Randomised Controlled Trial

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Optimizing serum electrolyte levels in stroke patients: a multimodal approach with soymilk supplementation

Babak Esmealy, BSc, MSc[a], Leyla Esmealy[b], Leila Gholizadeh, BSc, MSc, PhD[c], Saeid Nikookheslat, BSc, MSc, PhD[a], Vahid Sari-Sarraf, BSc, MSc, PhD[a,*]

Introduction: Electrolyte imbalances are common in stroke patients and can significantly impact their overall health, potentially leading to severe complications and even fatal outcomes. In this study, we investigated the impact of combining multiple exercise training modalities (METM) with soymilk supplementation on serum electrolyte levels in stroke patients.
Methods: In a single-blind, four-arm randomized clinical trial, 120 stroke patients were randomly assigned to one of the following groups: (1) the METM group, (2) the soymilk group, (3) the METM plus soymilk group, and (4) the control group. Changes in serum electrolyte levels were compared both within and across groups over four consecutive weeks.
Results: Upon admission, 38.3% of the participants presented with hyponatremia, 26.7% hypokalemia, and 73.3% hypocalcemia. Over time, there was an overall improvement in serum electrolyte imbalances across all study groups compared to the baseline. Between-group comparisons revealed that the METM plus soymilk group exhibited statistically significant improvements compared to the other groups with absolute reductions in the proportion of participants with hyponatremia, hypokalemia, and hypocalcemia by 43.3%, 33.3%, and 73.4%, respectively.
Conclusions: The study findings substantiate the common occurrence of hyponatremia, hypokalemia, and hypocalcemia during the acute phase of stroke. Implementation of the METM alongside soymilk intake demonstrated potential in rectifying electrolyte imbalances among stroke patients, hinting at a promising intervention strategy.

Keywords: electrolyte imbalance, exercise, rehabilitation, soymilk, stroke

Introduction

Stroke is a global health concern, causing significant disability and death worldwide, with over 12.2 million new cases annually[1]. Electrolyte imbalances are common issues in stroke patients, influenced by various factors such as dehydration, reduced mobility, medications, stress response, kidney function impairment, autonomic nervous system changes, and gastrointestinal issues. These imbalances can have profound effects on stroke outcomes, impacting functional recovery, hospital readmission rates, and mortality[2,3].

HIGHLIGHTS

- Electrolyte imbalances are common among patients with stroke.
- The multiple exercise training modalities (METM) alongside soymilk intake demonstrated potential in rectifying electrolyte imbalances among stroke patients.

Hyponatremia, characterized by low sodium levels, is associated with poorer functional outcomes and increased mortality among stroke patients due to its effects on intracranial pressure, cerebral edema, and vascular damage[4,5]. Hypernatremia, or high sodium levels, is also linked to worsened neurological deficits and higher in-hospital mortality[5]. Likewise, hypokalemia, a common occurrence in acute stroke patients, plays a significant role in the severity of the stroke and subsequent functional recovery[6]. It is associated with worsened ambulatory and lower-extremity motor function post-stroke[7]. Additionally, hypokalemia is linked to the development of both first-time and recurrent strokes, including ischemic and hemorrhagic types[8]. Acute stroke patients may also present with either hypocalcemia or hypercalcemia, with lower serum calcium levels correlating with more severe stroke outcomes in terms of infarct size[9] and neurological deficits[10].

Despite the significant impact of electrolyte imbalances on stroke outcomes, they are often overlooked and inadequately managed in clinical practice. Current guidelines lack emphasis on comprehensive electrolyte assessment and management in stroke

[a]Faculty of Physical Education and Sport Sciences, University of Tabriz, [b]Faculty of Nursing and Midwifery, Tabriz University of Medical Sciences, Tabriz, Iran and [c]Faculty of Health, University of Technology Sydney, Sydney, NSW, Australia

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*Corresponding author. Address: 29 Bahman Boulevard, Faculty of Physical Education and Sport Sciences, Tabriz University, East Azerbaijan, Iran. Tel.: +98 41 33341300 E-mail: sarraf@tabrizu.ac.ir (V. Sari-Sarraf).

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patients. Addressing these imbalances could potentially improve stroke prognosis[11].

Exercise has been proposed as a means to improve cardiorespiratory fitness, muscle strength, and mobility in stroke patients[12]. While the effects of exercise on serum electrolyte imbalances in stroke patients remain understudied, research in other populations suggests that exercise may influence potassium and calcium homeostasis[13]. Additionally, adequate protein intake, particularly from sources like soymilk, can support muscle preservation and enhance adaptations to exercise training, potentially benefiting stroke patient recovery outcomes[12].

This study aimed to evaluate the effects of multiple exercise modalities (METM) combined with soymilk supplementation on serum electrolyte profiles in stroke patients within 4 weeks post-acute stroke. By integrating exercise and nutritional supplementation, this approach seeks to address both the physical and nutritional aspects of stroke rehabilitation, potentially offering a novel and promising strategy for improving patient outcomes.

Methods

This was a single-blind, four-arm randomized clinical trial (RCT) including: METM plus soymilk, METM only, soymilk only, and a control group. Inclusion criteria encompassed participants aged 25–65 years with a confirmed stroke diagnosis, a level of consciousness of 14–16 based on the full outline of the unresponsiveness (FOUR) scale, a score of 5–15 in the National Institute of Health Stroke Scale (NIHS), stable vital signs, and absence of certain medical conditions or medications that could influence study outcomes. Exclusion criteria comprised worsening stroke symptoms during the study, transient ischemic attack, severe electrolyte abnormalities requiring medical intervention, use of specific medications affecting electrolyte levels, and participant withdrawal.

Sample size calculation

The sample size for this study was determined using G*Power software (v. 3.0.10). Based on a statistical power of 80%, a confidence level of 95%, and an effect size of 0.25, as reported in previous research (Shahidi and colleagues, 2021), a minimum of 28 participants per group was calculated. To accommodate potential withdrawals, the sample size was rounded up to thirty participants per group, resulting in the recruitment of 120 stroke patients for the study.

Randomization

During the study, 172 stroke patients were screened for eligibility within 24 h of admission, with 120 meeting inclusion criteria and enrolled (Fig. 1). Block randomization with block sizes of four and eight was employed to allocate participants into study groups. An individual outside the research team generated the allocation sequence using random assignment software. Allocation concealment was ensured through identical opaque sealed envelopes sequentially numbered. Researchers and patients became aware of allocations post-enrollment, while outcome assessors and data analysts remained blinded until the study's conclusion.

Participant recruitment

The study received ethics approval from Tabriz University of Medical Services (IR.TABRIZU.REC.1401.038) and was registered in the Iranian Registry of Clinical Trials (09/12/2022; IRCT20130816014371N3). Participants were recruited from the Stroke Care Units of Imam Reza Teaching Hospital in Tabriz, Iran, between 9 December 2022 and 10 February 2023. Imam Reza Hospital is a tertiary referral center in northwest Iran. Eligible patients were briefed about the study, invited to participate, and enrolled upon providing written consent.

Interventions

Participants in the METM group underwent a protocol comprising various exercises such as passive and active stretching, balance improvement, cycle ergometer, gait training, aerobic, and resistance exercises on upper and lower extremities (Fig. 2 and Figure 3). The intervention, initiated within hours after stroke onset, was administered twice daily during hospitalization and once daily post-discharge, totaling five sessions per week for 4 weeks. Exercise intensity was tailored to 50–70% of maximum heart rate and perceived exertion levels. Participants' oxygen saturation and pulse rate were continuously monitored during sessions. The soymilk group consumed two 250 ml servings of soymilk daily after routine physiotherapy sessions, while the METM plus soymilk group received the same dosage post-METM sessions. Soymilk provided 283.5 kilocalories, 32.0 g carbohydrates, 17.5 g protein, and 9.5 g fat per 500 ml. Participants were instructed to consume soymilk within 5-10 minutes, prepared by a hospital dietitian. The control group received routine physiotherapy sessions focusing on upper and lower extremities exercises, mobility education, and electrical stimulation without a predefined protocol.

Data analysis

Data analysis utilized IBM SPSS software (version 16.0) with a significance level set at $P < 0.05$. Serum sodium, potassium, and ionized calcium levels were non-normally distributed. Serum potassium levels were categorized as less than 3.5 mEq/l for hypokalemia, 3.5–5.1 mEq/l for normal, and greater than 5.1 mEq/l for hyperkalemia. Serum sodium levels were categorized as less than 135 mEq/l for hyponatremia, 135–145 mEq/l for normal, and greater than 145 mEq/l for hypernatremia[14]. Serum calcium levels were classified as less than 4.48 mg/dl for hypocalcemia, 4.0–5.6 mg/dl for normal, and greater than 5.6 mg/dl for hypercalcemia[15]. The Friedman test assessed changes in serum electrolyte levels over time within each group, while χ^2 tests compared differences between groups. Post hoc Bonferroni tests identified specific groups with significant differences in serum electrolyte levels, if applicable.

Results

The study participants, with an average age of 51.94 years ± 9.79 years, were predominantly male (60.83%) and married (78.33%), mostly admitted due to ischemic stroke (88.32%). They exhibited an average BMI of 26.50 ± 10.91 Kg/m^2 and hypertensive status with a mean systolic blood pressure of 142.39 ± 83.85 mmHg. Baseline assessments showed a mean FOUR Score of 15.26 ± 0.72, indicating full consciousness, and a

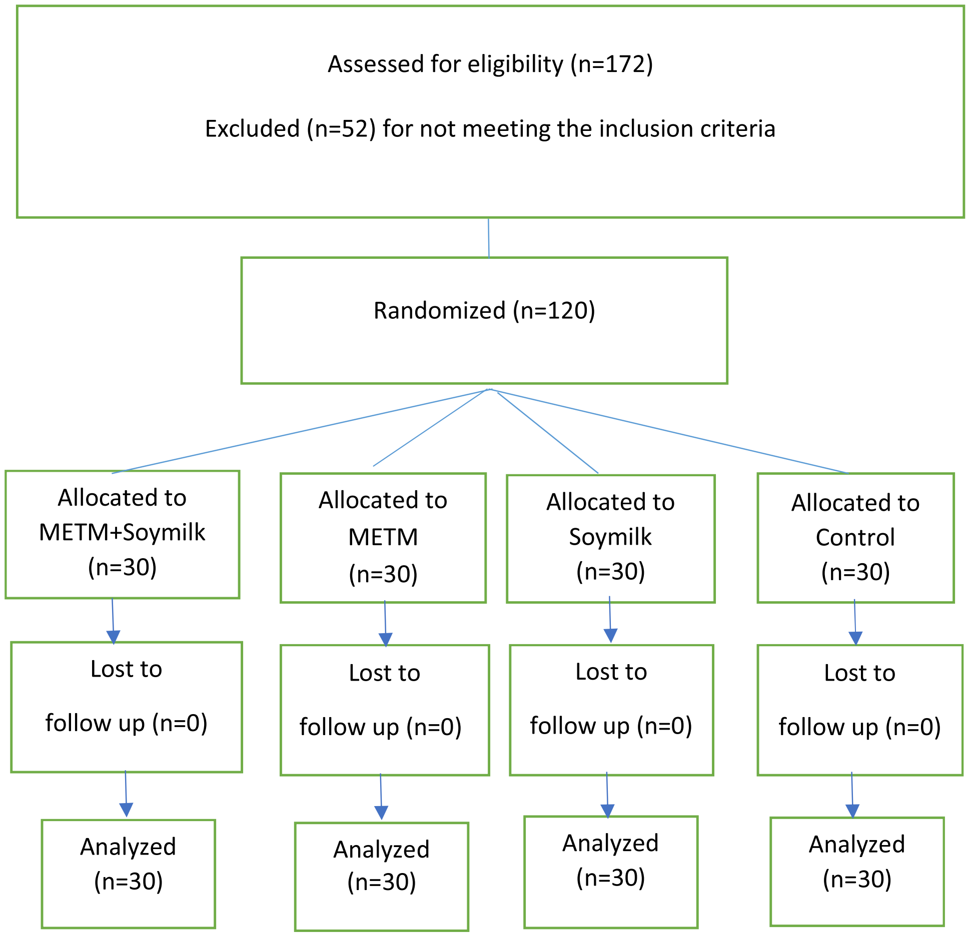

Figure 1. Study flow chart. METM, multiple exercise training modalities.

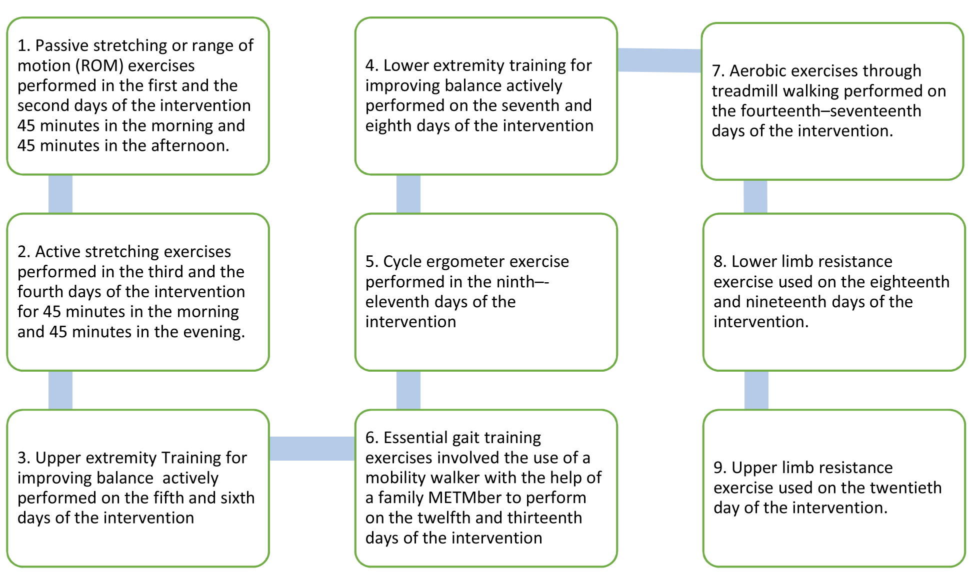

Figure 2. Summary of the multiple exercise training modalities (METM) protocol.

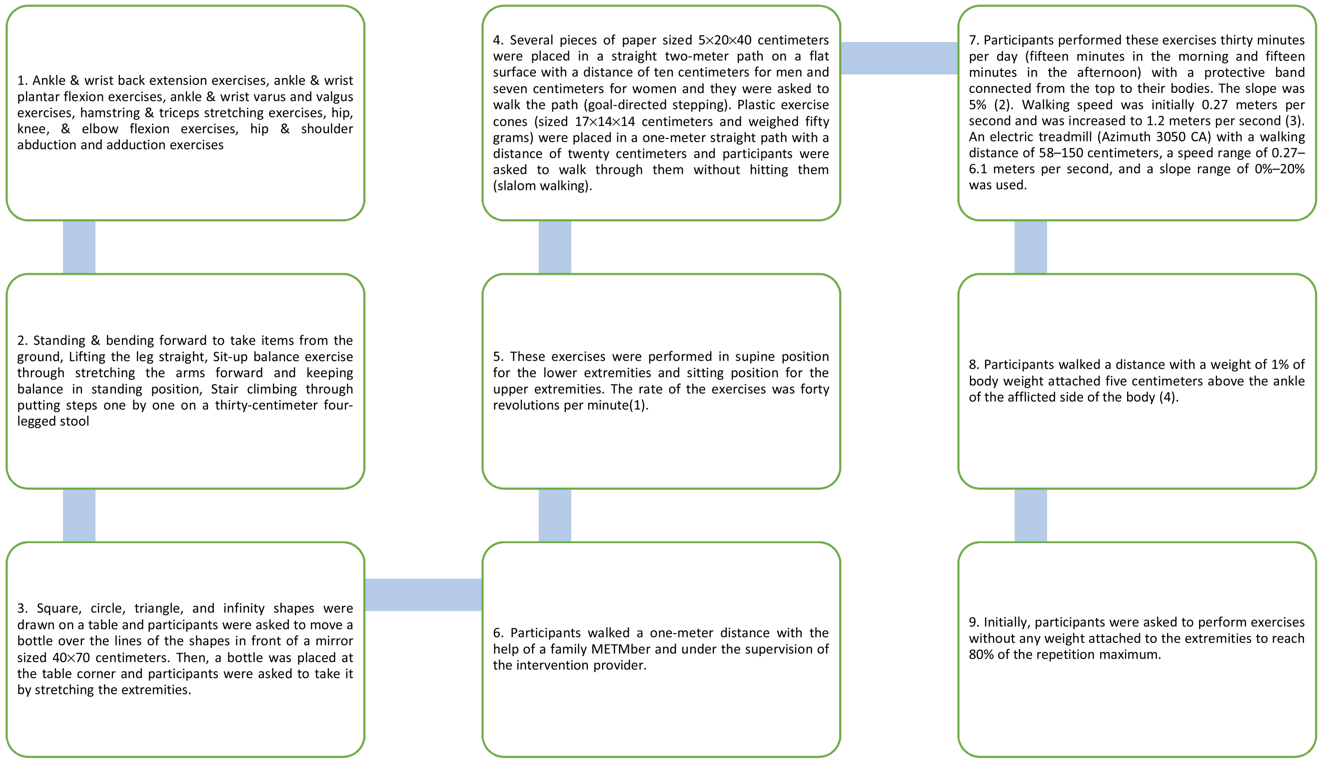

Figure 3. Description of the multiple exercise training modalities (METM) protocol.

Table 1

Participants' demographics and clinical characteristics.

Characteristics	All participants	METM + soymilk mean (SD) / *N* (%)	METM mean (SD) / *N* (%)	Soymilk mean (SD) / *N* (%)	Control mean (SD) / *N* (%)	*P*
Age (years)	51.93 (9.61)	48.60 (11.17)	53.26 (7.87)	52.43 (10.34)	53.46 (9.16)	0.184[a]
Sex						
Female	47 (39.17)	11 (36.7)	11 (36.7)	13 (43.3)	12 (40)	0.940[b]
Male	73 (63.3)	19 (63.3)	19 (63.3)	17 (66.7)	18 (60)	
BMI (kg/m2)	26.50 (10.91)	27.56 (3.28)	26.96 (2.61)	25.5 (2.09)	26 (2.93)	0.195[b]
Marital status						
Single	22 (18.33)	5 (16.7)	7 (23.3)	3 (10)	7 (23.3)	0.433[b]
Married	94 (78.33)	23 (76.7)	23 (76.7)	26 (86.70)	22 (73.3)	
Divorce	3 (2.5)	2 (6.7)	0	1 (3.3)	0	
Widow	1 (0.83)	0	0	0	1 (3.3)	
Type of stroke						
Ischemic	106 (88.32)	28 (93.3)	27 (90)	28 (93.3)	23 (76.7)	0.139[b]
Hemorrhagic	14 (11.66)	2 (6.7)	3 (10)	2 (6.7)	7 (23.3)	
Four score scale	15.26 (0.72)	15.2 (0.76)	15.3 (0.71)	15.3 (0.71)	15.23 (0.72)	0.849[a]
Ejection fraction (%)	50.03 (3.59)	49.16 (3.3)	49.83 (3.82)	49.83 (3.82)	51.33 (3.45)	0.382[a]
Systolic blood pressure (mmHg)	142.39 (83.85)	140.36 (23.58)	148.60 (21.21)	140.53 (17.53)	140.10 (21.53)	0.330[a]
Diastolic blood pressure (mmHg)	88.93 (54.62)	88.20 (17.22)	93.70 (11.56)	86.33 (7.94)	87.50 (17.90)	0.199[a]
Non-fasting blood glucose (mg/dl)	159.23 (58.20)	141.73 (44.03)	175.63 (72.20)	159.16 (55.84)	160.40 (60.79)	0.181[a]
Hemoglobin (g/dl)	12.93 (1.38)	12.78 (1.54)	12.83 (1.24)	12.82 (1.32)	13.32 (1.42)	0.382[a]
NIHSS	9.05 (3.04)	8.53 (2.66)	10 (2.94)	9.43 (3.20)	8.26 (3.39)	0.110[a]

METM, multiple exercise training modalities; NIHSS, National Institute of Health Stroke Scale.

[a]The results of the one-way analysis of variance.

[b]The results of the $\chi 2$ test.

mean NIHSS score of 9.05, indicating mild to moderate stroke severity (Table 1).

Serum electrolytes abnormalities

At baseline, 38.3% of study participants exhibited hyponatremia, which decreased to 12.5% after 4 weeks. Significant reductions in the proportion of participants with hyponatremia were observed across all study groups after four weeks, with absolute reductions ranging from 13.3 to 43.3%. While between-group differences in serum sodium levels were not significant at baseline, they became significant at the Week 4 follow-up, with significantly fewer participants experiencing hyponatremia in the METM + soymilk group compared to the control group (Table 2).

At baseline, 26.7% of the study sample had hypokalemia, which decreased to 6.7% after four weeks. Statistically significant reductions in the proportion of participants with hypokalemia were observed across all four groups after four weeks, with absolute reductions ranging from 10 to 33.3%. While between-group differences in serum sodium levels were not statistically significant at baseline, they became significant at the week 4 follow-up, with significantly fewer participants experiencing hypokalemia in all intervention groups compared to the control group (Table 3).

At baseline, 73.3% of the study sample had hypocalcemia, decreasing to 37.5% after 4 weeks. Statistically significant reductions in the prevalence of hypocalcemia were observed in the METM + soymilk and METM groups after 4 weeks, but not in the soymilk group or the control. The absolute reductions in the incidence of hypocalcemia were 73.4% for the METM + soymilk group, 20% for the METM group, 13.3% for the soymilk group, and 0.0% for the Control group. While between-group differences in serum calcium levels were not statistically different at baseline, they became significant at the 4-week follow-up, with significantly fewer participants experiencing hypocalcemia in the METM + soymilk group compared to the control group.

No statistically significant differences were found between ischemic and hemorrhagic stroke regarding serum sodium ($P = 0.339$), potassium ($P = 0.145$), and ionized calcium levels ($P = 0.689$) upon admission. Similarly, there were no statistically significant differences between genders in serum sodium ($P = 0.705$), potassium ($P = 0.59$), and ionized calcium levels ($P = 0.952$) upon admission.

Discussion

The study sought to evaluate the effectiveness of an alternative therapy combining exercise and dietary adjustments in restoring electrolyte balance among stroke patients. Hyponatremia was observed in 38.3% of the participants upon admission, which aligns with earlier research findings ranging from 13.8[16] to 38.61%[17]. Hyponatremia is primarily caused by cerebral salt

Table 2

Within group changes in serum electrolyte levels over a 4-week period.

	Serum potassium, *N* (%)			Serum sodium, *N* (%)			Serum ionized calcium, *N* (%)		
Time Group	**Hypokalaemia**	**Normal**	**Hyperkalaemia**	**Hyponatremia**	**Normal**	**Hypernatremia**	**Hypocalcaemia**	**Normal**	**Hypercalcemia**
METM + soymilk									
Baseline	10 (33.3)	20 (66.7)	0	13 (43.3)	17 (56.7)	0	24 (80.0)	6 (20.0)	0
Week 1	8 (26.7)	22 (73.3)	0	12 (40.0)	18 (60.0)	0	25 (83.3)	5 (16.7)	0
Week 2	4 (13.3)	26 (86.7)	0	8 (26.7)	22 (73.3)	0	17 (56.7)	13 (43.3)	0
Week 3	1 (3.3)	29 (96.7)	0	3 (10.0)	27 (90.0)	0	7 (23.3)	23 (76.7)	0
Week 4	0	30 (100)	0	0	29 (96.7)	1 (3.3)	0	29 (96.7)	1 (3.3)
	$\chi^2(4, n=120) = 27.85, P=0.000$*			$\chi^2(4, n=120) = 38.37, P=0.000$*			$\chi^2(4, n=120) = 68.79, P=0.000$*		
METM									
Baseline	7 (23.3)	23 (76.7)	0	11 (36.7)	19 (63.3)	0	23 (76.7)	7 (23.3)	0
Week 1	6 (20.0)	24 (80.0)	0	10 (33.3)	20 (66.7)	0	23 (76.7)	7 (23.3)	0
Week 2	3 (10.0)	27 (90.0)	0	10 (33.3)	20 (66.7)	0	23 (76.7)	7 (23.3)	0
Week 3	1 (3.3)	29 (96.7)	0	5 (16.7)	25 (83.3)	0	22 (73.3)	8 (26.7)	0
Week 4	0	30 (100)	0	2 (6.7)	28 (93.3)	0	16 (53.3)	14 (46.7)	0
	$\chi^2(4, n=120) = 19.57, P=0.001$*			$\chi^2(4, n=120) = 26.60, P=0.000$*			$\chi^2(4, n=120) = 36.57, P=0.000$*		
Soymilk									
Baseline	5 (16.7)	25 (83.3)	0	9 (30.0)	21 (70.0)	0	18 (60.0)	12 (40.0)	0
Week 1	4 (13.3)	26 (86.7)	0	9 (30.0)	21 (70.0)	0	18 (60.0)	12 (40.0)	0
Week 2	3 (10.0)	27 (90)	0	9 (30.0)	21 (70.0)	0	17 (56.7)	13 (43.3)	0
Week 3	2 (6.7)	28 (93.3)	0	7 (23.3)	23 (76.7)	0	17 (56.7)	13 (43.3)	0
Week 4	1 (3.3)	29 (96.7)	0	5 (16.7)	25 (83.3)	0	16 (53.3)	14 (46.7)	0
	$\chi^2(4, n=120) = 10.00, P=0.040$*			$\chi^2(4, n=120) = 12.80, P=0.012$*			$\chi^2(4, n=120) = 5.60, P=0.231$		
Control									
Baseline	10 (33.3)	20 (66.7)	0	13 (43.3)	17 (56.7)	0	24 (80.0)	6 (20.0)	0
Week 1	10 (33.3)	20 (66.7)	0	13 (43.3)	17 (56.7)	0	24 (80.0)	6 (20.0)	0
Week 2	10 (33.3)	20 (66.7)	0	13 (43.3)	17 (56.7)	0	24 (80.0)	6 (20.0)	0
Week 3	8 (26.7)	22 (73.3)	0	12 (40.0)	18 (60.0)	0	24 (80.0)	6 (20.0)	0
Week 4	7 (23.3)	19 (63.3)	0	8 (26.7)	22 (73.3)	0	24 (80.0)	6 (20.0)	0
	$\chi^2(4, n=120) = 10.00, P=0.040$*			$\chi^2(4, n=120) = 17.09, P=0.002$*					

METM, multiple exercise training modalities.
*Statistically significant.

Table 3

Comparison of between-group changes in serum electrolytes levels from baseline to the week 4 follow-up.

	Baseline, *N* (%)			Week 4, *N* (%)		
Time electrolyte group	**Hypokalaemia**	**Normal**	**Hyperkalaemia**	**Hypokalaemia**	**Normal**	**Hyperkalaemia**
Serum potassium						
METM + soymilk	10 (33.3)	20 (66.7)	0	0	30 (100)	0
METM	7 (23.3)	23 (76.7)	0	0	30 (100)	0
Soymilk	5 (16.7)	25 (83.3)	0	1 (3.3)	29 (96.7)	0
Control	10 (33.3)	20 (66.7)	0	7 (23.3)	19 (63.3)	0
Test and *P* values		$\chi^2 = 3.06$ $P = 0.381$			$\chi^2 = 18.21$ $P = 0.000$*	
Serum sodium						
METM + soymilk	13 (43.3)	17 (56.7)	0	0	29 (96.7)	1 (3.3)
METM	11 (36.7)	19 (63.3)	0	2 (6.7)	28 (93.3)	0
Soymilk	9 (30.0)	21 (70.0)	0	5 (16.7)	25 (83.3)	0
Control	13 (43.3)	17 (56.7)	0	8 (26.7)	22 (73.3)	0
Test and *P* values		$\chi^2 = 1.55$ $P = 0.671$			$\chi^2 = 8.654$ $P = 0.034$*	
Serum ionized calcium						
METM + soymilk	23 (76.7)	7 (23.3)	0	1 (3.3)	29 (96.7)	0
METM	23 (76.7)	7 (23.3)	0	13 (43.3)	17 (56.7)	0
Soymilk	18 (60.0)	12 (40)	0	16 (53.3)	14 (46.7)	0
Control	24 (80.0)	6 (20.0)	0	24 (80.0)	6 (20.0)	0
Test and *P* values		$\chi^2 = 4.306$ $P = 0.230$			$\chi^2 = 36.76$ $P = 0.000$*	

METM, multiple exercise training modalities.
*Statistically significant.

wasting syndrome and inappropriate antidiuretic hormone secretion in stroke patients[18]. It is a significant predictor of poor outcomes post-stroke, including prolonged hospital stays and increased mortality rates[4,19].

Our study demonstrated that METM with soymilk effectively normalized serum sodium levels, with all participants in this group showing improvement at the 4-week follow-up. While serum sodium levels also improved in other groups, these changes did not reach statistical significance. Although increasing protein intake has been associated with improved sodium levels and muscle strength in hyponatremic patients[20], this approach has not been explored in stroke patients. The exercise component of the intervention also played a role in normalizing serum sodium, as exercise can impact serum sodium levels through mechanisms such as stimulating cortisol production, which antagonizes anti-diuretic hormone receptors[21]. While high-intensity[22] and endurance exercise[23] have been linked to decreased serum sodium levels, our study focused on moderate-level exercise.

In this study, the admission rate of hypokalemia in 26.7% of participants was higher than reported prevalence rates, ranging from 15[24] to 20%[6] in previous studies. Elevated catecholamine levels, such as adrenaline or noradrenaline, during stress or the acute phase of stroke, may affect potassium regulation, potentially impacting kidney function and cellular potassium uptake. Activation of beta-2 adrenergic receptors by catecholamines can lead to potassium movement into cells, potentially causing hypokalemia[25].

In this study, serum potassium levels improved across all study groups over the study period, with the intervention groups, particularly the METM plus soymilk group, showing statistically significant improvement compared to the control group. Higher potassium intake and a lower sodium-to-potassium ratio are associated with reduced cardiovascular disease risk, including stroke[26–28]. Hypokalemia may worsen post-stroke functional prognosis, emphasizing the importance of maintaining normal potassium levels to reduce stroke risk and improve outcomes[7]. Moderate elevations of plasma and interstitial potassium levels during exercise can have beneficial effects on multiple physiological systems, including muscle sodium-potassium pump activity[29]. Additionally, soymilk is a great source of potassium[30]. Combining soymilk with exercise training in this study resulted in additional improvements in serum electrolyte levels within the METM plus Soymilk group.

The higher incidence of hypocalcemia upon admission in our study sample (73.3%) raises concerns when compared to prevalence rates in prior research, which range from 11.8[6] to 53%[31]. The variation in hypocalcemia prevalence can be partly attributed to differences in how the normal range is defined across studies. Serum calcium levels have been linked to stroke development[32], its severity[32], and prognosis[33]. Both low[9,10] and high[34] calcium levels contribute to an increased risk of stroke development and its severity. Hypocalcemia upon admission has been linked to higher mortality among intracerebral hemorrhage[35] and ischemic stroke patients[36].

Implementing interventions to restore normal calcium levels may positively influence outcomes in stroke patients (Zhang and colleagues, 2021). In our study, both the METM plus soymilk and the METM groups displayed statistically significant improvements in serum calcium levels over 4 weeks. Exercise contributes to maintaining healthy serum calcium levels through various mechanisms: weight-bearing and resistance exercises stimulate bone formation and strength, while also influencing hormones like calcitonin and parathyroid hormone that play a role in calcium balance[37,38]. Also, physical activity enhances the body's ability to absorb and utilize calcium from the diet[39], crucial for muscle function during exercise[40]. Regular exercise supports overall metabolic health, aiding in the regulation of various minerals, including calcium[41].

In addition, soymilk, which contains a significant amount of calcium, contributed to a more pronounced improvement in hypocalcemia within the METM plus soymilk group compared to the METM group[30].

While the beneficial effects of soy protein for stroke patients require further study, research on animal models suggests a potential protective role against neurological damage following stroke[42]. Additionally, cohort studies suggest an association between soy consumption and improved cardiovascular disease outcomes, though further randomized controlled trials are needed for confirmation[43]. It is encouraging to observe the potential of an alternative therapy involving exercise combined with a soymilk supplement for addressing serum electrolyte imbalances in stroke patients. The intervention proved to be both feasible and well-received by the patients. Although for the management of electrolyte imbalances, the underlying cause must be recognized, non-invasive treatments, which have fewer side effects compared to agent treatments can also be considered[44].

Limitations

This study stands out for its examination of the effects of a combined approach encompassing multiple exercise training and soymilk supplementation on serum electrolyte levels in patients with acute stroke. The randomized controlled trial design enhances the study's credibility. However, limitations include the absence of a true control group due to ethical constraints and the inability to blind participants and the research team, potentially introducing bias into the findings.

Conclusions

Hyponatremia, hypokalemia, and hypocalcemia are common occurrences in the acute phase of a stroke and are linked to worse patient outcomes. This study investigated the effectiveness of the METM protocol combined with soymilk consumption in addressing these electrolyte imbalances. While improvements in serum electrolyte levels were observed overall, the addition of exercise-based interventions alongside soymilk consumption led to more significant improvements, particularly in normalizing hypocalcemia. Future research should further explore the impact of similar interventions on normalizing serum electrolyte levels among stroke patients, considering various patient outcomes and disease-related variables such as hospital stay, in-hospital mortality rate, and out-of-hospital mortality rate.

Ethical approval

The study received ethics approval from Tabriz University of Medical Services (IR.TABRIZU.REC.1401.038) and was registered in the Iranian Registry of Clinical Trials (09/12/2022; IRCT20130816014371N3).

Consent

Eligible patients were briefed about the study, invited to participate, and enrolled upon providing written consent.

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This study has not received any funding.

Author contribution

V.S., L.E., S.N., and B.E. designed and conducted the study, making significant intellectual contributions and assisting in manuscript preparation. B.E. and L.E. collected data and S.N. analyzed the data. L.G. critically reviewed the manuscript, contributed to data analysis, and participated in manuscript writing.

Conflicts of interest disclosure

There is no conflict of interest about this research.

Research registration unique identifying number (UIN)

This RCT was registered in the Iranian Registry of Clinical Trials (09/12/2022; IRCT20130816014371N3).

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Babak Esmealy. Vahid Sari-Sarraf.

Data availability statement

The data for this article are available upon reasonable request.

Provenance and peer review

This paper was not invited.

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