n=12$), late presentation to the hospital i.e., >24 h ($n=27$), other neurological problems other than stroke such as Parkinson's disease ($n=2$), and declined consent ($n=2$).

Participants were recruited consecutively into this randomized clinical trial. The trial was retrospectively registered with the Pan African Clinical Trial Registry (PACTR202406755848901). Chan's sample size formula for two groups of experimental study, $M=C\times\pi1\ (1-\pi1)+\pi2\ (1-\pi2)/(\pi1-\pi2)$ was employed to calculate the sample size [29]. $C=7.9$ for 80% power, $\pi1$ and $\pi2$ are estimates which are 0.25 and 0.65 to observe a 40% difference (effect size) between the control and experimental group [22] at 5% error of probability, thus, $M=7.9\times(0.25\ (1-0.25)+0.65\ (1-\ 0.65)/\ (0.25-\ 0.65)=20.49$ approx. 21 for a group. Hence, $21\times2=42$; however, 4 extra participants (20%) were added to each group to make room for possible attrition and loss to follow-up, thus, making a total number of 50 participants. Therefore, 50 patients who met the inclusion criteria were recruited and randomly assigned to two groups with 25 participants in each group. However, only 48 participants completed the study. Two patients were lost to death and relocation during follow-up and their data was removed from the final analysis. There were no significant differences in the baseline socio-demographic, clinical outcomes, and inflammatory markers between participants lost to follow-up and those who completed the study. The participants' CONSORT flowchart is shown in Fig. 1.

Procedure

Patients diagnosed with acute ischaemic stroke and who met the specified inclusion criteria and consented to the study were consecutively recruited and randomly assigned using a simple balloting method, to two groups (very early exercise group [VEEG] and usual care group [UCG]). Participants were assigned to either of the groups by using a process of simple randomization of the ballot system, with a ratio of 1:1. The ballot consisted of an equal number of 'yes' and 'no' responses (25 each), written on identical pieces of paper, folded in opaque

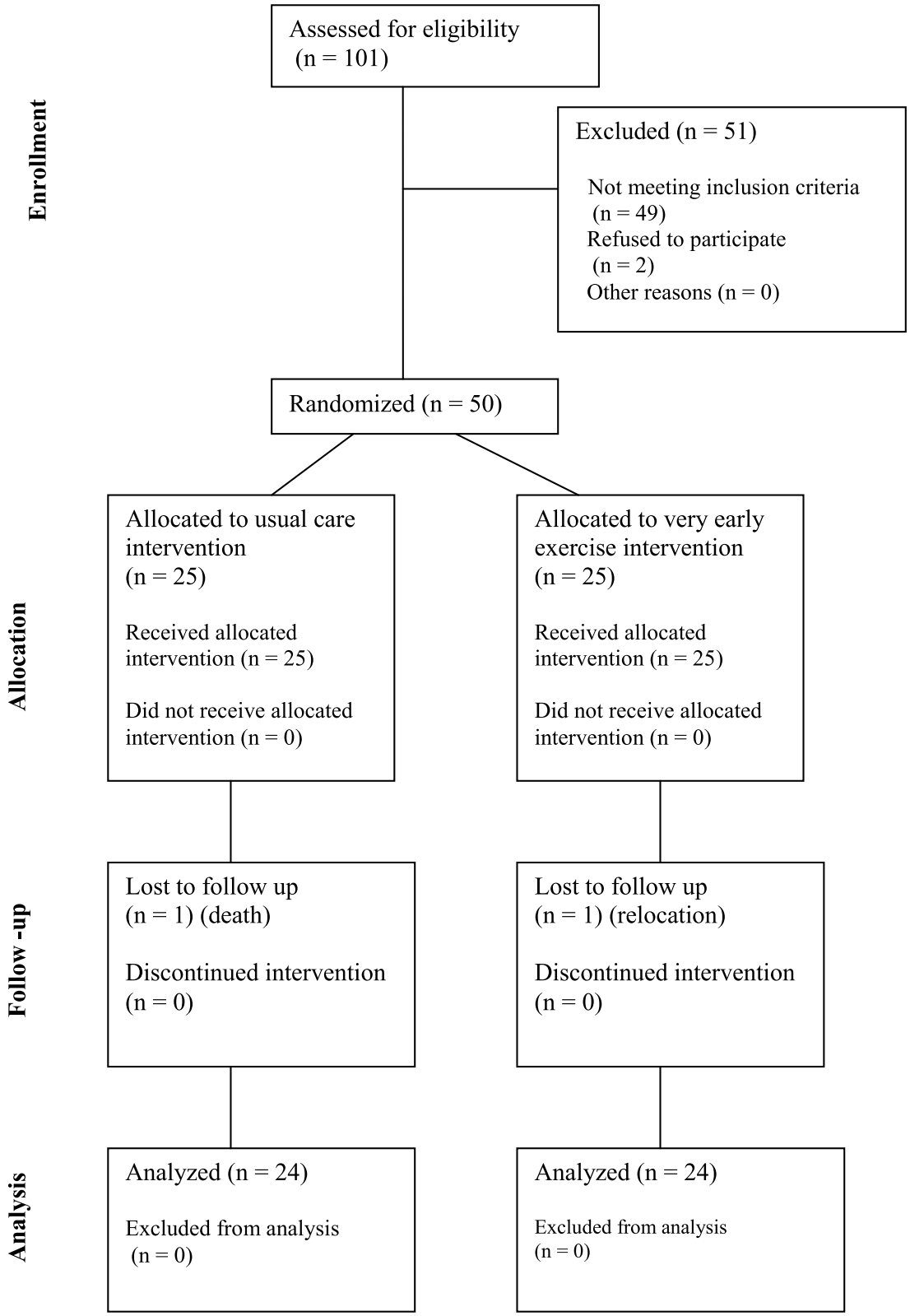

Fig. 1 CONSORT flow chart of participants in the study

and sealed envelopes, and placed within a non-transparent box. Participants were consecutively allocated to either VEEG (if 'yes' was drawn) or UCG (if 'no' was drawn). A research assistant, who was not involved with the intervention and evaluation processes, conducted the ballot drawing process, ensuring that each allocation was made without replacement. Clinical outcome assessors and laboratory analysts were masked from the group allocation. Before proceeding, ethical approval from the Ethical Committee of the Osun State University Teaching Hospital, Osogbo, Nigeria was obtained (UTH/REC/2023/05/766). Written informed consent was obtained from all participants or their nominees. Participants in both groups received identical basic care and attention (medical, nursing, etc.) outside of these specific interventions.

Baseline assessment

Following the randomization process, the participants' baseline data was collected, including socio-demographics. Participants with secondary education or less were categorized as having a low level of education, and while using the Nigerian minimum wage, monthly income of < #30,000, #30,000- #70,000, and > #70,000 were categorized as low, medium, and high income, respectively. The assessment also included stroke laterality and recommended drugs. In addition, the number and nature of stroke risk factors or co-morbidities among the participants, including hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, urinary tract infection, respiratory infection, and smoking and alcohol habits were documented [10]. The assessment of baseline stroke severity for each participant was conducted using the 11-item NIHSS, where each question is assigned a score ranging from 0 to 4. A greater score is suggestive of increased stroke severity [30]. The baseline levels of inflammatory markers such as interleukin-6 (IL-6), fibrinogen, leucocytes, neutrophils, lymphocytes, and monocytes were also assessed within 24 h of stroke incidence. Furthermore, the assessments of clinical variables including motor impairment, physical disability, functional independence, depression, anxiety, and cognition were undertaken.

Control group intervention

Participants in the control group, UCG, received usual care (positioning and regular turning). There is no consensus on the optimum positioning for acute stroke patients, however, the five recommended positioning in acute stroke in the literature are sitting in an armchair, side lying on the unaffected side, side lying on the affected side, sitting in a wheelchair and supine lying [31, 32]. Because patients were most often confined to bed at an acute stroke, the positioning adopted in this study was side and supine lying with the head elevated to at least 30 degrees [26]. For the unaffected side lying, the affected arm and elbow were straight, and the elbow was supported by a pillow, the affected leg was brought forward, the knee was bent and the leg was supported by a pillow. The head and waist were also supported. For the affected side lying, the affected shoulder was straight to ensure adequate shoulder support, and the affected leg was placed with the thigh to align with the trunk. The knee was bent slightly. The unaffected leg was placed with the bent knee with a pillow in front of the affected leg. The head was supported and bent forward a little. For the supine lying, the head was supported, bent slightly towards the affected shoulder, and gently turned towards the affected side. The buttock at the affected side was supported and extended towards the knee. The affected arm was supported while the elbow was straight and the palms facing upward [31, 32]. Patients were turned 2 hourly [33]. The intervention in the UCG lasted for seven days from the time of randomization. After the seven-day acute intervention, each participant was followed up for three months while continuing with conventional physiotherapy twice weekly.

Experimental group intervention

The patients in the experimental group (VEEG) underwent exercise intervention within 24 h of stroke incidence. The exercises included passive, active, resisted, and auto-assisted range of motion (ROM) exercises to all joints of both affected and unaffected sides, and graded and dose-titrated mobilization exercises i.e., out-of-bed activity including sitting out of bed, standing, transferring, and walking based on patient's condition [10, 13, 34]. The exercise intervention lasted 45 min, twice a day (morning and evening), amounting to 1.5 h/d, for seven days [10, 13, 34, 35], making potentially 14 sessions in all. The mean in-patient physiotherapy session for stroke survivors reported in a Nigerian tertiary hospital was eight sessions [36], while the average time of hospitalization of stroke patients in Nigeria is about 14 days [36, 37]. Similarly, each participant in this group continued with conventional physiotherapy twice weekly for three months after the acute intervention.

Evaluation of physiological parameters

Physiological measures including blood pressure, heart rate, temperature, and oxygen saturation, were routinely monitored and recorded daily for participants in both groups, before, during, and after treatment. The intervention was halted and rescheduled when some physiological parameters were altered, including systolic blood pressure falling below 110 mmHg or exceeding 220 mmHg,

diastolic blood pressure falling below 80 mmHg or exceeding 105 mmHg, resting heart rate falling below 40 beats per minute or exceeding 110 beats per minute, body temperature exceeding 38.5 °C, and oxygen saturation falling below 92% [8, 10].

Follow-up intervention

After the 7-day acute intervention for each group, patients in both groups continued to receive progressive, supervised, 90-min, twice-weekly physiotherapy interventions at follow-up for 3 months. The physiotherapy interventions during the follow-up period included ROM and flexibility exercises (3 sets, 10 reps), strengthening exercises (proprioceptive neuromuscular facilitation and Theraband exercises) (2 sets of 10 reps), balance exercises (step-ups, chair rises, wall exercise, marching, toe rises, ball kicking, sudden stop and turn on motion) (2–3 sets, 10 reps), upper limb functional exercises (opening of drawers, writing, hand exerciser, picking and counting) (3 sets, 10 reps), and endurance exercises (treadmill exercise (0.1–0.5 m/s, 5–10 inclination, 10–20 min)/ riding a stationary bicycle ergometry (2- to 5-min-increments with resistance until 20 to 30 min of continuous cycling at 40 rpm), stepping exercise (3 sets, 10 reps)) [38]. The flowchart of the intervention is presented in Fig. 2. Coupled with the direct supervision of the therapist, the use of an exercise diary, telephone calls/texts, and the involvement of family/caregivers for reminders were employed to monitor adherence.

Primary and secondary outcomes

Interleukin-6 is one of the main makers of inflammation in ischaemic stroke [24, 25, 28] while physical disability, assessed by mRS [10, 11, 18], is a common measure of stroke outcome in previous related studies, thus, IL-6 and physical disability were the primary outcomes for the inflammatory markers and clinical outcomes in this study. Fibrinogen, leukocytes, neutrophils, lymphocytes, and monocytes were the secondary outcomes for inflammatory markers, while motor impairment, functional independence, depression, anxiety, and cognition were the secondary clinical outcomes.

Assessment of inflammatory markers

To observe the trends in changes in the inflammatory markers during the acute stage of stroke (1–7 days), the levels of inflammatory markers in both groups were assessed immediately after randomization before any intervention took place, and on the 4th and 7th day of acute intervention. The concentrations of serum IL-6 and plasma fibrinogen were evaluated via the use of enzyme-linked immunosorbent assay and the Clauss method [39, 40]. The whole blood was analysed within 1 h of blood sample collection to evaluate the concentration of leucocytes and its derivative [41]. Meanwhile, the analysis of leukocytes, neutrophils, lymphocytes, and monocytes was performed utilizing a Beckman Coulter AcT 5 differential haematology analyzer.

Assessment of clinical outcomes

The clinical outcomes, namely motor impairment, physical disability, functional independence, depression, anxiety, and cognition were assessed for each group at three-time points: at baseline, 1st and 3rd month of follow-up. The motor impairment was assessed by the Supplemental Motor Scale of NIHSS (SMS-NIHSS). The SMS-NIHSS is a standardized assessment tool employed to evaluate objective motor function in stroke. This instrument has eight measures that assess motor dysfunction in the bilateral shoulder, wrist, hip, and ankle joints. The motor function in SMS-NIHSS was assessed using the six-point Likert ordinal grading scale, which encompasses a range from no movement (score of 5) to normal movement (score of 0) [42], with minimum to maximum score being between 0 to 40. A higher SMS-NIHSS score indicates worse motor impairment. According to previous studies conducted by Enrique et al. [42] and Albanese et al. [43] the SMS-NIHSS has been shown to possess adequate validity and sensitivity in evaluating motor function in individuals who have had a stroke.

The assessment of global physical disability was evaluated using the mRS, scored on a scale from 0 (no disability), 1 (no significant disability), 2 (slight disability), 3 (moderate disability), 4 (moderately severe disability), 5 (severe disability), and 6 (death). A lower mRS score corresponds to a greater level of physical functioning [10]. The Modified Barthel Index (MBI), which measures the ability of stroke survivors to perform 10 activities of daily life without assistance, was employed to assess functional independence. The MBI is evaluated using a five-point Likert scale, and its psychometric features are satisfactory in the evaluation of functional independence after a stroke, with higher scores indicating higher functional independence [44].

The Hospital Anxiety and Depression Scale (HADS), which has been validated and widely employed in assessing depression and anxiety among stroke survivors, was used to assess symptoms of depression and anxiety [45]. Each of the HADS subscales has seven items scored on a 4-point Likert scale (0–3), with 21 being the maximum score for depression and anxiety subscale. A higher HADS scores suggest more symptoms of depression or anxiety [46]. The Montreal Cognitive Assessment (MoCA) is a measure that is useful in evaluating the cognitive abilities of people after a

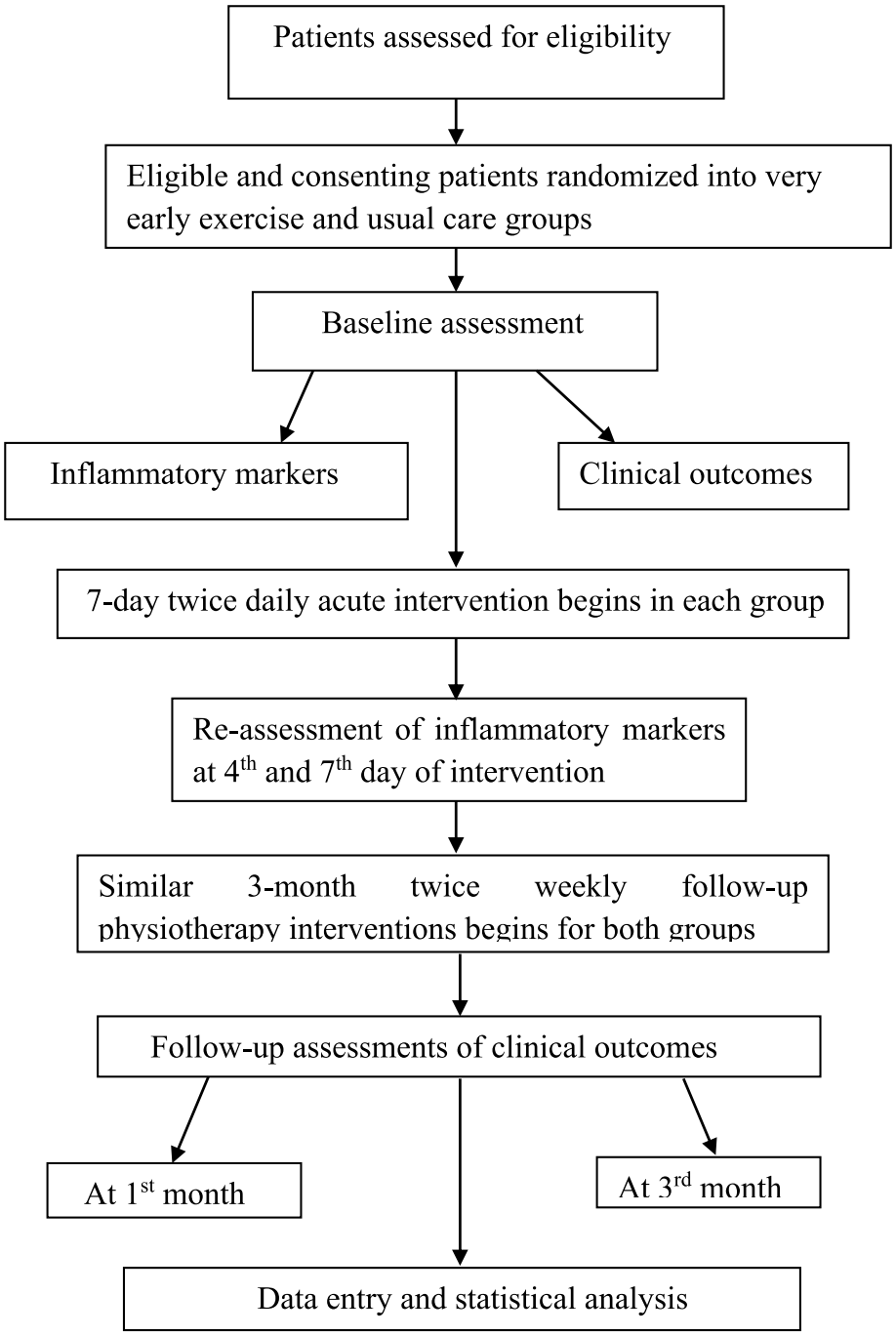

Fig. 2 Research intervention flow chart

stroke event. MoCA is a 30-point test administration that evaluates many areas of cognition [47]. The validity of the MoCA has been proven among individuals who have had a stroke [48, 49]. The maximum score for MoCA is 30, where higher scores on the MoCA have been associated with greater cognitive functioning [48–50].

Data analysis

The descriptive statistics of mean, standard deviation, median, interquartile range, frequency, and percentage

were used to summarize data. To compare the baseline parameters between the two groups, the independent t-test and chi-square were used for physical features, clinical characteristics, and inflammatory markers, while Mann Whitney U test was applied for clinical outcomes, which were measured with ordinal scales. Repeated Measure ANOVA and Bonferroni post hoc tests were used for within-group comparison of the inflammatory markers across baseline, 4th, and 7th day. Friedman's ANOVA and Wilcoxon signed ranked test (post-hoc corrections) were used to compare clinical outcomes across baseline, 1st, and 3rd month of follow-up. The independent t-test was employed to compare between-group mean changes of the inflammatory markers on the 4th and 7th day, while the Mann Whitney U test was utilized for clinical outcomes at the 1- and 3-month follow-up. To investigate the associations between changes in inflammatory markers on the 4th and 7th day and clinical outcomes at 1- and 3-month follow-up, Spearman rho correlation coefficients were applied. The alpha level was set at $p < 0.05$. Data was analysed using SPSS 21.0 version software (SPSS Inc, Chicago, Illinois, USA).

Results

The mean age, weight, height, and body mass index of the participants were 64.2 ± 9.36 years, 66.2 ± 7.05 kg, 1.60 ± 0.06 m, and 25.9 ± 2.66 kg/m^2, respectively. Overall, most of the participants were male (56.2%) and had right-sided stroke laterality (52.1%). The baseline mean values of all participants for IL-6, fibrinogen, and leucocytes were 6.34 ± 3.15 pg/ml, 417.3 ± 76.3 mg/dl, and 8.48 ± 3.88 × 10^3/uL, respectively. The results showed that participants in both groups were comparable in physical, socio-demographic, and stroke-related characteristics ($p > 0.05$) (Table 1). The results of the between-group comparison of baseline inflammatory markers and clinical outcomes showed that both groups were comparable ($p > 0.05$). The median and interquartile range of SMSNIHSS, mRS, and MoCA for all participants at baseline were respectively 4.50 (4.0–5.0), 4.0 (4.0–5.0), and 15.0 (10.2–19.7). The results further showed that the baseline of all clinical outcomes was comparable between both groups ($p > 0.05$) (Table 2).

The results examining the effects of interventions within each group on inflammatory markers and clinical outcomes are presented in Tables 3 and 4. The results

Table 1 Comparison of the participants' physical, socio-demographic, and stroke-related characteristics

Variable	Total ($N = 48$) Mean ± SD/ n (%)	VEEG ($n = 24$) Mean ± SD/ n (%)	UCG ($n = 24$) Mean ± SD/ n (%)	t/ χ^2	*p*-value
Age (Years)	64.2 ± 9.36	64.5 ± 9.37	63.8 ± 9.54	0.244[a]	0.808
Weight (Kg)	66.2 ± 7.05	66.8 ± 7.63	65.6 ± 6.53	0.589[a]	0.559
Height (m)	1.60 ± 0.06	1.61 ± 0.07	1.59 ± 0.06	0.640[a]	0.525
BMI (Kg/m^2)	25.9 ± 2.66	25.9 ± 2.91	25.8 ± 2.44	0.106[a]	0.916
Number of Co-morbidities	1.94 ± 0.59	2.04 ± 0.62	1.83 ± 0.56	1.213[a]	0.231
Baseline NIHSS	7.13 ± 2.90	7.50 ± 2.83	6.75 ± 2.98	0.894[a]	0.376
Laterality					
Right	25 (52.1)	14 (56.0)	11 (44.0)	0.75[b]	0.386
Left	23 (47.9)	10 (43.5)	13 (56.5)		
Gender					
Male	27 (56.2)	13 (48.1)	14 (51.9)	0.085[b]	0.771
Female	21 (43.8)	11 (52.4)	10 (47.6)		
Education level					
Low	35 (72.9)	15 (62.5)	20 (83.3)	2.637[b]	0.104
High	13 (27.1)	9 (37.5)	4 (16.7)		
Income					
Low	18 (37.5)	10 (41.7)	8 (33.3)	0.366[b]	0.833
Medium	19 (39.6)	9 (37.5)	10 (41.7)		
High	11 (22.9)	5 (20.8)	6 (25.0)		
Marital status					
Married[c]	36 (75.0)	20 (83.3)	16 (66.7)	1.778[b]	0.182
Single[d]	12 (25.0)	4 (16.7)	8 (33.3)		

[a] t-test, [b]Chi-square, [c]included those who cohabit with someone, [d]included the unmarried, divorced, widowed, and separated, n frequency, % percentage, SD standard deviation, NIHSS National Institute of Health Stroke Scale, VEEG very early exercise group, UCG usual care group

Table 2 Comparison of the participants' baseline inflammatory markers and clinical outcomes

Variable	Total ($N=48$) Mean ± SD/Median (IQR)	VEEG ($n=24$) Mean ± SD/Median (IQR)	UCG ($n=24$) Mean ± SD/Median (IQR)	t/U	*p*-value
Inflammatory markers					
Interleukin-6 (pg/ml)	6.34 ± 3.15	6.39 ± 3.34	6.28 ± 3.00	0.123[a]	0.903
Fibrinogen (mg/dl)	417.3 ± 76.3	424.5 ± 79.0	410.0 ± 74.5	0.650[a]	0.519
Leucocytes ($\times 10^3$/uL)	8.48 ± 3.88	7.60 ± 4.23	9.36 ± 3.36	1.591[a]	0.118
Neutrophils ($\times 10^3$/uL)	5.69 ± 3.68	5.38 ± 3.94	5.99 ± 3.45	0.575[a]	0.568
Lymphocytes ($\times 10^3$/uL)	2.87 ± 2.21	3.02 ± 2.78	2.71 ± 1.51	0.474[a]	0.638
Monocytes ($\times 10^3$/uL)	0.67 ± 0.34	0.63 ± 0.32	0.72 ± 0.35	0.968[a]	0.338
Clinical outcomes					
Motor impairment (SMSNIHSS)	4.50 (4.0–5.0)	5.0 (4.0–5.0)	4.0 (4.0–5.0)	248.0[b]	0.360
Physical disability (mRS)	4.0 (4.0–5.0)	5.0 (4.0–5.0)	4.0 (3.0–5.0)	215.5[b]	0.105
Functional independence (MBI)	65.0 (44.0–72.7)	66.5 (46.2–76.5)	60.0 (33.0–72.5)	250.0[b]	0.433
Depression (HADS-D)	9.0 (7.0–12.0)	8.5 (7.0–12.0)	9.0 (7.2–11.7)	275.5[b]	0.796
Anxiety (HADS-A)	10.0 (7.0–12.0)	9.5 (6.2–11)	10.0 (7.0–12.0)	246.0[b]	0.383
Cognition (MoCA)	15.0 (10.2–19.7)	14.0 (9.2–21.0)	16.0 (11.2–19.7)	278.0[b]	0.836

[a] t-test, [b]Mann–Whitney U test, IQR interquartile range, SD standard deviation, SMSNIHSS Supplemental Motor Scale National Institute of Health Stroke Scale, mRS modified Ranking Scale, MBI Modified Barthel Index, HADS-D Hospital Anxiety and Depression Scale-Depression Sub-scale, HADS-A Hospital Anxiety and Depression Scale-Anxiety Sub-scale, MoCA Montreal Cognitive Assessment, VEEG very early exercise group, UCG usual care group

Table 3 Within-group comparison of inflammatory markers across baseline, day four, and day seven of the study among participants in usual care and very early exercise groups

Variable	Baseline Mean ± SD	4th day Mean ± SD	7th day Mean ± SD	F	*p*-value
Usual care group					
Interleukin-6 (pg/ml)	6.28 ± 3.00[a]	7.83 ± 3.35[b]	7.99 ± 3.50[b]	26.646	< 0.001*
Fibrinogen (mg/dl)	410.1 ± 74.5[a]	421.5 ± 74.4[b]	432.1 ± 72.8[b]	21.402	< 0.001*
Leucocytes ($\times 10^3$/uL)	9.36 ± 3.37[a]	10.5 ± 3.65[b]	11.1 ± 4.07[c]	17.738	< 0.001*
Neutrophils ($\times 10^3$/uL)	5.99 ± 3.45[a]	7.18 ± 3.65[b]	7.95 ± 4.21[c]	9.742	0.004*
Lymphocytes ($\times 10^3$/uL)	2.72 ± 1.51[a]	2.29 ± 1.25[b]	1.80 ± 0.99[c]	18.250	< 0.001*
Monocytes ($\times 10^3$/uL)	0.72 ± 0.35	0.81 ± 0.30	0.83 ± 0.34	2.792	0.104
Very early exercise group					
Interleukin-6 (pg/ml)	6.40 ± 3.34[a]	7.27 ± 3.79[b]	7.28 ± 3.93[b]	12.061	0.001*
Fibrinogen (mg/dl)	424.5 ± 79.0[a]	436.7 ± 78.3[b]	439.4 ± 79.1[b]	43.931	< 0.001*
Leucocytes ($\times 10^3$/uL)	7.60 ± 4.23[a]	8.66 ± 3.96[b]	8.49 ± 3.84[ab]	4.192	0.046*
Neutrophils ($\times 10^3$/uL)	5.38 ± 3.94	5.63 ± 3.39	5.47 ± 3.49	0.222	0.720
Lymphocytes ($\times 10^3$/uL)	3.02 ± 2.78	2.81 ± 2.23	2.97 ± 2.52	1.277	0.285
Monocytes ($\times 10^3$/uL)	0.63 ± 0.32	0.69 ± 0.29	0.77 ± 0.36	3.741	0.057

* Indicates a significant difference, [a,b,c] mean values with different superscripts are significantly different while those with the same superscript are not significantly different

showed a significant increase in all examined biomarkers across baseline, 4th, and 7th day of the study among participants in UCG, except lymphocytes, which significantly decreased across study time ($p<0.05$), and monocytes with insignificant increase ($p>0.05$). However, only IL-6, fibrinogen, and leucocytes showed a significant increase across the study time among participants in VEEG ($p<0.05$) (Table 3). Furthermore, there was a significant decrease in motor impairment, physical disability, depression, and anxiety, and an increase in functional independence and cognition across baseline, 1st, and 3rd month of follow-up among participants in both groups ($p<0.05$) (Table 4).

The results of the mean change comparison of the inflammatory markers on the 4th and 7th day of the study between the two groups are presented in Table 5. On 4th day (difference between day four and baseline), the results showed a lower but insignificant mean change

Table 4 Within-group comparison of clinical outcomes across baseline, first month, and third month of the study among participants in usual care and very early exercise groups

Variable	Baseline Median (IQR)	1st Month Median (IQR)	3rd Month Median (IQR)	χ2	*p*-value
Usual care group					
Motor impairment	4.0 (4.0–5.0)[a]	4.0 (3.0–4.0)[a]	3.0 (2.0–3.0)[b]	38.711	< 0.001*
Physical disability	4.0 (3.0–5.0)[a]	3.0 (3.0–4.0)[b]	2.5 (2.0–3.0)[c]	33.899	< 0.001*
Functional independence	60.0 (33.0–72.2)[a]	63.0 (35.2–73.7)[b]	69.5 (43.5–77.2)[c]	32.386	< 0.001*
Depression	9.0 (7.2–11.7)[a]	8.0 (5.5–10.0)[b]	6.5 (4.0–8.7)[c]	45.600	< 0.001*
Anxiety	10.0 (7.0–12.0)[a]	8.5 (7.0–11.0)[b]	6.5 (4.2–9.0)[c]	42.636	< 0.001*
Cognition	16.0 (11.2–19.7)[a]	16.0 (12.0–20.7)[a]	17.5 (13.0–21.0)[b]	37.837	< 0.001*
Very early exercise group					
Motor impairment	5.0 (4.0–5.0)[a]	3.0 (2.0–3.0)[b]	1.0 (1.0–2.0)[c]	45.067	< 0.001*
Physical disability	5.0 (4.0–5.0)[a]	3.0 (2.0–4.0)[b]	1.0 (1.0–2.0)[c]	42.518	< 0.001*
Functional independence	66.5 (46.2–76.5)[a]	71.5 (55.7–81.7)[b]	82.0 (78.0–91.5)[c]	47.000	< 0.001*
Depression	8.5 (7.0–12.0)[a]	6.5 (5.0–9.0)[b]	4.0 (3.0–6.0)[c]	38.000	< 0.001*
Anxiety	9.5 (6.2–11.0)[a]	7.5 (4.0–9.0)[b]	4.5 (2.0–7.0)[c]	46.516	< 0.001*
Cognition	14.0 (9.2–21.0)[a]	16.0 (11.2–24.0)[b]	17.0 (14.0–26.5)[c]	46.261	< 0.001*

* Indicates a significant difference, [a,b,c] values with different superscripts are significantly different while those with the same superscript are not significantly different, IQR interquartile range

Table 5 Between-group comparison of the participants' inflammatory markers (mean change) on days four and seven of the study

Variable	VEEG ($n=24$) $\bar{x}$±SD	UCG ($n=24$) $\bar{x}$±SD	T	*p*-value	Cohen's d
Day 4					
Interleukin-6 (pg/ml)	0.88 ± 1.06	1.54 ± 1.34	1.898	0.064	0.55
Fibrinogen (mg/dl)	12.2 ± 2.53	11.3 ± 2.20	1.217	0.230	0.38
Leucocytes ($\times 10^3$/uL)	1.05 ± 1.99	1.11 ± 1.38	0.105	0.917	0.04
Neutrophils ($\times 10^3$/uL)	0.25 ± 1.59	1.18 ± 2.02	1.772	0.083	0.51
Lymphocytes ($\times 10^3$/uL)	−0.21 ± 0.83	−0.43 ± 0.54	1.072	0.289	0.31
Monocytes ($\times 10^3$/uL)	0.07 ± 0.19	0.09 ± 0.23	0.328	0.745	0.09
Day 7					
Interleukin-6 (pg/ml)	0.89 ± 1.30	1.70 ± 1.61	1.922	0.061	0.55
Fibrinogen (mg/dl)	14.8 ± 9.33	22.0 ± 19.9	1.595	0.117	0.46
Leucocytes ($\times 10^3$/uL)	0.88 ± 2.49	1.74 ± 1.92	1.332	0.190	0.39
Neutrophils ($\times 10^3$/uL)	0.09 ± 2.39	1.94 ± 2.94	2.329	0.021*	0.69
Lymphocytes ($\times 10^3$/uL)	−0.05 ± 0.62	−0.91 ± 0.93	3.742	0.001*	1.09
Monocytes ($\times 10^3$/uL)	0.14 ± 0.35	0.11 ± 0.32	0.380	0.705	0.09

* Indicates a significant difference, VEEG very early exercise group, UCG usual care group

in all inflammatory markers, except lymphocytes and fibrinogen, which had a higher value, among participants in VEEG compared to UCG ($p>0.05$). Meanwhile, on the 7th day (difference between day seven and baseline), neutrophils ($p=0.021$) had a significantly lower mean change, while lymphocytes ($p=0.001$) had a significantly higher mean change among participants in VEEG compared to those in UCG. At this same period, participants in VEEG again maintained a lower but insignificant mean change in other biomarkers compared to those in UCG. The effect size of VEE on inflammatory markers was largely small or medium. On 4th day, the effect size was small in fibrinogen (d = 0.38) and lymphocytes (d = 0.31) and was medium in interleukin-6 (d = 0.55) and neutrophils (d = 0.51) levels but the effect was negligible for monocytes and leucocytes. On the 7th day, the effect size was small in fibrinogen (d = 0.46) and leucocytes (d = 0.39), medium in interleukin-6 (d = 0.55) and neutrophils (d = 0.69), and large in lymphocytes (d = 1.09) concentration. Again, the effect size of VEE on monocyte concentration was negligible on the 7th day (Table 5). These results indicate that while VEE had minor/small

effects on some inflammatory markers, the modulatory effect of VEE was moderate to substantial in others, suggesting differences in the sensitivity of the inflammatory pathways to VEE. Furthermore, the effect on lymphocytes and leucocytes that increased from day 4 to day 7 suggests that VEE exerts time-dependent modulation of immune cell responses, indicating a progressive impact of VEE on inflammatory markers.

Furthermore, the clinical outcomes of the participants were compared in both groups at 1st and 3rd month relative to the baseline. The results (Table 6) showed that at 1st month (difference between the first month and baseline) and 3rd month (difference between the third month and baseline) of follow-up, participants in VEEG had a significant decrease in the median change in motor impairment, physical disability, depression, and anxiety, and a significant increase in functional independence and cognition than those in UCG ($p<0.05$). Meanwhile, the effect size of VEE on all clinical outcomes examined in this study was large at both 1st (≥ 0.52 $r \leq 0.66$) and 3rd (≥ 0.59 $r \leq 0.70$) month of follow-up, except in depression at 1st month ($r=0.49$) and depression ($r=0.38$) and anxiety ($r=0.43$) at 3rd month which was medium (Table 6). The large effects of VEE on most clinical outcomes assessed in this study at 1- and 3-month follow-up suggest its potential substantial and sustained benefits in stroke recovery.

The correlations between changes in inflammatory markers at days 4 and 7 from baseline and the clinical outcomes at 1- and 3-month follow-up are presented in Table 7. The results showed that change in IL-6 at day 4 was negatively correlated with MBI at 3 months ($r_s=-0.33$; $p=0.019$) while the change in the lymphocytes at day 4 was negatively correlated with anxiety-subscale of HADS ($r_s=-0.30$; $p=0.036$) at 1 month. Furthermore, change in IL-6 at day 7 had a positive correlation with SMSNIHSS ($r_s=0.30$; $p=0.039$) and a negative correlation with MBI ($r_s=-0.33$; $p=0.021$) at 3 months, while 3-month MBI and 7-day change in fibrinogen ($r_s=-0.29$; $p=0.044$), and 3-month mRS and 7-day change in lymphocytes ($r_s=-0.44$; $p=0.002$) had a negative correlation.

Discussion

Very early physical exercise has often been advocated and sometimes prescribed after a stroke incident; however, its effect on the clinical outcomes among stroke survivors is inconclusive. Furthermore, the neuro-biological effects of VEE in stroke and its contribution to the eventual stroke outcomes are largely unknown. This study demonstrates the positive modulation of inflammatory markers at the acute stage by VEE, indicating the benefits of early exercise intervention in stroke recovery. Importantly, the improved clinical outcomes at follow-up were associated with this modulation, suggesting the important role of VEE on both neuro-biological mechanisms and clinical recovery over time. The findings of this study add fresh insights into the mediatory functions of inflammation in post-acute stroke care and underscore the prospects of timely rehabilitation in enhancing long-term stroke outcomes.

There were no significant differences in terms of socio-demographics, stroke-related characteristics, biomarkers levels, and psycho-physical characteristics between

Table 6 Between-group comparison of the participants' clinical outcomes (median change) at the first and third month of follow-up

Variable	VEEG ($n=24$) Median (IQR)	UCG ($n=24$) Median (IQR)	U	*p*-value	Effect size r
1st month					
Motor impairment	−2.0 (−2.0,−1.0)	−1.0 (−1.0, 0)	91.000	< 0.001*	0.62
Physical disability	−2.0 (−2.0, −1.0)	−1.0 (−1.0, 0)	125.000	< 0.001*	0.52
Functional independence	6.0 (4.0, 8.7)	2.0 (1.0,4.0)	93.500	< 0.001*	0.58
Depression	−2.5 (−3.0, −1.2)	−1.0 (−2.0, −0.25)	126.000	0.001*	0.49
Anxiety	−2.0 (−3.0, −2.0)	−1.0 (−1.0, 0)	98.500	< 0.001*	0.58
Cognition	2.0 (2.0, 3.0)	1.0 (0, 1.0)	72.500	< 0.001*	0.66
3rd month					
Motor impairment	−3.5 (−4.0, −2.0)	−2.0 (−2.0, −1.0)	77.000	< 0.001*	0.66
Physical disability	−3.0 (−4.0, −2.0)	−2.0 (−2.0, −1.0)	76.500	< 0.001*	0.65
Functional independence	16.5 (12.0, 24.2)	5.5 (2.0, 8.7)	71.000	< 0.001*	0.70
Depression	−4.5 (−6.7, −3.0)	−3.0 (−4.0, −2.0)	165.000	0.009*	0.38
Anxiety	−5.0 (−5.0, −3.2)	−3.0 (−4.0, −2.0)	148.500	0.003*	0.43
Cognition	4.0 (3.0, 6.0)	2.0 (2.0, 3.0)	95.500	< 0.001*	0.59

* Indicates a significant difference, VEEG very early exercise group, UCG usual care group, IQR interquartile range

Table 7 Correlations between 4-and 7-day changes in inflammatory markers and clinical outcomes at follow-up

Markers Day 4	Clinical outcomes (One-month follow-up) r_s (*p*-value)						Clinical outcomes (Three-month follow-up) r_s (*p*-value)					
	SMSNIHSS	**mRS**	**MBI**	**HADS-D**	**HADS-A**	**MoCA**	**SMSNIHSS**	**mRS**	**MBI**	**HADS-D**	**HADS-A**	**MoCA**
IL-6	0.18(0.220)	0.09(0.521)	0.15(0.311)	0.14(0.332)	0.07(0.656)	−0.14(0.358)	0.24(0.097)	0.19(0.180)	**−0.33(0.019)**	−0.21(0.149)	−0.09(0.506)	−0.11(0.454)
Fib	−0.09(0.548)	−0.21(0.159)	0.14(0.332)	−0.09(0.560)	−0.23(0.113)	0.0(0.998)	−0.18(0.234)	−0.28(0.054)	0.20(0.166)	−0.13(0.372)	**−0.34(0.020)**	0.06(0.687)
Leu	0.06(0.693)	0.07(0.662)	−0.16(0.293)	0.02(0.890)	0.06(0.667)	−0.11(0.454)	−0.05(0.729)	0.04(0.795)	0.0(1.000)	−0.08(0.590)	0.10(0.497)	−0.0(0.975)
Neu	0.14(0.347)	0.05(0.762)	−0.19(0.176)	**0.32(0.027)**	−0.06(0.703)	−0.09(0.526)	0.12(0.429)	0.14(0.328)	−0.08(0.584)	0.25 (0.075)	0.04(0.806)	0.06(0.701)
Lym	−0.25(0.091)	−0.27(0.065)	0.25(0.085)	−0.14(0.345)	**−0.30(0.036)**	0.16(0.267)	−0.24(0.105)	−0.26(0.078)	0.21(0.151)	−0.18(0.211)	−0.18(0.218)	0.22(0.412)
Mono	−0.02(0.921)	0.02(0.918)	−0.03(0.851)	−0.11(0.938)	−0.09(0.521)	0.07(0.658)	−0.02(0.887)	0.01(0.933)	0.08(0.553)	−0.19 (0.187)	0.12(0.408)	0.16(0.291)
Markers Day 7												
IL-6	0.26(0.070)	0.11(0.450)	−0.13(0.368)	0.19(0.174)	0.18(0.425)	−0.17(0.251)	**0.30(0.039)**	0.13(0.363)	**−0.33(0.021)**	−0.18(0.215)	−0.07(0.651)	−0.14(0.338)
Fib	0.23 (0.111)	0.24(0.096)	−0.24(0.095)	0.23(0.124)	0.06(0.674)	−0.27(0.063)	0.16(0.272)	0.24(0.107)	**−0.29(0.044)**	0.04(0.779)	0.19(0.177)	−0.17(0.239)
Leu	0.18(0.222)	0.19(0.208)	**−0.29(0.039)**	0.13(0.371)	0.16(0.293)	−0.26(0.071)	0.11(0.446)	0.18(0.213)	−0.11(0.440)	0.09(0.557)	0.17(0.254)	−0.16(0.282)
Neu	0.25(0.088)	0.18(0.217)	−0.28(0.056)	0.23(0.123)	−0.02(0.895)	−0.19(0.205)	0.21(0.152)	0.25(0.085)	−0.12(0.434)	0.27(0.065)	−0.10(0.484)	−0.06(0.680)
Lym	**−0.35(0.016)**	−0.28(0.059)	**0.38(0.008)**	**−0.35(0.015)**	−0.26(0.070)	0.22(0.134)	**−0.35(0.014)**	**−0.44(0.002)**	**0.42(0.003)**	−0.24(0.100)	−0.20(0.167)	0.19(0.182)
Mono	0.0(1.000)	0.06(0.682)	−0.01(0.996)	−0.15(0.326)	−0.10(0.488)	0.04(0.801)	−0.05(0.714)	0.02(0.822)	0.13(0.353)	**−0.32(0.027)**	0.20(0.170)	0.12(0.417)

SMSNIHSS Supplemental Motor Scale National Institute of Health Stroke Scale, *mRS* modified Ranking Scale, *MBI* Modified Barthel Index, *HADS-D* Hospital Anxiety and Depression Scale-Depression Sub-scale, *HADS-A* Hospital Anxiety and Depression Scale-Anxiety Sub-scale, *MoCA* Montreal Cognitive Assessment, *IL-6* interleukin-6, *Fib* fibrinogen, *Leu* Leucocytes, *Neu* Neutrophils, *Lym* Lymphocytes, *Mono* Monocytes, r_s Spearman rho correlation coefficients, bold indicates a significant correlation

patients in both groups at baseline, showing that patients in both groups were homogenous and comparable, and thus, the observed differences cannot be attributable to these parameters. The findings of this study showed significant up-regulation of the pro-inflammatory markers (IL-6, fibrinogen, leucocytes, neutrophils, and monocytes) and reduction in the anti-inflammatory marker (lymphocytes) assessed in this study from baseline to 4th and 7th day of assessment within each group. The upregulation of the pro-inflammatory markers and the reduction in lymphocyte concentration at the acute stage of stroke observed in this study has been reported earlier in several studies [40, 51–55]. For instance, the increase of IL-6 among survivors of ischaemic stroke is said to begin within 2 h of stroke onset and reach a peak point the first week of ischaemic event [40, 51, 53]. Meanwhile, fibrinogen, which is the main plasma protein, is involved in haemostasis, coagulation, and blood viscosity [54]. However, reports have shown that there is an increase in the level of circulating fibrinogen after a stroke event [54]. The incidence of stroke causes early depletion of circulating peripheral lymphocytes, i.e., lymphopenia [56]. Lymphocytes are major white blood cell parameters involved with innate immunity, however, their depletion after stroke incidence, termed stroke-induced immune suppression, is common [55]. Unfortunately, the upregulation of pro-inflammatory and reduction in anti-inflammatory molecules within the first week of stroke are consistently associated with worse short- and long-term clinical outcomes of stroke patients [51, 52, 54–56].

Despite this, the results showed that patients with VEE intervention had better inflammatory outlook than those with just usual care. The results of the between-group mean change showed a lower mean concentration of IL-6, leucocytes, neutrophils, and monocytes on the 4th and 7th day from baseline among patients in VEEG. Furthermore, concerning lymphocytes, the results showed that patients in VEEG had a higher lymphocyte concentration on the 4th and 7th day compared to those in UCG. The results, for instance, showed that while patients in UCG showed a 24.7% and 27.2% increase in IL-6 concentration on the 4th and 7th day, the increase was just 13.6% and 13.8% for patients in VEEG at the same time points. Furthermore, lymphocyte concentration decreased by 15.8% and 33.8% on the 4th and 7th day among patients in UCG, while the decrease was just 6.95% and 1.66% on the 4th and 7th day among patients in VEEG. In short, this study found that VEE had a moderate effect on some inflammatory markers, including IL-6. Although the reduction in IL-6 concentrations in patients exposed to exercise interventions within 24 h of stroke compared with those who started physical exercise after a week did not reach the threshold of conventional statistical significance ($p = 0.064$ at day 4; $p = 0.061$ at day 7), the moderate effect size observed at both time points ($d = 0.55$) suggests an important biological influence.

As observed in this study, empirical data has shown that physical exercise is a potent modulator of inflammatory mechanisms in individuals with chronic illnesses such as systemic lupus erythematosus, spinal cord injury, etc. [57–59]. Exercise has been shown to not only reduce inflammatory activity but also improve the anti-inflammatory process in disease conditions [58, 59]. Thus, VEE is robust in reducing the pro-inflammatory (e.g., IL-6 or neutrophils) or improving the anti-inflammatory markers (e.g., lymphocytes) in stroke. Among stroke survivors, there is limited data on the effect of exercise on biomarkers at the acute stage; however, the results of related studies are in line with the findings of this study. For instance, Kirzinger et al. [60] reported a non-significant reduction of IL-6, tumor necrosis factor-alpha, and C-reactive protein among sub-acute stroke patients after four weeks of aerobic exercise. However, contrary to the linear increase in fibrinogen levels observed in patients in UCG, the findings of this study showed a non-linear effect of VEE on fibrinogen concentration across the intervention timeline. The results showed a higher increase in fibrinogen levels of patients in VEEG compared with UCG from baseline to 4th day of intervention. However, there was a higher reduction in the fibrinogen level among patients in VEEG on the 7th day compared to baseline. In other words, very early exercises initially caused a higher increase in fibrinogen level, then a higher reduction in the course of intervention than those with regular turning and positioning. Other authors have also reported a decrease in fibrinogen levels after physical exercise in individuals with cardiovascular diseases [61]. A study by Kirzinger et al. [60] showed a similar non-significant change in fibrinogen levels among sub-acute stroke survivors after a 4-week aerobic exercise compared with a relaxation technique.

The non-linear effect of exercise on plasma fibrinogen concentration has been mentioned earlier in the literature [39, 61, 62]. Reports state that exercise training induces an acute rise of fibrinogen levels between days 1–3 of exercise training, and reduction at day 5 of the exercise [39, 62]. This phenomenon has been attributed to several factors including acute inflammatory and hormonal responses to exercise which may initiate the production of acute-phase protein, such as fibrinogen, as part of the body's stress response [39, 61, 62]. Furthermore, exercise may cause mobilisation of stored fibrinogen into the plasma, leading to its transient increase [39, 61, 62]. However, as exercise continues, the anti-inflammatory mechanisms are activated, fibrinolysis processes are promoted, and pro-inflammatory cytokines

activities are downregulated, which may have resulted in the observed decline in fibrinogen over time [39, 61, 62]. These findings indicate the important complex interactions between exercise, inflammation, and coagulation, suggesting the potential modulating role of VEE on the dynamics of post-stroke haemostasis over time.

Meanwhile, although there was a transient higher increase in the plasma fibrinogen among patients in VEEG from baseline to day 4 in this study, it was negligible compared to the increase observed among patients in UCG in the same period (2.9% vs. 2.8%). This suggests that the percentage of the transient increase among patients with VEE (0.1%) may be clinically negligible and unlikely to have adverse effects. However, to minimize coagulation responses to exercise in this patient population, the prescription of low to moderate-intensity exercises and a gradual increase in exercise intensity over time during early rehabilitation is crucial. Furthermore, careful monitoring of coagulation markers and signs of blood clots (e.g., chest pain, leg swelling, warm skin, pain in the calf, foot, or leg, etc.) is also important, especially among patients with a high risk of thrombosis.

Similarly, the findings of this study showed that motor function, physical disability, functional independence, depression, anxiety, and cognition significantly improved from the baseline to 1st and 3rd month of follow-up in each group. This finding is not unexpected as patients in both groups received medical and nursing care concurrently during their admission. Furthermore, after the seven days of acute exercise intervention for patients in VEEG, patients in both groups continued to receive physiotherapy twice weekly for the 3-month follow-up. Therefore, some form of improvement in the physical and psychological health of the stroke survivors in this study is expected for patients in UCG as well. Although the physical exercise was delayed for a week among patients in UCG, starting exercise a week or even two weeks after a stroke incident is still considered an early rehabilitation with better clinical outcomes than stroke patients who started exercise intervention after two weeks [14]. So, in theory, patients in UCG who started physiotherapy a week after stroke onset in this study are still categorized as being exposed to early rehabilitation intervention and should show a considerable improvement in their clinical outlook as observed in this study.

Furthermore, the concurrent improvement from the baseline to 1st and 3rd month in the clinical outcomes of patients within each group can also be attributed to early spontaneous motor recovery. At the early stage of stroke, there is a phenomenon called 'spontaneous biological recovery' [4]. This recovery occurs within a few days of ischaemic event due to a spontaneous mechanism called neuroplasticity, and according to the 'proportional recovery rule', may lead to many patients recovering 70% (+/−15%) of their pre-stroke functional abilities within three months of stroke [4, 5, 63–66]. This phenomenon has been described as a major cofounder of early therapeutic exercise in stroke rehabilitation [67]. However, this rule only fits patients with mild-to-moderate stroke [68, 69].

Although many patients with stroke may recover spontaneously within 3 months of stroke incidence [56, 57], however, the rate of recovery is based on many factors, including co-morbidities, social support, and exposure to early rehabilitation intervention [66]. Even a delay of a few days in starting intervention after stroke incidence negatively affects the pace of motor recovery [65, 70]. In the present study, the findings of median change comparison showed that patients in VEEG showed a significantly lower motor impairment, physical disability, depression, and anxiety, and significantly higher functional independence and cognition than patients in UCG at both two-time points of follow-up. Specifically, physical disability, for instance, was reduced by 25% in 1st month and 37.5% in 3rd month of follow-up among patients in UCG, whereas physical disability was reduced by 40% and 80% at 1st and 3rd month among those in VEEG. In line with the findings of this result, previous studies have shown that VEE intervention in bed [34, 71] or out of bed [11, 17, 20, 71] resulted in better clinical outcomes in individuals with stroke than those who started later. However, reports from other studies showed no significant positive effects of very early out-of-bed exercises [11, 14, 17, 56, 72]. The results of AVERT II and III studies, published in 2008 and 2015, showed worse outcomes (frequency of death at 3 months and 0–2 mRS scores) at 3 months among participants in very early mobilization [11, 17]. Similarly, Tong et al. [22] showed that very early intensive mobilization (within 24 h) did not show a better favourable outcome (mRS scores 0–2) compared to early intensive mobilization (after 24 h) at a 3-month follow-up.

The discrepancy has been attributed to timing and dosage of intervention [22, 72]. Tong and colleagues observed that a mobilisation dosage of ≥ 3 h/d, though ideal and beneficial after 24 h of stroke onset, was considered high intensity and was associated with worse clinical outcomes if implemented within 24 h [22]. Thus, a short period and higher frequency of intervention have been shown and described as ideal for patients undergoing very early exercise therapy [14, 22]. In what could be considered as moderate intensity, in this study, patients in VEEG underwent exercise training for a total of 1.5 h/d, delivered in two 45-min sessions (morning and evening) for seven days. Thus, better outcomes obtained in this

study in patients with VEE may result from not only the timing but also the dosage and frequency of the exercise intervention.

While the better clinical outcomes observed among patients with very early exercise intervention can be linked with the direct promotion of neuroplasticity by the exercise, the exercise-related changes in the selected inflammatory markers are another plausible reason for the better clinical outcomes obtained in the VEEG. In this study, there were significant associations between exercise-induced changes in some inflammatory markers on the 4th and 7th day post-stroke and improved clinical outcomes, such as functional independence, motor function, depression, and anxiety, at follow-up. For instance, the positive modulation of IL-6 concentrations by VEE at days 4 ($r = -0.33$; $p = 0.019$) and 7 ($r = -0.33$; $p = 0.021$) were weakly and negatively associated with improved functional independence at 3 months. Interleukin-6 is a main marker of acute inflammation and tissue damage and a major indicator and mediator of neuronal repair after stroke, therefore, this result highlights the potential clinical importance of targeting the acute inflammatory processes in stroke through timely rehabilitation and the importance of moderate VEE in shaping the process of recovery. Although weak correlations were observed between inflammatory markers and clinical outcomes in this study, these results indicate that inflammatory markers, e.g., IL-6, may serve as targets for therapeutic monitoring of very early rehabilitation. The up-regulation of the pro-inflammatory markers in the first week of stroke has been associated with worse clinical outcomes in individuals with stroke even months and years after the initial ischaemic event [24]. The theoretical basis for these worse outcomes is that the up-regulation of these neurobiological molecules early after stroke impairs optimal neuroplasticity and promotes more oxidative stress and cell apoptosis of the injured neural tissues and the surrounding areas [8, 24]. As shown by the results of the correlation analyses in this study, the positive modulation of the biomarkers at the acute stage, occasioned by VEE, may have contributed to the better clinical outcomes observed in the VEEG exercises group.

Although the implementation of moderate-intensity VEE intervention in this study shows promising results in promoting positive inflammatory mechanisms and clinical outcomes, certain precautions should be undertaken to ensure safety, including close monitoring of the patient's clinical stability (heart rate, blood pressure, neurological status, oxygen saturation, etc.). Patients with a high risk of thrombosis, with severe stroke, with some type of stroke such as large vessel occlusions, brainstem stroke, and intracerebral haemorrhage, and older patients may require careful consideration.

Limitations to the study

This study presents with some potential limitations. The use of a relatively homogenous small sample size may limit the chance of detecting the true effect of VEE [73, 74], while recruiting from one center may reduce the external validity of the findings. The findings of this study are also limited to patients with first-ever mild to moderate ischaemic stroke and those without pre-stroke disability. Patients with severe stroke or haemorrhagic stroke are often associated with higher cerebral oedema and haemodynamic instability and therefore may present with a more profound inflammatory response to VEE. Furthermore, patients with recurrent stroke or pre-stroke disability may present with more baseline functional problems causing heterogeneity in recovery patterns, and may also introduce floor effects where intervention effects are difficult to detect. The use of self-reports in some measure, e.g., in the assessment of clinical depression, may also introduce report bias and social desirability. The lack of a placebo group and a short period of follow-up may also serve as a limitation. Thus, considering these factors, further studies with larger samples or from multiple locations with longer follow-up periods are recommended. To address the small sample size and potential imbalances in the dataset, the use of augmentation and balancing methods could also be applied in future studies to improve the robustness of the results [75].

Conclusion

This study highlights the potential benefits of moderate-intensity VEE in positively modulating the inflammatory markers, including IL-6, during the acute stage of stroke and improving physical disability, motor, cognitive, and affective functioning at 3 months in patients with first-ever mild-to-moderate ischaemic stroke. The effects of moderate-intensity VEE on inflammatory markers, particularly IL-6, were associated with improved clinical outcomes, suggesting the important role of moderate timely exercise intervention in promoting recovery through inflammatory modulation.

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Authors' contributions

ABA, TOA, and MOD were involved in the design and conceptualization of the study. ABA, SOI, SOB, FWA, and OO were involved in data collection, analysis, and interpretation. ABA wrote the initial draft of the manuscript. ABA, TOA, MOD, SOI, SOB, FWA, and OO contributed to the writing of the final draft of the manuscript. All authors read and approved the final manuscript.

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Data availability
The data generated in this study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in line with the Declaration of Helsinki (as revised in 2013). Ethical clearance was obtained from the Ethical Review Committee of the Osun State University Teaching Hospital, Osogbo, Nigeria (UTH/REC/2023/05/766). All participants gave written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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