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The effects of multicomponent rehabilitation exercise plus soymilk on cognitive impairment and ischemic lesion growth in stroke patients: A randomized controlled trial

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ABSTRACT

Objectives: This study aimed to examine the effects of a multicomponent rehabilitation exercise, coupled with soymilk intake post-exercise, on cognitive impairment and ischemic lesion growth among acute stroke patients.
Methods: In a four-arm, single-blind, randomized clinical trial, 120 patients with acute stroke were randomly allocated to one of the following groups: 1) the MRE + soymilk, 2) the MRE, 3) the soymilk, and 4) the control group. Each group underwent their respective intervention for a continuous duration of 20 days. Cognitive impairment was assessed using the Montreal Cognitive Assessment, and the growth of ischemic lesions was evaluated through CT scans.
Results: The MRE combined with soymilk intervention demonstrated statistically significant improvements in cognitive impairment among acute stroke patients ($\chi^2 = 51.055$, $p = 0.000$). Group differences began to emerge from Week, with improvements observed across all dimensions of cognitive function, except for abstraction. No significant differences were observed between groups in terms of ischemic lesion growth ($\chi^2 = 0.934$, $p = 0.810$).
Conclusion: The incorporation of a multicomponent rehabilitation exercise combined with soymilk ingestion demonstrated effectiveness in alleviating cognitive impairment among acute stroke patients. Nevertheless, it did not influence the growth of ischemic lesions.

Background

Stroke is the second leading cause of death globally and a significant contributor to disability. The incidence of stroke is on the rise, driven by the aging population. Additionally, an alarming trend is emerging, with an increasing number of young individuals being affected by stroke, particularly in low- and middle-income countries.[1] A stroke occurs when the brain is deprived of blood supply, leading to a cascade of events that ultimately result in the death of nerve cells due to hypoxia, changes in neuronal structure, and the development of mild or major neurocognitive disorders.[2] Stroke-induced neuronal damage is known to result in distinct types of cognitive impairments. The prevalence of post-stroke cognitive impairment (PSCI) has been reported to range from 20 % to 80 %, exhibiting variations across countries, races, diagnostic criteria, and the timing of assessments.[3] Cognitive impairment can significantly affect patients' daily lives, their capacity to engage in rehabilitation programs, and increase their risk of developing dementia and recurrent stroke. Consequently, addressing PSCI becomes an important outcome in the care of stroke patients.[4]

The precise mechanisms of PSCI are not fully understood, [5] and currently, no pharmacological treatment has gained approval for addressing PSCI (Rost et al., 2022). Yes, it is known that PSCI is contingent on factors such as the location and extent of the stroke, as well as the duration of hypoperfusion.[6] It is suggested that the primary cause of neurological deficits linked to ischemic stroke is the localized disruption of cerebral blood flow. The ischemic core has traditionally been viewed as irreversibly damaged tissue due to the deprivation of oxygen and glucose delivery. Consequently, a series of degenerative

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mechanisms is initiated within the stroke territory, including acute neuroinflammation, apoptosis, and edema. Cerebral white matter is particularly vulnerable to ischemic injury as it receives limited collateral blood circulation.[7, 8] Following an ischemic stroke, cerebral white matter continues to deteriorate, potentially contributing to PSCI and the expansion of ischemic lesions.[9]

In theory, the promotion of neurogenesis, angiogenesis, and oligodendrogenesis may facilitate nerve repair.[9, 10] Timely re-establishment of cerebral blood flow can contribute to enhanced neuronal repair, reduced neuroinflammation, and the promotion of synaptogenesis and vascular health,[10] and thus may have potential to improve PSCI. Some promising results have been seen in interventions involving cognitive training exercises or physical exercise.[5] Physical exercise has been shown to play a role through modifying hippocampal neurogenesis and neuroplasticity, reducing oxidative stress, promoting brain angiogenesis, and inducing various morphological changes to enhance cognitive function and mitigate the growth of cerebral infarct volume.[11] The cognitive advantages of physical exercise are likely to stem from increased cerebral blood flow and the release of nerve growth factors (BDNF, IGF-1), fostering structural and functional plasticity in areas of the brain that have suffered damage.[12]

Furthermore, exercise has been demonstrated to have a positive impact on brain structure, enhancing both memory function and cognitive status.[13] The release of endorphin hormones triggered by exercise contributes to an increased capacity of the brain to modify cognitive abilities.[14] In a study, participation in treadmill running was found to enhance cognitive status by increasing the production of nitric oxide in the hippocampus and vascular endothelial growth factor, while also fostering angiogenesis.[15] In addition, an early initiation (24-48 h after stroke) of moderate exercise training (10 meter/minute, 5-7 days per week for about 30 min) had a significant effect on reducing stroke lesion volume growth and protecting the tissue around the lesion against oxidation-related inflammation.[16]

Another modifiable risk factor for cognitive impairment is diet. Mediterranean diet has been linked to cardiovascular health as well as enhanced cognitive performance.[17] A defining feature of this diet involves the consumption of lower amounts of red and processed meat.[17] Soy serves as a high-protein substitute for red meat and processed meat.[18] A systematic review study found that a higher intake of soybean, but not tofu, was associated with better cognitive function.[18] Further, soy peptide has been shown to improve both brain and increase muscle mass and function.[19] The present article presents the results of a study that explored the effectiveness of a rehabilitation program, consisting of mixed exercise training and soymilk supplementation components, in addressing cognitive impairment and the growth of ischemic lesions in stroke patients.

Methods

This was a randomized clinical trial (RCT) with a single-blind design comprising four arms: the MRE plus soymilk group, the MRE group, the soymilk group, and the control group. Inclusion criteria for the study involved participants who: willingly provided written informed consent; were diagnosed with a stroke (ischemic or hemorrhagic) by a neurologist; were aged between 25 and 65 years; demonstrated a level of consciousness ranging from 14 to 16 on the full outline of unresponsiveness (FOUR) scale;[20] scored between 5 and 15 on the National Institute of Health Stroke Scale (NIHSS);[21] did not receive tissue plasminogen activator for acute ischemic stroke; did not exhibit aphasia, as determined by the NIHSS; maintained stable vital signs (i.e., systolic blood pressure $>$ 90 mm Hg, heart rate $>$ 40 beats per minute, and arterial oxygen saturation $>$ 94 %); did not have fractures or orthopedic injuries in the extremities; did not suffer from respiratory failure or long-term diseases according to medical records; did not take inotropes and vasopressor agents (e.g., dopamine or dobutamine); did not exhibit clinically apparent heart disease (such as heart failure, angina, myocardial infarction, cardiomyopathy, or serious arrhythmia) within the preceding 4 months; did not have inflammatory or infectious diseases; and did not exhibit diseases of skeletal muscles, such as muscular dystrophy, myasthenia gravis, or myotonia, as per medical records. Patients with worsening stroke symptoms during the study, experiencing a transient ischemic attack, taking medications for treating electrolyte abnormalities, and those who withdrew from the study were excluded from the study.

Sample Size

To calculate the sample size for this study, we utilized G*Power software (version 3.0.10). Considering a statistical power of 80 %, a confidence level of 95 %, and an effect size of 0.25, as reported in a previous study,[22] a minimum of 28 participants per group was determined. To accommodate potential withdrawals, the sample size was rounded up to thirty participants per group, leading to the recruitment of 120 stroke patients for the study.

Randomization

During the study period, 172 patients diagnosed with stroke were assessed for eligibility within the initial 24 h after the onset of the stroke. Among them, 120 patients satisfied the study inclusion criteria and were subsequently enrolled in the trial (Figure 1). The allocation of participants into the study groups employed a block randomization approach with block sizes of four and eight. An individual not affiliated with the research team generated the allocation sequence using random assignment software. The concealment of allocations was achieved through identical opaque sealed envelopes, sequentially numbered. Information about the allocations was disclosed to both researchers and patients upon the completion of enrollment. However, the outcome assessor and data analyst remained blinded to the allocations until the conclusion of the study.

Recruitment of participants

The research obtained ethics approval from the Research Ethics Committee of Tabriz University of Medical Services (Approval Code: IR.TABRIZU.REC.1401.038) and was registered in the Iranian Registry of Clinical Trials (Registration Date: December 9, 2022; IRCT20130816014 371N3). Recruitment of participants took place at the Stroke Care Units of Imam Reza Teaching Hospital in Tabriz, Iran, spanning from December 9, 2022, to February 10, 2023. Imam Reza Hospital stands as a tertiary referral center in the northwest region of Iran. Researchers provided a detailed explanation of the study to individuals meeting the inclusion criteria and extended invitations for their participation. Those expressing interest in the study were requested to sign the study consent form, and subsequently, they were officially enrolled.

Interventions

Participants assigned to the MRE group underwent the MRE + soymilk intervention. The exercise component was developed based on prior research. This encompassed a combination of both passive and active stretching exercises,[23] activities designed to enhance balance [24], cycle ergometer exercises,[25] gait training exercises,[24] aerobic workouts,[26] and resistance exercises targeting both upper[27] and lower[28] extremities. An overview of the MRE protocol is presented in Figures 2 and Table 1. The initiation of the intervention occurred on the day of admission, contingent upon the patient's health status permitting.[29] Implementation was overseen by two members of the research team- a registered nurse and an exercise physiologist.

While in the hospital ward, participants engaged in twice-daily exercise sessions scheduled from 08:00 to 09:30 and from 16:00 to 18:30.

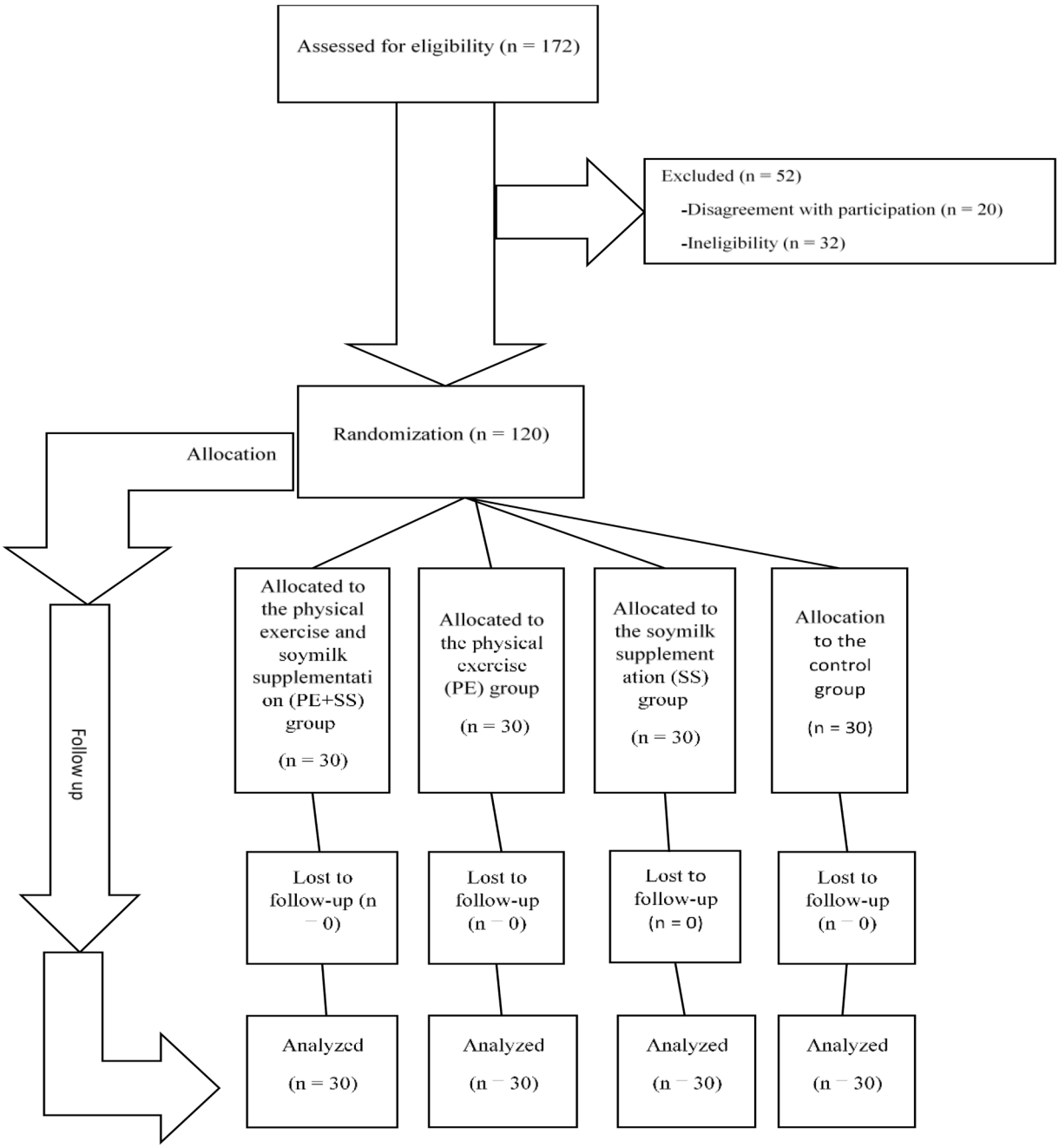

Figure 1. The study flow chart.

Post-discharge, the intervention transitioned to the hospital's rehabilitation center, with exercise frequency adjusted to once a day.[30] The daily exercise duration ranged from 30 to 90 min (averaging 60 min), totaling nearly twenty hours for each participant.

Prior to each session, participants were assessed for their readiness to partake in exercise. If unprepared, the session was postponed. Exercise intensity was set between 50 and 70 percent of the participant's maximum heart rate (calculated as 220 minus their age), maintaining a perceived exertion level within the range of 11-14, as assessed by the Borg Rating of Perceived Exertion Scale (RPE).[31] Overall, participants demonstrated favorable tolerance to the interventions, with encouragement to take breaks as needed. Continuous monitoring of oxygen saturation (SpO2) and pulse rate was ensured throughout each session using a portable pulse oximeter (device model C101A3).

This was followed by two daily servings of 250 milliliters, administered after each exercise rehabilitation session. The overall daily soymilk intake amounted to 500 milliliters, contributing 283.5 kilocalories, 32.0 grams of carbohydrates, 17.5 grams of protein, and 9.5 grams of fat. Initial carbohydrate and protein doses were calculated at 0.50.04 and 0.270.01 grams per kilogram of body weight, respectively. Participants were instructed to consume their soymilk within a 5 to 10-minute timeframe.[11] The preparation of the soymilk beverages was overseen by a hospital dietitian.

The MRE group received identical exercise rehabilitation without the soymilk component, while the soymilk group received the identical daily soymilk quantities, administered around 9:00 and 17:00, following their routine physiotherapy sessions. Participants in the control group only underwent routine physiotherapy sessions, encompassing passive and active exercises targeting both upper and lower extremities, education on mobility, and electrical stimulation for both upper and lower

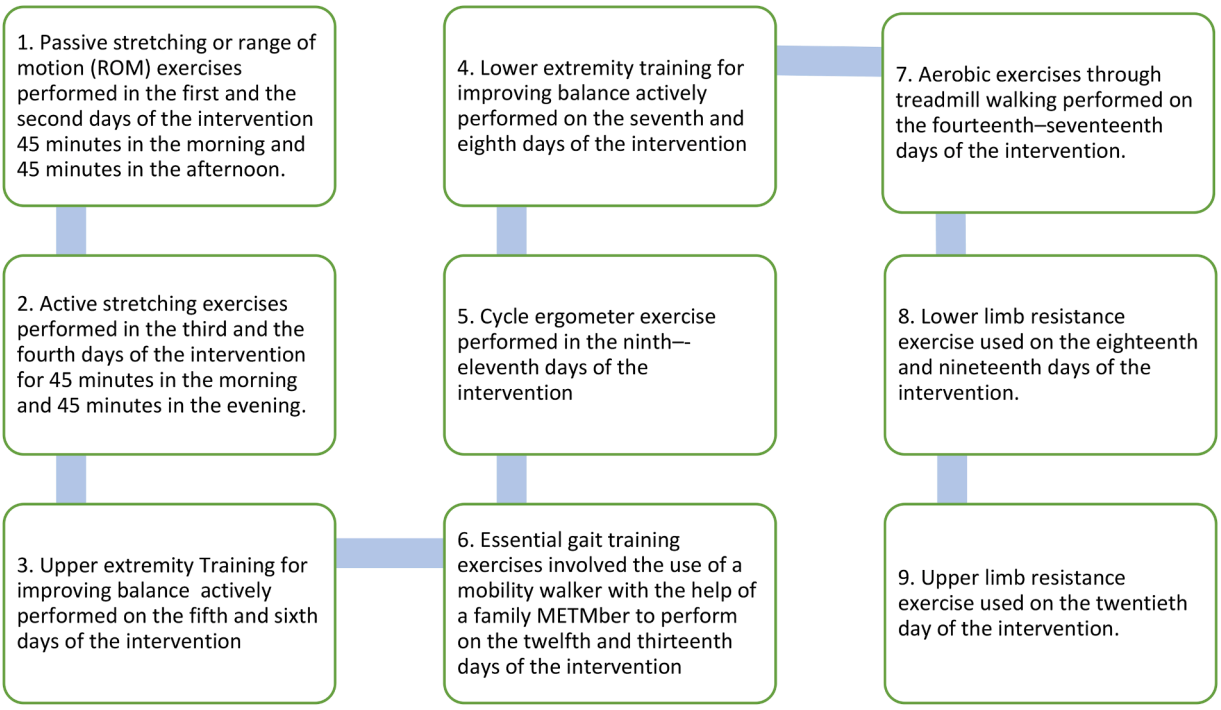

Figure 2. Summary of the multicomponent rehabilitation exercise.

extremities. These exercises were not governed by a predetermined protocol but were carried out based on the discretion of the attending physiotherapist.

Study instruments

Data collection was carried out using a questionnaire developed by the research team, capturing information about participants' demographics such as age, gender, body mass index, and marital status, as well as clinical characteristics such as the type of stroke, ejection fraction, systolic and diastolic blood pressure, blood glucose, and haemoglobin level. This questionnaire was completed through participant interviews and the review of their clinical records.

The Montreal Cognitive Assessment (MoCA)

The MoCA was used to assess cognitive impairment in the study participants. The tool consists of 12 items assessing alternating trail making (0–1 point), figure copy (0–1 point), clock drawing (0–3 points), animal naming (0–3 points), digit span (0–2 points), sustained attention (0–1 point), serial subtraction (0–3 points), sentence repetition (0–2 points), verbal fluency (0–1 point), abstract reasoning (0–2 points), memory (delayed recall, 0–5 points), and orientation (0–6 points). Total scores can range between 0 and 30, with lower scores indicating poorer cognitive functioning.[32] According to a meta-analysis, a cutoff of <23 was considered indicative of cognitive impairment.[33]

The MoCA stands out due to its brevity, user-friendly interface, multilingual support, and free accessibility, distinguishing it from other tools. Its widespread utilization in clinical contexts underscores its significance as a valuable research instrument, employed in both academic and non-academic settings worldwide, including those who have experienced a stroke [34]. The MoCA has been recommended for use in stroke patients; early cognitive testing by MoCA predicts long-term cognitive outcomes, functional outcomes, and mortality after stroke.[35]

Ischemic lesion growth

In participants with ischemic stroke, the growth of the ischemic lesions were evaluated through CT scans,[36] with data from the CT scans analyzed by a neurologist.

Statistical analysis

Data were analyzed using IBM SPSS software (version 16.0), and the significance level was established at $p < 0.05$. The distribution of data on MoCA scores was found to be non-normal at baseline and during all follow-up assessments. As a result, non-parametric tests were employed for data analysis. Friedman's test was utilized to examine the impact of time on MoCA scores, while differences between groups were assessed using the Kruskal-Wallis test. In the case of a statistically significant result from the Kruskal-Wallis test at any follow-up point, Dunn's test was subsequently applied to identify specific groups exhibiting differences. We used the Pair wise post-hoc Test for Multicomponent Comparisons of Mean Rank Sums for the MoCA data.

Results

The participants had a mean age of 51.95 years (SD± 9.78; range 25-65) and around 60.83 % of the participants were male. The majority were married (78.33 %), and 88.32 % were admitted with a diagnosis of ischemic stroke. Systolic hypertension (83.85 %) and high blood glucose (58.20 %) were prevalent risk factors across all groups. Sociodemographic and clinical characteristics of the participants are outlined in Table 2. No significant differences were observed across groups in terms of baseline demographic and clinical characteristics. The median MoCA score at baseline was 20.0 (IQR 18-23.7), with 35 (29.2 %) of participants having MoCA scores <23, indicating cognitive impairment.

The effects of the interventions on the total MoCA scores

The impact of time on the MoCA scores for the entire sample was statistically significant ($\chi^2 = 184.711$, $p = 0.000$). While baseline MoCA

Table 1
Types of exercise and their descriptions.

Types of exercise	Descriptions the activities
Passive stretching or range of motion (ROM) was conducted on the first and second days of the intervention, with sessions lasting 45 min each in the morning and evening.	• Ankle and wrist back extension exercises • Ankle and wrist plantar flexion exercises • Ankle and wrist varus and valgus exercises • Hamstring and triceps stretching exercises • Hip, knee, and elbow flexion exercises • Hip and shoulder abduction and adduction exercises
Dynamic stretching exercises were implemented on the third and fourth days of the intervention, with sessions lasting 45 min each in the morning and evening.	• Standing and bending forward to take items from the ground • Lifting the leg straight • Sit-up balance exercise by stretching the arms forward and maintaining balance in a standing position • Stair climbing by placing steps one by one on a thirty-centimeter four-legged stool
Upper extremity training focused on improving static and dynamic balance was carried out on the fifth and sixth days of the intervention.	• Square, circle, triangle, and infinity shapes were drawn on a table, and participants were directed to move a bottle over the lines of the shapes in front of a mirror measuring 40 x 70 centimeters. Following that, a bottle was placed at the table corner, and participants were assigned the task of reaching for it by stretching their extremities.
Lower extremity training aimed at improving static and dynamic balance was conducted on the seventh and eighth days of the intervention.	• Several pieces of paper, each sized 5 x 20 x 40 centimeters, were arranged in a straight two-meter path on a flat surface, with a distance of ten centimeters for men and seven centimeters for women. Participants were then instructed to walk along this path, emphasizing goal-directed stepping. • Plastic exercise cones, measuring 17 x 14 x 14 centimeters and weighing fifty grams, were positioned in a one-meter straight path with a distance of twenty centimeters. Participants were tasked with walking through them without hitting the cones, incorporating a slalom walking technique.
Cycle ergometer exercises were performed on the ninth to eleventh days of the intervention.	• These exercises were executed in the supine position for the lower extremities and sitting position for the upper extremities. The exercise rhythm was maintained at forty revolutions per minute (Ofori et al., 2019).
Essential gait training exercises, involving the use of a mobility walker with the assistance of a family member, were conducted on the twelfth and thirteenth days of the intervention.	• Participants walked a one-meter distance with the assistance of a family member and under the supervision of the intervention provider.
Aerobic exercises, specifically treadmill walking, were incorporated on the fourteenth to seventeenth days of the intervention.	• Participants engaged in these exercises for thirty minutes daily, split into fifteen-minute sessions in the morning and afternoon, while wearing a protective band connected from the top to their bodies. The treadmill had a 5 % slope (da Silva et al., 2019), and the walking speed progressed from an initial 0.27 meters per second to 1.2 meters per second, following the protocol by Cleland & Madhavan (2021). The exercises were conducted on an electric treadmill (Azimuth 3050 CA) with a walking distance of 58–150 centimeters, a speed range of 0.27–6.1 meters per second, and a slope range of 0 %–20 %.
Lower limb resistance exercises were performed on the eighteenth and nineteenth days of the intervention.	• Participants walked a distance with a weight equal to 1 % of their body weight attached five centimeters above the ankle on the affected side of the body (Hwang et al., 2017).
Upper limb resistance exercises were conducted on the twentieth day of the intervention.	• Initially, participants were instructed to perform exercises without any weight attached to the extremities, aiming to achieve 80 % of their repetition maximum.

scores were similar across groups ($\chi^2 = 4.734$, $p = 0.192$), significant differences emerged during Week 1 ($\chi^2 = 9.065$, $p = 0.065$), Week 2 ($\chi^2 = 19.726$, $p = 0.000$), Week 3 ($\chi^2 = 35.532$, $p = 0.000$), and Week 4 ($\chi^2 = 51.055$, $p = 0.000$) (Table 3).

Post hoc test results highlighted significant differences in Week 1 between the MRE+soymilk group and Control group ($p = 0.038$). In Week 2, significant differences were observed between the MRE+soymilk group and Control group ($p = 0.000$), and between the MRE+soymilk group and the MRE group ($p = 0.006$). In Week 3, significant differences were revealed between the MRE+soymilk group and Control group ($p = 0.000$), the MRE+soymilk group and the MRE group ($p = 0.000$), and the MRE+soymilk group and the soymilk group ($p = 0.001$). Similarly, in Week 4, significant differences were observed between the MRE+soymilk group and Control group ($p = 0.000$), the MRE+soymilk group and the MRE group ($p = 0.000$), and the MRE+soymilk group and the soymilk group ($p = 0.000$).

The effects of the interventions on various dimensions of MoCA

Visuospatial executive: The impact of time on visuospatial executive function within the sample was statistically significant ($\chi^2 = 151.829$, $p = 0.000$). Baseline visuospatial executive scores did not differ significantly across groups ($\chi^2 = 6.140$, $p = 0.105$); however, significant differences emerged during subsequent assessments: Week 1 ($\chi^2 = 9.351$, $p = 0.025$), Week 2 ($\chi^2 = 12.228$, $p = 0.007$), Week 3 ($\chi^2 = 13.430$, $p = 0.004$), and Week 4 ($\chi^2 = 15.787$, $p = 0.001$) (Table 4). Post hoc analyses revealed significant differences in visuospatial executive scores during Week 1 between the MRE+soymilk group and the Control group ($p = 0.034$). In Week 2, significant differences were noted between the MRE+soymilk group and the Control group ($p = 0.023$) and between the MRE+soymilk group and the MRE group ($p = 0.012$). Week 3 showcased significant differences between the MRE+soymilk group and the Control group ($p = 0.000$), MRE+soymilk group and MRE group ($p = 0.025$), and MRE+soymilk group and Soymilk group ($p = 0.005$). Similarly, in Week 4, significant differences were observed between the MRE+soymilk group and the Control group ($p = 0.006$), MRE+soymilk group and the MRE group ($p = 0.010$), and MRE+soymilk group and the Soymilk group ($p = 0.006$).

Naming: The effect of time on naming within the sample was found to be statistically significant ($\chi^2 = 42.810$, $p = 0.000$). Although baseline naming scores were similar across groups at baseline ($\chi^2 = 6.190$, $p = 0.103$), Week 2 ($\chi^2 = 7.597$, $p = 0.55$), Week 3 ($\chi^2 = 6.250$, $p = 0.10$), and Week 4 ($\chi^2 = 5.625$, $p = 0.131$), the difference between groups was significantly different in Week 1 ($\chi^2 = 8.635$, $p = 0.035$) (Table 4). Post hoc analysis indicated significant differences between the MRE+soymilk group and the Control group ($p = 0.046$) in Week 1.

Attention: The impact of time on attention within the sample was statistically significant ($\chi^2 = 121.96$, $p = 0.000$). While attention scores were similar across groups at baseline ($\chi^2 = 1.904$, $p = 0.593$), Week 1 ($\chi^2 = 4.494$, $p = 0.213$), and Week 2 ($\chi^2 = 3.389$, $p = 0.336$), statistically significant differences were observed across groups in Week 3 ($\chi^2 =$

Table 2
Socio demographic and clinical characteristics of the participants

Variables		MRE+Soymilk ($n = 30$)	MRE ($n = 30$)	Soymilk ($n = 30$)	Control ($n = 30$)	p values
Age (years)		48.6 (11.1)	53.2 (7.8)	52.4 (10.3)	53.4 (9.1)	0.184[a]
Sex	Female	11 (36.7 %)	11 (36.7 %)	13 (43.3 %)	12 (40 %)	0.940[b]
	Male	19 (63.3 %)	19 (63.3 %)	17 (66.7 %)	18 (60 %)	
Body Mass Index (kg/m^2)	Normal	7 (23.3 %)	5 (16.7 %)	8 (26.7 %)	9 (30 %)	0.195[b]
	Overweight	15 (50.0)	20 (66.7)	21 (70)	18 (60)	
	Obese	8 (26.7)	5 (16.7)	1 (3.3)	3 (10.0)	
Marital status	Single	5 (16.7)	7 (23.3)	3 (10.0)	7 (23.3)	0.433[b]
	Married	23 (76.7)	23 (76.7)	26 (86.7)	22 (73.3)	
	Divorce	2 (6.7)	0	1 (3.3)	0	
	Widow	0	0	0	1 (3.3)	
Stroke type	Hemorrhagic	28 (93.3)	27 (90.0)	28 (93.3)	23 (76.7)	0.139[b]
	Ischemic	2 (6.7)	3 (10.0)	2 (6.7)	7 (23.3)	
Four-score		15.2 (0.7)	15.3 (0.7)	15.3 (0.7)	15.2 (0.7)	0.849[a]
Ejection fraction		49.1 (3.3)	49.8 (3.8)	49.8 (3.8)	51.3 (3.4)	0.382[a]
Systolic blood pressure		140.3 (23.5)	148.6 (21.2)	140.5 (17.5)	140.1 (21.5)	0.330[a]
Diastolic blood pressure		88.2 (17.2)	93.7 (11.5)	86.3 (7.9)	87.5 (17.9)	0.199[a]
Blood sugar		141.7 (44.0)	175.6 (72.2)	159.1 (55.8)	160.4 (60.7)	0.181[a]
NIHSS		8.5 (2.6)	10.0 (2.9)	9.4 (3.2)	8.2 (3.3)	0.110[a]

NIHSS: The National Institutes of Health Stroke Scale.
[a] One-way ANOVA,.
[b] Chi-squared test;.

Table 3
The comparisons of median (IQR) of MoCA scores across groups at the five follow-up points ($n = 90$)

Groups	Baseline Median (IQR)	Week 1 Median (IQR)	Week 2 Median (IQR)	Week 3 Median (IQR)	Week 4 Median (IQR)	Test results & p value[a]
MRE+Soymilk	19.00 (5.25)	22.00 (4.25)*	23.00 (4.00)*	25.50 (2.00)*	28.00 (2.00)*	χ^2 =184.711 $p = 0.000$
MRE	19.50 (4.00)	20.00 (3.25)	20.50 (2.25)	21.00 (3.25)*	23.00 (3.00)*	
Soymilk	22.05 (6.25)	22.50 (6.25)	22.50 (5.25)*	22.50 (5.00)*	22.50 (4.00)*	
Control	20.00 (4.25)	20.00 (4.25)*	20.00 (3.25)*	20.50 (2.25)*	22.00 (2.50)*	
Test results & p value [b]	χ^2 =4.734	$\chi^2 = 9.065$	$\chi^2 = 19.726$	$\chi^2 = 35.532$	$\chi^2 = 51.055$	
	$p = 0.192$	$p = 0.028$	$p = 0.000$	$p = 0.000$	$p = 0.000$	

MRE: multicomponent rehabilitation exercise;.
[a] p value = the results of Fridman's test demonstrating the effect of time on the MoCa scores;.
[b] p value= the results Kruskal Wallis tests demonstrating the differences across the groups.
* groups which were statistically significantly different.

13.866, $p = 0.003$), and Week 4 ($\chi^2 = 21.071$, $p = 0.000$) (Table 4). Post hoc analysis highlighted significant differences in attention during Week 3 between the MRE+soymilk group and the Control group ($p = 0.003$) and between the MRE+soymilk group and the Soymilk group ($p = 0.039$). In Week 4, significant differences were observed between the MRE+soymilk group and the Control group ($p = 0.001$), MRE+soymilk group and the MRE group ($p = 0.008$), and MRE+soymilk group and the Soymilk group ($p = 0.000$).

Language: The effect of time on language within the sample was statistically significant ($\chi^2 = 100.806$, $p = 0.000$). Although language scores were similar across groups at baseline ($\chi^2 = 2.381$, $p = 0.497$), Week 1 ($\chi^2 = 1.039$, $p = 0.792$), and Week 2 ($\chi^2 = 4.031$, $p = 0.258$), statistically significant differences were observed across groups in Week 3 ($\chi^2 = 16.825$, $p = 0.001$), and Week 4 ($\chi^2 = 9.721$, $p = 0.021$) (Table 4). Post hoc analysis highlighted significant differences in language during Week 3 between the MRE+soymilk group and the Control group ($p = 0.022$), the MRE+soymilk group and MRE group (0.001), MRE+soymilk group and Soymilk group ($p = 0.038$). In Week 4, significant differences were observed between the MRE+soymilk group and the Soymilk group ($p = 0.031$).

Abstraction: The effect of time on abstraction within the sample was statistically significant ($\chi^2 = 88.803$, $p = 0.000$). However, no statistically significant differences were observed across groups at baseline or any other follow-ups.

Delayed Recall: The effect of time on delayed recall within the sample was statistically significant ($\chi^2 = 92.800$, $p = 0.000$). While delayed recall scores were similar across groups at baseline ($\chi^2 = 2.949$, $p = 0.400$), Week 1 ($\chi^2 = 3.698$, $p = 0.296$), and Week 2 ($\chi^2 = 4.910$, $p = 0.178$), statistically significant differences were observed across groups in Week 3 ($\chi^2 = 15.267$, $p = 0.002$), and Week 4 ($\chi^2 = 32.521$, $p = 0.000$) (Table 4). Post hoc analysis highlighted significant differences in delayed recall between the MRE+soymilk group and the Control group ($p = 0.002$), and the MRE+soymilk group and MRE group (0.010) in Week 3. In Week 4, significant differences were observed between the MRE+soymilk group and the Control group ($p = 0.000$), MRE+soymilk group and MRE group (0.000), and MRE+soymilk group and the Soymilk group ($p = 0.000$).

Orientation: The effect of time on orientation within the sample was statistically significant ($\chi^2 = 141.936$, $p = 0.000$). While orientation scores were similar across groups at baseline ($\chi^2 = 4.097$, $p = 0.251$) and Week 1 ($\chi^2 = 6.316$, $p = 0.097$), statistically significant differences were observed across groups in Week 2 ($\chi^2 = 10.790$, $p = 0.013$), Week 3 ($\chi^2 = 24.186$, $p = 0.000$), and Week 4 ($\chi^2 = 42.308$, $p = 0.000$) (Table 4). Post hoc analysis highlighted significant differences in orientation scores between the MRE+soymilk group and the Control group ($p = 0.008$) in Week 2, between the MRE+soymilk group and the Control group ($p = 0.000$), MRE+soymilk group and MRE group ($p = 0.002$), and the MRE+soymilk group and the Soymilk (0.042) in Week 3, and between the MRE+soymilk group and the Control group ($p = 0.000$), MRE+soymilk group and MRE group (0.000), and MRE+soymilk group and the Soymilk group ($p = 0.000$) in Week 4 (.

The effects of the interventions on ischemic lesion growth: The analysis of CT scan data indicated that the effects of the interventions on the ischemic lesion growth were not statistically significant ($p = 0.81$) (Table 5).

Table 4
Changes in the MoCA dimensions across groups at the five follow-up points ($n = 90$)

The MoCA Dimensions	Groups	Baseline Median (IQR)	Week 1 Median (IQR)	Week 2 Median (IQR)	Week 3 Median (IQR)	Week 4 Median (IQR)	Test results & p value [a]
Visuospatial executive	MRE+Soymilk	3.50 (1.00)	4.00 (1.00)	5.00 (1.00)	5.00 (0.25)	5.00 (0.25)	$\chi^2 = 151.829$ $p = 0.000$
	MRE	3.00 (1.00)	4.00 (0.00)	4.00 (0.25)	4.00 (1.00)	4.00 (1.00)	
	Soymilk	4.00 (2.00)	4.000 (2.00)	4.00 (1.25)	4.00 (1.00)	4.00 (1.00)	
	Control	4.00 (1.25)	4.00 (2.00)	4.00 (2.00)	4.00 (1.00)	4.00 (1.00)	
	Test results & p value [b]	$\chi^2 = 6.140$ $p = 0.105$	$\chi^2 = 9.351$ $p = 0.025$*	$\chi^2 = 12.228$ $p = 0.007$*	$\chi^2 = 13.430$ $p = 0.004$*	$\chi^2 = 15.787$ $p = 0.001$*	
Naming	MRE+Soymilk	3.00 (1.00)	3.00 (1.00)	3.00 (0.00)	3.00 (0.00)	3.00 (0.00)	$\chi^2 = 42.810$ $p = 0.000$
	MRE	2.5 (1.00)	3.00 (1.00)	3.00 (0.00)	3.00 (0.00)	3.00 (0.00)	
	Soymilk	3.00 (0.00)	3.00 (0.00)	3.00 (0.00)	3.00 (0.00)	3.00 (0.00)	
	Control	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	3.00 (0.25)	3.00 (0.00)	
	Test results & p value [b]	$\chi^2 = 6.190$ $p = 0.103$	$\chi^2 = 8.635$ $p = 0.035$*	$\chi^2 = 7.597$ $p = 0.55$	$\chi^2 = 6.250$ $p = 0.10$	$\chi^2 = 5.625$ $p = 0.131$	
Attention	MRE+Soymilk	3.00 (2.00)	4.00 (2.00)	4.00 (2.00)	5.00 (1.00)	5.00 (1.00)	$\chi^2 = 121.96$ $p = 0.000$
	MRE	3.00 (2.00)	3.50 (2.00)	3.50 (2.00)	3.50 (2.00)	4.50 (2.00)	
	Soymilk	3.00 (2.00)	3.00 (2.00)	3.00 (2.00)	3.50 (2.00)	4.00 (2.00)	
	Control	3.00 (2.00)	3.00 (2.00)	3.00 (2.00)	3.00 (2.00)	4.00 (2.00)	
	Test results & p value [b]	$\chi^2 = 1.904$ $p = 0.593$	$\chi^2 = 4.494$ $p = 0.213$	$\chi^2 = 3.389$ $p = 0.336$	$\chi^2 = 13.866$ $p = 0.003$*	$\chi^2 = 21.071$ $p = 0.000$*	
Language	MRE+Soymilk	2.00 (1.00)	2.00 (1.00)	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	$\chi^2 = 100.806$ $p = 0.000$
	MRE	2.00 (1.00)	2.00 (1.00)	2.00 (1.00)	3.00 (1.00)	3.00 (1.00)	
	Soymilk	2.00 (1.00)	2.50 (1.00)	2.50 (1.00)	3.00 (1.00)	3.00 (1.00)	
	Control	2.00 (1.00)	2.00 (1.00)	2.00 (1.00)	2.50 (1.00)	3.00 (1.00)	
	Test results & p value [b]	$\chi^2 = 2.381$ $p = 0.497$	$\chi^2 = 1.039$ $p = 0.792$	$\chi^2 = 4.031$ $p = 0.258$	$\chi^2 = 16.825$ $p = 0.001$*	$\chi^2 = 9.721$ $p = 0.021$*	
Abstraction	MRE+Soymilk	1.00 (1.00)	2.00 (1.00)	2.00 (0.00)	2.00 (0.00)	2.00 (0.00)	$\chi^2 = 88.803$, $p = 0.000$
	MRE	1.00 (1.00)	1.50 (1.00)	2.00 (1.00)	2.00 (1.00)	2.00 (0.00)	
	Soymilk	2.00 (1.25)	2.00 (1.00)	2.00 (0.25)	2.00 (0.00)	2.00 (0.00)	
	Control	2.00 (1.00)	2.00 (1.00)	2.00 (1.00)	2.00 (0.00)	2.00 (0.00)	
	Test results & p value [b]	$\chi^2 = 5.426$ $p = 0.143$	$\chi^2 = 2.159$ $p = 0.540$	$\chi^2 = 7.01$ $p = 0.071$	$\chi^2 = 3.934$ $p = 0.269$	$\chi^2 = 3.805$ $p = 0.283$	
Delayed Recall	MRE+Soymilk	3.50 (1.00)	4.00 (1.00)	4.00 (0.00)	4.00 (1.00)	5.00 (0.00)	$\chi^2 = 92.800$ $p = 0.000$
	MRE	4.00 (1.00)	4.00 (1.00)	4.00 (1.00)	4.00 (1.00)	4.00 (1.00)	
	Soymilk	4.00 (1.00)	4.00 (1.00)	4.00 (1.00)	4.00 (1.00)	4.00 (1.00)	
	Control	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	
	Test results & p value [b]	$\chi^2 = 2.949$ $p = 0.400$	$\chi^2 = 3.698$ $p = 0.296$	$\chi^2 = 4.910$ $p = 0.178$	$\chi^2 = 15.267$ $p = 0.002$*	$\chi^2 = 32.521$ $p = 0.000$	
Orientation	MRE+Soymilk	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	4.00 (1.00)	5.00 (1.00)	$\chi^2 = 141.936$ $p = 0.000$
	MRE	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	3.00 (2.00)	4.00 (2.00)	
	Soymilk	3.00 (3.00)	3.30 (3.00)	3.50 (3.00)	3.50 (3.00)	3.50 (3.00)	
	Control	2.00 (1.00)	2.00 (1.00)	2.00 (1.00)	2.5.00 (1.25)	3.00 (2.00)	
	Test results & p value [b]	$\chi^2 = 4.097$ $p = 0.251$	$\chi^2 = 6.316$ $p = 0.097$	$\chi^2 = 10.790$ $p = 0.013$	$\chi^2 = 24.186$ $p = 0.000$	$\chi^2 = 42.308$ $p = 0.000$	

MRE: multicomponent rehabilitation exercise;.
[a] p value = the results of Fridman's test demonstrating the effect of time;.
[b] p value = the results Kruskal Wallis tests demonstrating the differences across the groups;.
* groups which were statistically significantly different.

Table 5
The effects of interventions on the ischemic lesion growth ($n = 90$)

Changes in ischemic lesion	MRE+Soymilk ($n = 28$)	MRE ($n = 27$)	Soymilk ($n = 28$)	Control ($n = 23$)	p-value[a]
No	28 (93.3)	29 (96.7)	29 (96.7)	28 (93.3 %)	$\chi^2 = 0.934$
Yes	2 (6.7)	1 (3.3)	1 (3.3)	2 (6.7)	$p = 0.81$

[a] : Chi-squared test.

Discussion

To the best of our knowledge, the present study is the first study that examined the effect of a multicomponent exercise program plus soymilk on cognitive impairment and ischemic lesion growth in stroke patients. Stroke patients in this study were relatively young, with a mean age of 51.94 ± 9.6 years. This highlights the growing concern surrounding strokes occurring at younger ages, particularly in low- and middle-income nations.[1] This underscores the critical need to implement effective early rehabilitation programs to mitigate the adverse effects of post stroke cognitive impairment on patients' social, health and economic wellbeing.[37] Using a cutoff of 23 on the MoCA, about 30 % of the participants in our study demonstrated cognitive impairment at baseline in this study, which is not considered very high when compared to the reported range of 20-80 % in the literature.[3]

This article presented findings on the effectiveness of a targeted rehabilitation program involving both exercise and soymilk components in enhancing cognitive function among stroke patients during the acute phase. The results indicated that the influence of time on cognitive impairments was statistically significant across all groups. This suggests that, regardless of the interventions, participants in all groups including those in the control group, who underwent a standard rehabilitation program, demonstrated improvements in their cognitive function over the 4-week study period. However, the improvement observed in the MRE plus soymilk group was statistically significantly greater than other groups and this difference became apparent from Week 2. Both the exercise and soymilk comonnnet contrubted to the psitiev effcst of this inetrevntion. This finding aligns with the results of two meta-analysis studies, indicating an overall positive impact of physical activities on PSCI.[37,38]

The mechanisms through which exercise influences cognitive improvement encompass enhancing cognitive function by reducing

blood pressure and protecting endothelial cells against oxidative stress and inflammation- potential contributors to cerebrovascular disease and cognitive decline.[39-41] Additionally, exercise facilitates neurogenesis, elevates brain-derived neurotrophic factor, enhances neuroplasticity, increases levels of epinephrine, improves insulin sensitivity, and fosters biochemical and molecular changes.[42] During exercise, free radicals are effectively removed by enhancing the antioxidant defense system. Oxidative stress plays a crucial role as a disruptor in cognitive complications, given the high rate of oxidative stress in brain tissue.[43]

Several factors may influence the cognitive effects of interventions after a stroke, including time since the injury, the duration of the intervention, and specific exercise characteristics, such as frequency and intensity. The interventions in our study were of a brief duration, specifically lasting one month. Nevertheless, they were implemented twice daily during the hospital ward phase and five days a week throughout the outpatient stage. A meta-analysis demonstrated overall positive effects of physical activity on PSCI and found that exercise programs yield positive effects on cognitive improvement, regardless of their length (<3 months vs. ≥ 3 months). It is worth noting that trials with extended durations (≥ 3 months) often featured fewer intervention sessions per week, indicating a potential trade-off between frequency and duration that might have influenced the observed lack of difference.[37]

The exercise component of our rehabilitation program consisted of a combination of exercises, including aerobic, resistance, balance, and stretching routines. According to the meta-analysis study by Oberlin et al., findings from exclusive aerobic exercise did not reach statistical significance, and the study proposed that cognitive benefits may be more pronounced when combining aerobic and strength training programs.[37]

In our study, the interventions commenced on the admission day, as soon as participants' conditions allowed. Previous studies have trailed the effectiveness of various rehabilitation programs in different phases of stroke, acute, subacute, and chronic phases. The results of the metanalysis suggest that physical activity can have favorable effects on cognition even when introduced during the chronic stroke.[37]

In regard to safety, our trial included patients with relatively stable health conditions (refer to the inclusion and exclusion criteria outlined in the study). Prior to each session, participants indicated their readiness to begin the intervention, and the intensity of exercises was individually tailored based on factors such as maximum heart rate and perceived exertion level. Continuous monitoring of oxygen saturation and heart rate occurred throughout the interventions. Participants responded positively to the intervention, and they were actively encouraged to take adequate rest as required. No adverse events were observed. According to our study and other research,[29] initiating interventions on the admission day appears feasible, especially for patients with ischemic stroke. However, it is crucial to note that inappropriate mobilization or aerobic exercise may lead to adverse effects such as arterial blood pressure dysregulation, cardiac complications, blood-brain barrier disruption, hemorrhagic stroke transformation, and ischemic penumbra viability. Therefore, when progressing exercise intensity, it is essential to consider the integrity of cerebral autoregulation to protect the brain. Precautions, such as avoiding prolonged standing or incorporating periodic lower limb movement to activate the venous muscle pump, can help prevent blood pooling after an exercise session. This approach minimizes the activation of the coagulation cascade and mitigates potential cerebral hypoperfusion in these patients.[44]

Importantly, improvement in cognitive function was observed in all dimensions except for the abstraction dimension. The results of the meta-analysis study by Oberling et al. showed positive moderate treatment effects of physical activity on attention/processing speed measures in stroke patients with PSCI, while the executive function and working memory domains did not reach significance.[37]

The incorporation of soymilk, as protein supplementation, into the intervention significantly enhanced its effectiveness in our study. Soymilk ingestion immediately after therapeutic exercise has demonstrated efficacy in improving hand grip strength and walking performance and speed in chronic stroke patients,[11] as well as increasing muscle mass in very old individuals with sarcopenia.[45]

This study did not observe a statistically significant effect of the intervention on the growth of ischemic lesions. Meta-analysis of studies testing exercise in animal models have shown the effects of exercise in reducing infarct volume.[4, 16] However, this topic has not been adequately studied in humans.

Implications

Cognitive impairment commonly accompanies stroke, posing challenges to recovery and rehabilitation engagement, and increasing the risk of complications like dementia and recurrent stroke.[4] This underscores the significance of early screening and assessments to identify cognitive impairment in stroke patients. Timely screening for cognitive impairment is important for effective rehabilitation planning.[46] Healthcare professionals should actively implement cognitive rehabilitation interventions, such as exercise therapy, to enhance the cognitive function of stroke patients.

Limitations

Participant blinding was unfeasible due to the nature of the intervention; however, we reduced bias by blinding outcome assessors. Despite our inclusion of a control group to mitigate the influence of these natural recovery mechanisms, participants in the control group were still undergoing a standard rehabilitation program. Establishing a true control group without any rehabilitation intervention was ethically impractical. It is important to recognise that the actual benefits of the intervention may have been partially obscured by the inherent restorative processes observed in stroke patients. These mechanisms are typically more robust during the subacute stage compared to the chronic stage (Mori et al., 2021). Our trial comprised patients with relatively stable health conditions; consequently, we excluded both very young and elderly individuals. Furthermore, individuals with aphasia were not included, as our objective was to evaluate participants' perceived exertion levels during exercise. These factors may affect the generalisability of our study results. In addition, this study did not consider the long-term effect of the intervention. It is recommended that this rehabilitation intervention is trailed on diverse populations and longer follow ups are considered.

Conclusion

This study found that administering a combination of multicomponent rehabilitation exercises and a soymilk supplement during the acute phase of stroke improved cognitive impairment post-stroke. Significant improvements were noted across all cognitive dimensions except abstraction. However, the intervention did not reduce or prevent ischemic lesion growth.

CRediT authorship contribution statement

Babak Esmealy: Writing – original draft, Project administration, Methodology, Data curation, Conceptualization. **Leyla Esmealy:** Writing – original draft, Methodology, Data curation, Conceptualization. **Leila Gholizadeh:** Writing – review & editing, Validation, Formal analysis. **Saeid Nikookheslat:** Formal analysis. **Vahid Sari-Sarraf:** Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

None.

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