ORIGINAL RESEARCH

Combined Effects of Transcranial Magnetic Stimulation and Argatroban on Balance Function and Daily Living Activities in Hemiplegic Patients Following Cerebral Infarction

Shasha Zhu, BM; Di An, MM; Tao Yan, MD; Li Ling, MD

ABSTRACT

Objective • This study aimed to investigate the impact of combining transcranial magnetic stimulation (TMS) with argatroban on balance function and activities of daily living in patients with hemiplegia following cerebral infarction (CI).

Methods • A retrospective analysis was conducted on the clinical data of 104 patients with hemiplegia after CI who were admitted to our hospital from July 2020 to July 2021. The patients were randomly assigned to either the experimental group (EG) or the control group (CG), with 52 patients in each group. The EG received TMS in combination with argatroban, while the CG received argatroban alone. The Berg Balance Scale (BBS) and modified Barthel index (BI) were used to assess the balance function and activities of daily living in both groups after treatment.

Results • After treatment, the EG demonstrated significantly higher BBS and BI scores compared to the CG ($P < .001$). Additionally, the EG showed significantly improved upper limb and lower limb Functional Ambulation Profile (FAM) scores compared to the CG ($P < .05$).

Conclusions • The combination of TMS and argatroban proves to be an effective approach for enhancing balance function and activities of daily living in hemiplegic patients with CI. Therefore, it is recommended as a valuable rehabilitation treatment for such patients. (*Altern Ther Health Med.* 2023;29(7):41-45).

Shasha Zhu, BM, Attending Doctor; Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China; Department of Neurology, Affiliated Hospital of Hebei University, Baoding, Hebei, China. **Tao Yan,** MD, Chief Physician; Department of Neurology, Tianjin Medical University General Hospital, Heping District, Tianjin, China. **Di An,** MM, Attending Doctor; **Li Ling,** MD, Chief Physician; Department of Neurology, Affiliated Hospital of Hebei University, Lian Chi District, Baoding, Hebei, China.

Corresponding author: Li Ling, MD
E-mail: an_mmm@163.com

INTRODUCTION

Cerebral infarction (CI), or ischemic stroke, refers to cerebral blood supply disorders caused by various factors.[1] This condition results in irreversible damage to local brain tissue, leading to ischemic and hypoxia-induced necrosis of the affected brain tissue.[2] The global annual incidence of CI is approximately 110 to 250 per 100 000 individuals, while in China, the yearly incidence ranges between 53.39 and 182.60 per 100 000 individuals.[3] Studies have indicated significant gender disparities in the incidence of CI, with males exhibiting higher rates compared to females, with a ratio of approximately 1.48:1 to 1.8:1.[4] Based on foreign survival data following CI, the 30-day mortality rate ranges from 10% to 30%,[5] making CI one of the leading causes of morbidity and mortality among cardiovascular diseases.

Patients with cerebral infarction often experience acute onset or no aura, leading to complications such as hemiplegia, limb paralysis, muscle movement disorders, dysphagia disorders, memory loss, and mood disorders when the infarct lesions affect vital functional areas in the cerebral cortex. These complications significantly impact their quality of life (QOL).[4,5] Anticoagulant therapy plays a crucial role in the acute phase by preserving cells in the ischemic penumbra, preventing micro thrombosis in distal small vessels, promoting collateral circulation, and improving cerebral blood flow. It is indicated for patients with a hypercoagulable state, cardiogenic embolism, unstable carotid atherosclerotic plaque, severe stenosis or occlusion of intracranial or cervical large vessels, arterial dissection, sinus of the dura mater, or venous thrombosis. Anticoagulant therapy effectively prevents and treats thrombosis.[6]

Historically, low-molecular-weight heparin was the primary anticoagulant of choice in China.[6] However, its use was associated with an increased risk of hemorrhagic complications. In contrast, argatroban effectively inhibits fibrin formation, prevents platelet aggregation, and maintains

a stable blood concentration in pharmacodynamics. As a result, argatroban has emerged as a promising alternative to low-molecular-weight heparin for anticoagulant therapy.[7] Moreover, administering trophic nerve drugs (such as vitamin B1, vitamin B6, piracetam, and neural ganglioside) during the rehabilitation period of patients with cerebral infarction has shown promise in facilitating the recovery of various bodily functions.

Transcranial magnetic stimulation (TMS) has emerged as an innovative therapy in recent years. It is a non-invasive technique that harnesses the physiological activation of neuroelectricity. TMS involves applying a pulse magnetic field to the cerebral cortex, inducing changes in the current that are then utilized for patient treatment. This approach offers distinct advantages, including being painless, non-invasive, simple, and safe.[8] TMS has shown impressive outcomes in the clinical management of central nervous system disorders such as Parkinson's disease and spinal cord injury.[9]

However, there is limited evidence on the clinical efficacy of combining TMS with argatroban for treating hemiplegia following CI. This study aims to observe the impact of TMS combined with argatroban on balance function and QOL in patients with hemiplegia after CI. The findings aim to provide novel directions for the rehabilitation treatment of such patients.

MATERIALS AND METHODS

Study Design

A retrospective analysis was conducted on the clinical data of 104 patients with hemiplegia after cerebral infarction who were admitted to our hospital between July 2020 and July 2021. The patients were randomly divided into two groups: the experimental group (EG, n = 52) and the control group (CG, n = 52), following the principles of random grouping. This study was conducted in accordance with the Declaration of Helsinki (2013)[10] and received approval from the hospital ethics committee. Informed consent was obtained from the patients and their families, who were provided with detailed information about the study's objectives and procedures.

Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Patients who met the diagnostic criteria for hemiplegia after cerebral infarction as outlined in the Diagnosis Guidelines of Cerebrovascular Diseases[11]; (2) Patients without active intracranial bleeding (including hemorrhagic transformation after cerebral infarction and recurrent hemorrhage after cerebral hemorrhage) or seizures; (3) Patients with stable conditions; (4) Patients diagnosed with hemiplegia after cerebral infarction; and (5) Patients demonstrating good compliance and ability to actively participate in the study.

Exclusion Criteria: (1) Patients with severe cardiovascular and cerebrovascular diseases, as well as liver and kidney dysfunction; (2) Patients with cognitive impairment, senile dementia, or inability to communicate effectively with others; (3) Patients with known allergies to the drugs used in the study; (4) Patients who withdrew from the study due to intolerance; (5) Patients with severe complications or conditions that impeded their ability to participate and complete the trial actively.

Treatment Procedure

All patients received standard treatment protocols upon admission, including anti-platelet aggregation, neurotrophic support, and cerebral protection, to ensure airway patency and proactive management of complications.

In the control group, patients were administered argatroban injection (manufacturer: Tianjin Institute of Pharmaceutical Research; NMPA approval No.: H20050918; specification: 20 ml: 10 mg) within 48 hours of symptom onset and the initial two days involved a 60 mg infusion, appropriately diluted, administered through continuous intravenous infusion over 24 hours. Subsequently, a daily infusion of 20 mg, suitably diluted, was given for the following five days, twice a day (morning and evening), with a dosage of 10 mg per administration. The intravenous infusion was performed for a duration of 3 hours each time. The doctors adjusted the drug dosage based on the patient's age and symptoms.

In the experimental group, patients underwent TMS in addition to the treatment received by the control group. The TMS procedure involved the following steps: Patients were positioned supine to measure the refined motor threshold (RMT) of the affected side. A repetitive TMS instrument with an 8-shaped coil measuring 12 cm in diameter was placed on the primary somatomotor area of the patient's cerebral cortex, ensuring that the center of the coil was tangent to the scalp. The TMS parameters were set as follows: stimulation intensity of 80% RMT, stimulation frequency of 12 Hz, a single sequence duration of 5 seconds, and an interval of 20 seconds. A total of 2000 pulses were administered during each 20-minute treatment session. The treatment was conducted once a day for 5 consecutive days, followed by a 2-day rest period. This 4-week treatment protocol was repeated for the duration of the study.

Observation Indexes

Balance Function. The balance function of both groups of patients after treatment was assessed using the Berg Balance Scale (BBS).[12] The BBS score evaluated various aspects of balance, including standing up from a sitting position, standing without support, sitting without support, sitting down from a standing position, transferring, standing with eyes closed, standing with feet together, moving ahead with forward stretching of upper limbs, picking up items from the ground, turning back to look backward, 360° turning, placing one foot on a step or stool, standing with both feet in tandem, and standing on one leg. The scale consisted of a total of 14 items, ranging from easy to difficult.

Based on the completion status of the subjects, each evaluation item was assigned a score using five functional registrations (0, 1, 2, 3, 4). The maximum achievable score

was 56. Scores between 0 and 20 indicated poor balance function, suggesting the need for wheelchair assistance. Scores between 21 and 40 suggested a certain level of balance ability, enabling patients to walk with assistance. Scores between 41 and 56 indicated better balance function, allowing patients to walk independently. A BBS score below 40 indicated an increased risk of falls.

Activities of Daily Living. The activities of daily living (ADL) of both groups of patients after treatment were evaluated using the Barthel Index (BI) score.[13] The BI score assessed various aspects of daily living, including eating, bathing, personal hygiene, dressing, controlling defecation, controlling urine, toileting, bed-chair transfer, level walking, and stair activity.

Each activity was classified into five levels based on the completion status of the subjects: (1) Level 1: Patients who were completely dependent on others to complete the entire activity; (2) Level 2: Patients who required assistance for more than half of the activity; (3) Level 3: Patients who required assistance for half or less of the activity; (4) Level 4: Patients who needed supervision or prompts during the activities; and (5) Level 5: Patients with complete independence in performing the activities. The total score on the BI ranged from 0 to 100 points. A higher score indicated a higher level of independence and ability to perform daily living activities.

Motor Function. Motor function of the upper and lower limbs after treatment was assessed using the Fugl-Meyer Assessment (FMA) score.[14] The FMA score consisted of two components: the lower limb score and the upper limb score. The lower limb score comprised 17 items, and each was assigned a score of 0, 1, or 2 based on the observed situation. The maximum achievable score for the lower limb score was 34. The upper limb score had a total of 33 items, with each item scored on a scale of 0 to 2. The highest possible score for the upper limb score was 66 points. A higher FMA score indicated better motor function in the patient's upper and lower limbs.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics 26.0 software (Armonk, NY, USA), and graphical representations of the data were created using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). Both categorical (enumeration) data and continuous (measurement) data were analyzed in this study. The chi-square (χ^2) test was used for categorical data, while the *t* test was employed for continuous data. A statistically significant difference was considered when the *P* value was less than .05 ($P < .05$).

RESULTS

Comparison of Clinical Data

Table 1 presents the comparison of clinical data, including age, BMI value, educational level, and place of residence, between the two groups. The results indicated no significant differences in these variables between the groups ($P > .05$).

Table 1. Comparison of clinical data between the two groups

Items	EG (n = 52)	CG (n = 52)	χ^2/t	*P* value
Gender			0.369	.543
Male	34 (65.38)	31 (59.62)		
Female	18 (34.62)	21 (40.38)		
Age ($\bar{x} \pm s$, years)	68.44 ± 3.73	68.60 ± 3.59	0.230	.819
BMI value ($\bar{x} \pm s$, kg/m^2)	21.14 ± 1.49	21.19 ± 1.31	0.190	.850
Courses of disease ($\bar{x} \pm s$, months)	1.92 ± 0.79	2.04 ± 0.82	0.704	.485
Classification of hemiplegia			0.650	.420
Completeness	22 (42.31)	18 (34.62)		
Incompleteness	30 (57.69)	34 (65.38)		
Locations of hemiplegia			0.000	1.000
Left side	24 (46.15)	22 (42.31)		
Right side	28 (53.85)	30 (57.69)		
Education level			1.152	.765
College and above	2 (3.85)	1 (1.92)		
Senior middle school	5 (9.62)	4 (7.69)		
Junior high school	16 (30.77)	13 (25.00)		
Primary school and below	29 (55.77)	34 (65.38)		
Place of residence			0.362	.547
Urban area	22 (42.31)	19 (36.54)		
Rural area	30 (57.69)	33 (63.46)		

Note: Values are presented as frequency (percentage) or mean ± standard deviation (SD). EG, Experimental Group; CG, Control Group.

Table 2. Comparison of motor function in both groups ($\bar{x} \pm s$)

Groups	n	FAM score of upper limbs (points)	FAM score of lower limbs (points)
EG	52	43.46 ± 5.02	23.69 ± 1.53
CG	52	40.48 ± 4.88	19.44 ± 2.36
t		3.049	11.770
P value		.004	<.001

Note: Values are presented as mean ± standard deviation (SD). EG, Experimental Group; CG, Control Group. The *t* test was used to determine the statistical significance between the groups.

Comparison of Balance Function

The BBS score of patients in the EG after treatment was significantly higher than that of the CG ($P < .001$). Please refer to Figure 1 for detailed information

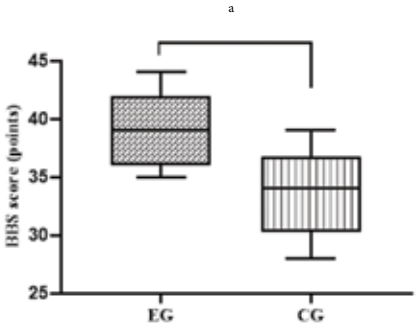
Comparison of Activities of Daily Living

The results demonstrated that patients in the EG had significantly higher BI scores after treatment compared to those in the CG ($P < .001$), indicating improved activities of daily living in the EG. Please refer to Figure 2 for a visual representation of the results.

Comparison of Motor Function

The results revealed that the EG exhibited significantly higher FMA scores for both the upper limb and lower limb compared to the CG ($P < .05$), indicating improved motor function in the EG. Please consult Table 2 for a comprehensive

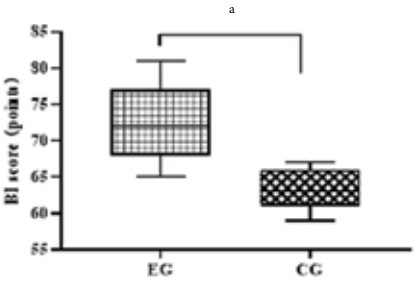
Figure 1. Comparison of BBS scores between the two groups after treatment (mean ± SD).



[a]indicates a significant difference in the BBS scores between the two groups ($t = 9.918$, $P < .001$).

Note: The average BBS scores in the experimental group (EG) and control group (CG) were (38.98 ± 3.01) points and (33.44 ± 3.49) points, respectively.

Figure 2. Comparison of BI scores between the two groups (mean ± SD).



[a]indicates a significant difference in the BI scores between the two groups ($t = 13.675$, $P < .001$).

Note: The average BI scores in the experimental group (EG) and control group (CG) were (72.81 ± 4.85) points and (63.00 ± 2.88) points, respectively.

breakdown of the results.

DISCUSSION

Patients with CI commonly experience varying degrees of limb dysfunction within one month of onset, primarily due to damage to the higher nerve centers. This damage leads to difficulties in controlling the mobility of the lower nerve centers, resulting in neural hyperreflexia. As a consequence, the coordination ability of muscle groups in these patients is compromised, leading to exercise and walking impairments.[15] Hemiplegia is a prevalent form of limb dysfunction in CI patients, primarily characterized by the loss of lower limb motor function, which significantly impacts the patients' activities of daily living and quality of life.[16] Several researchers have emphasized the close association between trunk control in hemiplegic patients and their activities of daily living.[17] In addition to targeted treatments for CI patients, restoring balance function and activities of daily living in this population has become an urgent concern in the medical community. Conventional rehabilitation training, characterized by limited effectiveness and insufficient improvement in muscle tension and motor function, often fails to correct gait abnormalities in these patients.[18]

TMS, a cerebral regulation technology, primarily stimulates the primary motor cortex of the patient's brain to modulate the level of excitability. It enhances the sensitivity of the central motor system to limb function training, medication, and other rehabilitation techniques.[19] Following cerebral infarction, there is an imbalance between the two cerebral hemispheres, leading to motor dysfunction. TMS employs low-frequency stimulation in the unaffected hemisphere's primary motor cortex to decrease its excitability while applying high-frequency stimulation in the affected hemisphere's primary motor cortex to increase its excitability. This approach aims to restore a balance between the hemispheres and improve limb function.[20]

Argatroban, a synthetic arginine derivative with a low molecular weight 527, offers rapid onset and good safety. It enters the thrombus and inactivates thrombin that has bound to fibrin. Additionally, it quickly and reversibly binds to the catalytic site of thrombin, thereby exerting anticoagulant effects. Previous studies have reported that argatroban reduces inflammatory factor levels in patients with acute cerebral infarction, suggesting its potential anti-inflammatory role.[21]

This clinical controlled study aimed to assess the impact of combining TMS with argatroban on the balance function and activities of daily living in patients with hemiplegia after CI. The study demonstrated a significant improvement in the BBS score for patients in the EG compared to the CG after treatment ($P < .001$). The notable improvement can be attributed to the unique characteristics of argatroban, a novel direct thrombin inhibitor. Argatroban exhibits high selectivity by specifically inhibiting the binding of free-state blood clots to thrombin.[22] Furthermore, its strong interaction allows reversible binding to the active sites of thrombin, thereby interfering with the activation of protease C and coagulation factors V, VIII, and XII, as well as the production of plasma fibrin. At the same time, argatroban can potentially improve the hemorheology of patients with hemiplegia after cerebral infarction by blocking platelet aggregation. This mechanism reduces blood viscosity, which is beneficial for the recovery of balance function.[23]

Balance, a critical factor for normal motor recovery, refers to the ability to maintain an upright body position under specific conditions. It serves as a crucial prerequisite for walking and performing daily activities, and balance dysfunction is a key symptom observed in patients with hemiplegia following cerebral infarction. TMS utilizes pulsed magnetic fields to stimulate brain tissue, inducing the generation of corresponding induced currents. This process promotes the formation of excitatory postsynaptic potentials and neuronal excitation, reversing the inhibitory effects on cortical excitability.[24] Furthermore, TMS exerts a noticeable

impact on the physiological parameters of neuroelectricity, leading to improvements in both balance function and motor function in patients. These findings are consistent with the research conducted by international scholars.[25]

Research Implications

The application of TMS combined with argatroban in patients with hemiplegia after cerebral infarction effectively enhances their balance function. This outcome holds significant positive implications for improving the prognosis of the disease. Moreover, it offers a novel direction for the development and selection of rehabilitation programs specifically designed for individuals with hemiplegia following cerebral infarction.

Study Limitations

It is important to acknowledge the limitations of this study. Firstly, the study design was based on a retrospective analysis of clinical data, which may introduce inherent biases and limitations. Secondly, the sample size was relatively small, which could impact the generalizability of the findings to a larger population. Additionally, the study focused on a specific treatment approach involving TMS combined with argatroban, and the results may not be applicable to other therapeutic interventions. Moreover, the study primarily assessed short-term outcomes, and the long-term effects and sustainability of the observed improvements remain unclear. Lastly, the study did not include a follow-up period to evaluate the durability of the treatment effects. These limitations should be considered when interpreting the findings, and further research with larger sample sizes and longer follow-up periods is warranted to validate and expand upon these initial results.

CONCLUSION

In conclusion, the findings of this study demonstrate that the combination of transcranial magnetic stimulation and argatroban is an effective rehabilitation method for improving the balance function and motor function of both upper and lower limbs in patients with hemiplegia after cerebral infarction. However, it is important to acknowledge the limitations of this study, including the small sample size and the lack of long-term efficacy assessment. Future studies should address these limitations by expanding the sample size, incorporating additional objective observation indicators, and conducting long-term follow-up assessments to track the clinical efficacy over time. Therefore, further refinement and optimization of the clinical intervention program is warranted. It would enhance standardization and wider clinical applicability of the treatment approach.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHORS' CONTRIBUTIONS

SZ, DA, and LL designed the study and performed the experiments; SZ, DA, and TY collected the data; LL and TY analyzed the data; SZ, DA, and LL prepared the manuscript. All authors read and approved the final manuscript. SZ and DA contributed equally to this article

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