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Sex Differences in Neuroanatomy of the Human Mirror Neuron System: Impact on Functional Recovery of Ischemic Hemiparetic Patients

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Background: Considering the higher activity of mirror neuron system in females, they frequently have better performance in empathy, interpersonal sensitivity, and emotional recognition compared to males.
Objectives: The purpose of this study was to assess whether gender difference in neuroanatomy of the human mirror neuron system has any impact on functional recovery of ischemic hemiparetic patients.
Patients and Methods: This single-blind clinical trial was conducted on 24 patients with cerebrovascular accident (CVA) in the age range of 45 - 60 years, referring at a rehabilitation center in Tehran, Iran, during 2013 - 2014. Sampling method was stratified random sampling. The subjects were assigned to 2 groups of 12 males and 12 females. Then, each group was randomly divided into 2 groups (totally 4 groups, n = 6 for each group): women watching functional movies, control women, men watching functional movies, and control men. Movies were shown to patients and then, they were evaluated by Timed Up and Go (TUG), Six-minute walk test (SMW), Barthel index (BI), and Berg balance scale (BBS).
Results: Comparison of all variables related to functional activities of all groups before and after watching movies revealed significant differences. The highest percentage of change and improvement was observed in groups 1 and 3 watching the functional movies ($P = 0.0001$). Percentage of improvement in women of groups 1 and 2 was higher than men in groups 3 and 4 ($P = 0.0003$). The changes in group of females watching the functional movies (group 1) were significantly greater than in other groups ($P < 0.0001$).
Conclusions: The Sex differences in the neuroanatomy of the human mirror neuron system affect functional recovery of patients with hemiparesis. The improvement in studied women was found to be significantly greater than studied men. The results indicate a higher chance of recovery among hemiparetic women, especially those watching functional movies.

Keywords: Sex Characteristics; Neuroanatomy; Mirror Neurons; Recovery of Function

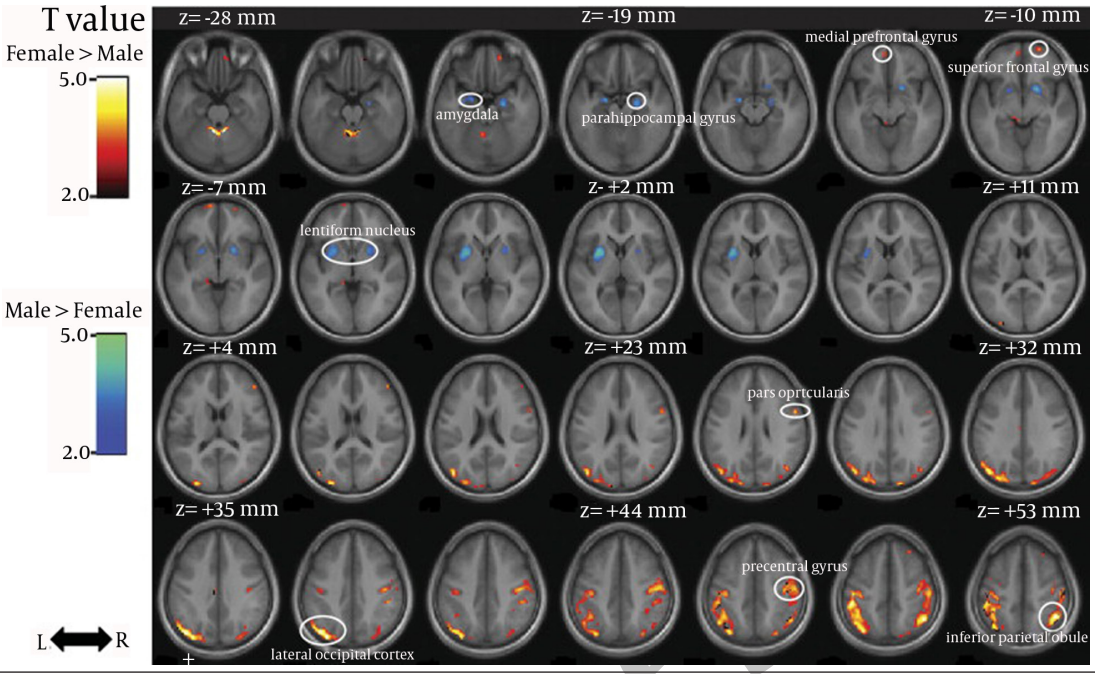
1. Background

A high number of patients survived from Cerebrovascular Accident (CVA) suffer from sensory, motor, cognitive, and emotional disturbances causing limitations in daily functional activities (1). A new approach for the treatment of stroke patients has been developed by observing and imitating the movement of the mirror neurons. Mirror neurons are a group of gray matter neural cells stimulated by the observation of an activity, which enables the observer to imitate the movement (2). In humans, these neurons are located in the premotor and intraparietal cortex (3).

Neuroanatomy of the mirror neuron system is different in males and females. Morphological voxel-based analysis demonstrates differences in brain volumes by functional magnetic resonance imaging (fMRI). Also empathic actions indicate that adult women have a significantly larger volume of gray matter in the pars opercularis and frontal-parietal lobes compared to males. Females have a higher volume of gray matter in the right infra-frontal sinus groove, infra-parietal lobe, and internal anterior brain cortex (2, 4-6) (Figure 1) (2). Electroencephalography (EEG) evidence also supports sex differences with regard to empathy for pain (7).

Observation of the movement triggers the mirror neuron system to recognize and imitate it (8). Mirror neurons can effectively help memory formation and motor learning following observation of a movement. (9). Superior performance of women in empathy, emotional interpersonal communications, and emotional recognition compared to men indicates neuroanatomical sex differences and explains greater activity of this system in females (2). Observation and imitation of movement are expected to have superior efficacy in women with neural injury and this higher efficacy may be used for functional recovery of female hemiparetic patients.

Figure 1. Gender Differences in Regional Brain Volume



The gray matter regions showing significant sexual dimorphism were rendered onto the averaged horizontal images of the whole sample (N-24) (voxel threshold: uncorrected $P < 0.001$). The gray matter regions that are larger in females than males are presented in red to yellow. Conversely, the gray matter regions that are larger in males are presented in blue to green. The Z-coordinate for each coronal slice in the MNI space is given in mm. L: left. R: right. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

2. Objectives

This is a new research field and there are too many papers about it. The purpose of this study was to assess whether gender differences in neuroanatomy of the human mirror neuron system has any impact on functional recovery of patients with ischemic hemiparesis.

3. Patients and Methods

3.1. Patients

This single-blind clinical trial was conducted on 24 ischemic hemiparetic patients (12 males and 12 females) who had a cortical thromboembolic ischemic lesion around the middle meningeal artery during 2013 - 2014. The study setting was a referral governmental rehabilitation center in Tehran (Iran). All patients had first ischemic hemiparesis without previous experience of treatment with the action observation.

On arrival, all patients were examined by a neurologist. If patients were eligible for the study they were enrolled. Sampling strategy was stratified random sampling. The subjects were randomly assigned to 2 groups of 12 men and women. To detect the sample size, a pilot study was done on 3 patients in each group. According to the results, regarding an effect size of 0.85 in response variable with an error probability of 5%, and a power of 90%, by using ANOVA sample size formulation (10) and G*Power software (11), it was found that at least 6 patients per group was necessary.

Candidates were selected using convenience random and block randomization sampling. The inclusion criteria were having history of CVA within the past 3-6 months, age range of 40 - 65 years, normal level of consciousness, normal field of vision and visual power, spasticity between +1 - 2 (according to the modified Ashworth scale), and BMI < 30 kg/m^2.

The exclusion criteria were having Wernicke's aphasia, cardiac or respiratory diseases, history of neural surgery, mental disorder, neglect in the right hemisphere, depression, high psychological stress, and advanced osteoarthritis in lower extremities. Candidates were divided into 4 groups in a single-blind fashion as follows: women watching the functional movies (group 1), control women (group 2), men watching the functional movies (group 3) and control men (group 4). All patients remained in the study until the end of the experiment. All experiments on human subjects were conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written consent of the subjects. The study protocol was approved in the Ethics Committee of Shahid Beheshti University of Medical Sciences (EC/75/H/341, date: March 1, 2013).

3.2. Treatment

The rehabilitation treatment consisted of twelve 60-minutes sessions (15 minutes of watching a functional movie and 45 minutes of routine physiotherapy) for groups watching the functional movies (groups 1 and 3) and twelve

45-minutes sessions (only routine rehabilitation program without watching the functional movie) for control groups (groups 2 and 4) every other day. Routine physiotherapy of patients in all groups included use of infrared light for lower extremities for 5 minutes, use of electrical current (functional faradic stimulation) on quadriceps and tibialis anterior in the hemiparetic side for 10 minutes (5 minutes for quadriceps and 5 minutes for tibialis anterior) and different exercises (floor exercises on mattress, supplemental and reinforcement exercises for lower extremities, balance exercises and weighing on limbs and functional exercises on lower extremities) for 30 minutes. (12).

Patients in groups 1 and 3 were seated in front of a 25-inch monitor at 2 m distance and watched the functional movie. After watching, they tried to imitate the same movements on the movie. A total of 29 silent video clips (to stimulate only the visual sensation) of movements routinely used for physiotherapy of hemiparetic patients were shown to groups 1 and 3 in the form of separate 1-minute clips with 5 repetitions (Figure 2). Clips started with the simplest to the most difficult movements and 3 clips were shown per session. The process of showing the movies was based on the patient's ability and started with simple movements towards more difficult and complex ones.

Figure 2. Images From the Video Clips of Functional Activities in Groups 1 and 3 (Original Pictures)

3.3. Demographic and Clinical Data Collection

Demographic data including age, sex, height, weight, BMI, duration of affliction, and affected side were collected using a questionnaire. Visual acuity was measured by the Snellen chart (The patient was placed at a distance of 6 m, while putting his hands on his eyes, trying to see the letters on the chart and determine their direction. It was determined on the basis of the patient's visual power) and visual field was assessed by manually visual field test (Visual field test is a quick and basic method of measuring the visual field that can detect dysfunction in central and peripheral vision). The examiner asks the patient to cover one eye and stares at the examiner. Ideally, when the patient covers his or her right eye, the examiner covers his or her left eye, and vice versa. The examiner will then move his or her hand out of the patient's visual field and then bring it back in. The examiner usually uses a slowly wagging finger or a hat pin for this action. The patient signals the examiner when his or her hand comes back into view. This is frequently done by an examiner as a simple and preliminary test.

Power of muscles was scored using manual muscle testing as described by Kendall in 9 different degrees from -2 (poor) to + 4 (good) (13). Intensity of spasticity was assessed using modified Ashworth scale (in 5 scales of 1, indicative of minimum spasticity to 4, indicative of maximum spasticity). Objective assessment of patient mobility was done using the following tests: standard test of timed up and go (TUG) (time that a person takes to rise from a chair, walk 3 m, turn around, walk back to the chair, and sit down), Six-Minute Walk (SMW) (the maximum distance walked over 6 minutes), Barthel index (BI) checking the patient's independence in conducting the daily activities and personal care (a numerical scale scoring the quality of conducting 10 functions: 0 indicates completely dependent and 10 indicates completely independent with a maximum score of 100 and minimum score of 0), and Berg Balance Scale (BBS) comprising 14 different skills to assess the patient's balance and function while performing them. With regard to BBS, each skill is scored from 0 to 4 (total score of 56) based on the time required to maintain a specific position or complete a task. A total score of 56 indicates that the patient is capable of independently performing all tasks. Low scores (36 - 45) indicate that the patient is not capable of performing the skill independently during the required time and is at relative risk of fall and injury. Scores lower than 36 indicate that the patient is fully dependent and is at high risk of fall and injury. All mentioned tests are standard and have high validity and reliability. The study did not use special equipment (just using standard techniques and tests listed). Demographic and clinical data collection was carried out by a qualified and experienced physiotherapist.

3.4. Statistical Analysis

All statistical analyses were performed using SPSS, version 16.0 (SPSS Inc, Chicago, IL, USA). Considering the normal distribution of data, confirmed by the Kolmogorov-Smirnov test, parametric tests were used for data analysis. Pre- and post-intervention values in each group were compared using paired t test. After calculation of the changes in each variable in all groups, results were analyzed using ANOVA and Tukey test with 95% confidence interval (CI) and significance level of 0.05.

4. Results

At baseline, patients were matched in terms of demographic information (age, sex, height, weight, BMI, duration of affliction, and affected side) and had no significant difference with respect to these variables ($P > 0.05$ for all variables) (Table 1).

According to ANOVA, functional activities (TUG, SMW, BI, BBS) of all groups were similar at baseline with no significant differences (Table 2).

The changes in values before and after the intervention for all functional activities (TUG, SMW, BI, BBS) in each group were significant and showed improvement after the treatment. The highest degree of change and improvement occurred in groups watching the functional movies (1 and 3) ($P = 0.0001$). Among 4 groups, females (1 and 2) showed greater improvement than males at the same intervention group (3 and 4) ($P = 0.0003$). The change in each variable was significant ($P < 0.0001$ for TUG, $P < 0.0001$ for SMW, $P = 0.0001$ for BI, and $P = 0.0003$ for BBS). Changes in women watching the functional movies (group 1) were significantly greater than other groups ($P < 0.0001$) (Table 3).

Table 1. Demographic Information of Patients [a]

Variable	Women Watching Functional Movies	Control Women	Men Watching Functional Movies	Control Men	P Value
Age, y	54.8 ± 6.2	54.3 ± 7.3	54.8 ± 7.4	54.7 ± 7.6	0.89
Height, cm	170 ± 3.3	169 ± 6.8	170 ± 6.7	170.2 ± 3.2	0.75
Weight, kg	73 ± 0.4	76.8 ± 7.3	75.3 ± 9.5	77.8 ± 5.7	0.68
BMI, kg/m^2	26.3	27.8 ± 1	26.7 ± 0.5	26.3 ± 1.4	0.82
Affected side, right/left	5/1	2/4	4/2	5/1	-
Duration of affliction, mo	5.5 ± 1	5.8 ± 0.7	5 ± 0.9	4.7 ± 0.8	0.63
Intensity of spasticity, degree	1+	1+	1	1+	0.92

[a] Data are reported as mean ± SD.

Table 2. Results of ANOVA for Quantitative Comparison of Functional Activities at Baseline [a,b]

Variable	Women Watching Functional Movies	Control Women	Men Watching Functional Movies	Control Men	P Value
TUG	24.8 ± 1.5	25.3 ± 1	24.5 ± 3.8	24.5 ± 4.5	0.28
SMW	147.8 ± 6	144.1 ± 14.3	142.1 ± 10.2	142 ± 22.1	0.22
BI	80.8 ± 8.6	75.3 ± 6	75 ± 4.5	75.1 ± 2	0.16
BBS	47.7 ± 1.9	46.7 ± 1.6	47.7 ± 1	47.8 ± 1.5	0.24

[a] Data are reported as Mean ± SD.
[b] Abbreviations: BBS, Berg balance Scale; BI, Barthel index; SMW, Six-minute walk; and TUG, Timed up and go.

Table 3. Functional Activities in Research Groups [a]

Variable	Women Watching Functional Movies (Group 1)			Control Women (Group 2)			Men Watching Functional Movies (Group 3)			Control Men (Group 4)			P Value
	Before	After [a]	% change [b,c,d]	Before	After [a]	% change	Before	After	% change [b,d]	Before	After [b]	% change	
TUG	24.8 ± 1	21.5 ± 1.2	84 ± 3	25.3 ± 1	23 ± 1.4	78.5 ± 1	19.5 ± 3.8	16 ± 3	80.8 ± 4.4	21.5 ± 4.5	19.2 ± 4.5	77 ± 1.4	0
SMW	117.8 ± 6	138.6 ± 4.3	73.3 ± 12	104.2 ± 14	120.8 ± 10	38.7 ± 4 [d]	149.2 ± 10	173.3 ± 12 [a]	43.3 ± 24.4	130 ± 22.1	143.3 ± 24	20.8 ± 10	0
BI	75.8 ± 9	86.7 ± 9.8	24.2 ± 4.9	68.3 ± 6	75.8 ± 5	13.3 ± 9	85 ± 4.5	97.7 ± 2.6 [a]	17.1 ± 3.7	85.8 ± 3.8	92.2 ± 2	13.3 ± 3	0.001
BBS	47.6 ± 2	50.8 ± 2.5	54.5 ± 1.7	46.6 ± 1.6	48.5 ± 1.7	47.1 ± 2	50.7 ± 1	53.8 ± 0.7 [a]	49.3 ± 1.7	48.8 ± 1.5	50.7 ± 1.7	46.1 ± 1	0.003

[a] Significant difference with the baseline value of the same group.
[b] Significant percentage of change compared to control women.
[c] Significant percentage of change compared to men watching functional movies.
[d] Significant percentage of change compared to control men.

ANOVA revealed significant improvement in all functional activities (TUG, SMW, BI, BBS) after the intervention (Table 3).

5. Discussion

Neural rehabilitation requires repetition of exercises, conduction of active movements by the paralyzed limb, and positive effects of neural plasticity (14). Experimental evidence shows that activity of motor cortex enhances the process of neuroplasticity and improves motor disturbances (15). A combination of observing targeted daily activities and physical practice seems to be more effective than physical rehabilitation alone (16).

Comparison of values before and after the intervention in the current study showed significant improvement and indicated that physiotherapy exercises regardless of gender differences of mirror neurons or viewing a functional movie, improved muscle power and functional activities of patients with CVA. Based on the literature, the main factors affecting muscle power include active and dynamic exercises (17); intense, repetitive, targeted activities (14); facilitation of the observation and imitation of movements and mobilization of all related functional mechanisms (previously acquired skills, the power to predict and perceive the learned dynamic movements, using intermediary feedback as a side mechanism, further activation of cortical system, and mobilization of function in the respective muscle) (3); muscle contractures (18); use of existing defective pattern (to increase muscle power and endurance) (12); and improvement of proprioceptive disorders (12), weighing, and balance (19, 20), which all of them were also observed in this study.

This study showed a significant improvement in all functional activities of experimental groups. The time required to do TUG decreased in all groups (22.7 ± 2 second before and 19.9 ± 1 second after the intervention). Mihara et al. stated that longer TUG time in patients was due to shorter steps, less number of steps per minute, and difficulty in standing up or sitting down on the chair (21). In general, the decreased time required for TUG in patients with CVA reported in other studies may be due to physiotherapy along with targeted repetitive exercise (14), improvement in the function of plantar flexor, hip flexor and extensor (22), as well as increase in muscle power and endurance (17, 18), and improvement in weighing, balance, and posture of walking (23); which were also observed in the present study.

SMW was also improved in all patients (120.3 ± 17 m before and 146 ± 15 m after the intervention). Dickstein stated that speed of walking was a main parameter related to walking after CVA and the final speed after the completion of intervention is an important parameter for social activities (24). The improvement in patients was probably due to interventions, which increased the power and contractures of muscles (17, 18); improved walking function (18); as well as physiotherapy along with targeted repetitive exercises; improvement in neuromuscular coordination in walking (14), ability to use the existing defective pattern (due to increased muscle power and endurance) (17, 18), asymmetric muscle tone in extremities (25), proprioception (12), weighing, balance (19, 20), and balance

indexes (20), improvement in the function of plantar flexor and hip flexor and extensor (22), in the posture control (19), longer steps and increased number of steps per minutes (21); and the facilitation of observation and imitation of movement, especially in women with its effect on neuroplasticity and motor rehabilitation; which all confirm our findings.

BI indicated improved independence in functional activities (mean score of 74.2 ± 1.7 out of 100 before and 84.8 ± 1.5 after the intervention). Lost skills in patients with CVA can be acquired again via continuous, intense, targeted instruction, an effective motor response, having a normal neuromuscular system, adequate muscle strength, adequate trunk stability for balance, and use of extremities, flexibility, adequate proprioception, and positive effects of neural plasticity. Evidence shows that mobilization of motor cortex occurs whenever doing a motor activity, mental exercise, or watching a movement. This enhances plasticity and improves motor disturbances (15). A combination of observing targeted daily activities and physical practice seems to be more effective than physical rehabilitation alone. According to Buccino et al. (16), increased activity of mirror neurons indicates that recovery of patients depends on reactivation of motor skills as the result of observation of movement. Another study reported that improvement in BI in patients with CVA was attributed to spontaneous recovery of the condition, increase in power and tolerance of muscles, improvement in balance and increase in independence of patients in daily activities (26). Improved muscle power, balance, stability indices and independence in personal activities were also noted in the current study.

BBS significantly improved in all groups in the current study (47.2 ± 1.35 before and 50.9 ± 1.7 after the intervention). CVA damages the sensory and motor pathways and causes motor and balance impairment in the affected side; which is the main cause of disability following CVA. Patients with CVA have less stability and balance and are at higher risk of falling and injury (27). Impaired posture control (19, 23), neuromuscular coordination (14), coordination between nerve segments; hyperreflexia or spasticity; unilateral weakness and impaired proprioception (28); motor and sensory changes (presence of abnormal sensation); and lack of synchronization in movement (29) are responsible for imbalance. Improvement in motor and communication skills (via plasticity); intense, targeted treatments (active and repetitive daily exercise of paralyzed limbs) (14); quick reorganization of injured nerves (14); activation of brain changes in sensory and motor systems (30); earlier initiation of movements and exercises at the affected side and use of healthy limbs (to stimulate the affected side) (31); early, intense physical activity (increased tolerance of patients to postural alterations and decreased alterations) (32); and progressive long-term exercises (improved muscle power, positive effect on perception and muscle contractures and function of walking) (17, 18) are methods to improve impaired balance in these patients. Improving the motor function and balance enhances the functional activities and independence of these patients.

The greatest improvement in the current study was observed in groups watching the functional movies (1 and 3) ($P = 0.0001$). Among all groups, women experienced greater improvement than men after the same intervention. The improvement in all variables was significant in all groups ($P < 0.0001$ for TUG, $P < 0.0001$ for SMW, $P = 0.0001$ for BI, and $P = 0.0003$ for BSS). Changes in group 1 variables (women watching functional movies) were significantly greater than those variables in other groups ($P < 0.0001$).

Considering the similarity of physiotherapy exercises in all 4 groups, significant changes in the degree of improvement were probably due to watching the functional movies and its effect on plasticity and motor rehabilitation. Observation and imitation of targeted movements and mobilization of functional mechanisms (previously acquired skills, prediction and perception of dynamic movement, their coordination, use of interstitial feedback as a side functional mechanism, further activation of cortical system, and mobilization of function in respective muscles) can activate premotor cortex when watching simple activities and change synaptic attachments and form new pathways for motor rehabilitation (3). Activity of motor areas is reinforced by observation of active movements (1). Study of the functional activity in patients watching the movement reveals increased activity of bilateral anterior premotor cortex, bilateral temporal superior groove, supplementary motor area, and supramarginal groove resulting in the coordination of observation and conduction of movement in mirror neuron system. Improved motor function of patients is related to activation of the physiological network of motor areas that have a history of previous movements and instructed activities (3). Activity of mirror neuron system in women is greater than men (2, 3). Percentage of change in functional activities in groups 1 and 2 was expected to be higher than those in groups 3 and 4. On the other hand, it has been demonstrated that a rehabilitation program comprising a combination of movement observation and intense repetitive exercise has resulted in significant motor improvement in the affected limb. However, such improvement was not observed in any control group (3), which is in accord with the results of the current study.

In conclusion, we showed that gender differences in neuroanatomy of mirror neuron system affect functional improvement in hemiparetic patients. This effect is more significant in women and it appears that women have higher chance of recovery, especially those watching functional movies.

5.1. Study Limitations

Variability of inclusion and exclusion criteria and difficulty of finding patients were among the limitations

of this study. This study was conducted on outpatients whom at least 3 months had passed from their CVA. Thus, these results may not be generalizable to hospitalized patients with a history of recent CVA (less than 3 months). Furthermore, this study was conducted on ischemic CVA patients and the results may not be generalized to those with hemorrhagic CVA. We could not assess patients in the long run (25 - 30 sessions) to evaluate long-term efficacy of treatment. A follow up at 3 or 6 months could not be done due to difficulty in accessing patients. Finally, other neurophysiological tests (Electromyography (EMG), Electroencephalography (EEG), Functional Magnetic Resonance Imaging (fMRI), Transcranial Magnetic Stimulation (TMS), Positron emission tomography (PET)) could not be done due to limited equipment.

5.2. Strong Points of the Study

This research was conducted in a new field inspired by previous basic research results, and tries to establish a link between theoretical research and applied clinical research. We used a new approach in the treatment of patients with ischemic stroke, and published an article with this approach.

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Authors' Contributions

Monireh Motaqhey, Ali Ghanjal, and Reza Mastri Farahani participated in all stages of the research (study design, data analysis, literature review, preparation, and editing the manuscript). Mojdeh Ghabaee contributed in the clinical examination and referral of the patients for participating in the study. Gholamreza Kaka, Mohsen Noroziyan, and Fatemeh Fadaee Fathabadi participated in consulting.

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