

Original Article

# Predicting the efficacy of early non-invasive neuromuscular electrical stimulation in post-stroke upper extremity motor recovery and their correlation with blood biomarkers

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## ABSTRACT

**Objectives:** Non-invasive neuromuscular electrical stimulation (NMES) enhances cortical excitability and muscle protein synthesis. Serum neurofilament light chain (NFL) and matrix metalloproteinase-9 (MMP-9) levels are negatively correlated with the modified rankin score (mRS) and predict poor outcomes 3 months following a stroke. This study aimed to assess the effect of non-invasive early NMES on upper limb paresis and serum NFL and MMP-9 levels at 3-month follow-up.

**Materials and Methods:** This quasi-experimental trial was conducted in the inpatient department from February 2021 to January 2023, included 54 first-ever ischemic stroke patients with stroke severity 2–4 on mRS, divided into intervention and control groups. The intervention group received non-invasive early NMES plus standard rehabilitation, and the control group received standard rehabilitation only. Primary outcomes included upper extremity Fugl–Meyer assessment (FMA) sub-sections A, A-D, and mRS. Secondary outcomes were serum NFL and MMP-9 levels, which were assessed at baseline and a 3-month follow-up.

**Results:** Significant differences were observed between intervention and control groups at 3 months follow-up in mRS, 1 (1–2) and 3 (2–3)  $P < 0.01$ , Fugl–Meyer assessment-upper extremity (FMA-UE)- A 29 (19–32) and 15 (11–19),  $P < 0.01$ , FMA-upper extremity sub-scale A-D-FU 53 (33–60) and 34 (25–49)  $P = 0.02$ . There was no significant difference in biomarker levels between groups at follow-up.

**Conclusion:** Early non-invasive NMES demonstrated superior efficacy in improving motor outcomes compared to standard rehabilitation, but its association with blood biomarkers needs further exploration.

**Keywords:** Acute stroke, Biomarkers, Early rehabilitation, Hand function, Neuromuscular electrical stimulation

## INTRODUCTION

Stroke is the second leading cause of death and disability.<sup>[1]</sup> Rehabilitation is the key to regaining lost motor function; early intervention increases the favorable outcome and decreases the secondary complications.<sup>[2]</sup> Neuromuscular electrical stimulation (NMES) is one of the major therapeutic approaches for restoring lost motor function of the upper and lower extremities.<sup>[3]</sup>

Non-invasive NMES evokes cortical excitability similar to voluntary muscle contractions.<sup>[4]</sup> It influences phosphorylation of mammalian target of rapamycin complex 1 (mTORC1) and ribosomal protein S6 kinase 1 (S6K1), enhancing muscle protein synthesis.<sup>[5]</sup> In addition, it promotes acetylcholine receptor

clustering, nerve terminal differentiation, and neuromuscular junction formation.<sup>[6]</sup> Combined with voluntary contractions, it increases oxygen consumption, blood lactate concentration, and respiratory gas exchange ratio.<sup>[7]</sup>

The neurofilament light chain (NFL) maintains axoplasmic transport and nerve elasticity. After the stroke, serum NFL levels rise within 12 h, peak at day 7, and remain elevated for 3 months.<sup>[8]</sup> It correlates negatively with the Scandinavian stroke scale and positively with the modified Rankin score (mRS), predicting functional recovery at 3 months.<sup>[9,10]</sup>

Matrix metalloproteinase-9 (MMP-9) plays a role in tissue remodeling. After the stroke, it affects the blood–brain

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barrier, the basal lamina. Post-stroke, MMP-9 levels are elevated compared to healthy controls, correlating with poor outcomes, mortality, and hemorrhagic transformation.<sup>[11,12]</sup>

### Study objectives

The study aimed to evaluate the effect of early NMES on upper limb paresis in patients with acute ischemic stroke and its effect on blood biomarkers.

The primary objective was to evaluate the early NMES effect on shoulder and hand function after 3 months of follow-up. The secondary objective was to assess its effect on serum NFL and MMP-9 at 3-month follow-up.

## MATERIALS AND METHODS

This quasi-experimental trial was conducted in the inpatient department from February 2021 to January 2023. Participants were recruited using a convenience sampling method. Although randomization was not done in this study, efforts were made to minimize the selection bias by matching controls for age and sex, and by recruiting both groups from the same population base. The group allocation was done by a physician who was not involved in the study. Patients were unaware of the group allocation. Ethical approval was obtained, and informed consent was taken from eligible stroke patients.

### Sample size calculation

The sample size was estimated a priori using G-power software version 3.1.9.4. Accepting a 5% alpha risk ( $\alpha = 0.05$ ), a 20% beta risk ( $\beta = 0.2$ ), and an expected effect size (Cohen's *d*) of 0.78, the required sample size was 27 participants per group (total  $n = 54$ ). Accordingly, 54 participants who completed the follow-up assessments were included in the final analysis.

### Participants

Inclusion criteria: First-ever ischemic stroke, age  $\geq 18$ , mRS 2–4, and ability to follow verbal commands. Exclusion criteria: Hemorrhagic/recurrent stroke, neurodegenerative diseases, implanted electronic devices, epilepsy, respiratory insufficiency, pregnancy, peripheral neuropathies, skin ulcers at electrode sites, or inability to follow commands.

### Intervention

Patients were seated with arms resting on a pillow, elbows flexed at 90° in pronation. The skin was cleaned with 2% ethyl alcohol to minimize impedance.

## Electrode placement and NMES applications

### Shoulder

Four carbonized electrodes, an active electrode placed on the supraspinatus and posterior deltoid, and an indifferent electrode on the middle and anterior deltoid.

### Elbow

Two electrodes, one on the extensor muscles at the lateral epicondyle, and another 10 cm above the epicondyle at the radial nerve point for wrist extension. Electrodes were secured with Velcro or hypoallergenic tape. A 33 Hz frequency current (NMS 498, Johari Digital), biphasic rectangular pulses (350  $\mu$ s), with intensity tolerable and able to produce purposeful contraction, with 10 s on and 10 s off cycle.

The intervention was given for 30 min every day, for 8 consecutive days, based on the availability of the patients in acute care. After the acute period, most of the patients were discharged, and they received rehabilitation services at home or a nearby health facility. Standard rehabilitation was given to both groups, which included active or passive mobilization of limbs, optimal limb positioning, repeated task-specific training, prevention of secondary complications, and chest physiotherapy. Post-discharge, both groups were guided and monitored telephonically, and video demonstrations and printouts of exercise protocols were provided. Adherence to the study protocol was monitored through telephonic and in-person visits at 1-month and 3-month follow-up.

### Assessment

The primary outcome measures were (a) upper extremity sub-section of Fugl-Meyer assessment (FMA),<sup>[13]</sup> (A and B), and upper extremity sub-section of FMA, sub-scale A-D (English Version). The assessment was conducted at 2 time points: First, within 10 days of stroke onset, and 2<sup>nd</sup>, 3 months after the stroke, during follow-up, by a postgraduate physiotherapist who was aware of the group allocation.

Our secondary outcome measures were NFL and MMP-9 at baseline and 3 months in both groups. Blood sampling: Venous blood was taken within 10 days of the ischemic stroke and after 3 months, during the follow-up in the hospital. For the serum NFL, blood was collected in a red tube, then centrifuged at 2500 rpm for 10 min, and the serum was collected. For MMP-9, venous blood was taken in ethylenediaminetetraacetic acid tubes, kept for 30 min and then centrifuged for 10 min at 2500 rpm. The aliquots were immediately stored at  $-80$  °C until the blood analysis by enzyme-linked immunosorbent assay. The Elabscience kit was used for the serum NFL and MMP-9 assessment, and the protocol provided by the manufacturer was followed for biomarker estimation.

## Statistics

The statistical analysis was performed using International Business Machines (IBM) Statistical Package for the Social Sciences software for Windows version 24. The normality of continuous variables was assessed using the Shapiro–Wilk test. As none of the continuous variables followed a normal distribution, these data were summarized as median (interquartile range) and analyzed using non-parametric tests. The Mann–Whitney U test was used for between-group comparisons, while the Wilcoxon signed-rank test was applied for within-group analyses. For comparisons across more than two groups, the Kruskal–Wallis test was used. Categorical variables were expressed as counts and percentages and compared using the Chi-square test or Fisher’s exact test, as appropriate. A  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 54 stroke patients meeting the inclusion and exclusion criteria were selected after screening, with

27 patients in each group. The study flow diagram [Figure 1] illustrates participant selection and recruitment. Baseline demographics and clinical characteristics were comparable between groups, with no significant differences [Table 1].

## Outcomes

### Primary outcomes

Within-group analysis showed significant improvement in mRS, FMA-upper extremity sub-scale A (UE-A), and FMA-UE-A-D from baseline to follow-up in both groups, with greater improvement in the intervention group [Table 2]. The inter-group comparison revealed significant improvement in mRS ( $P = 0.00$ ), FMA-UE-A ( $P = 0.00$ ), and FMA-UE A-D ( $P = 0.02$ ) in the intervention group, indicating the intervention’s positive effect on the shoulder [Supplementary Table 1].

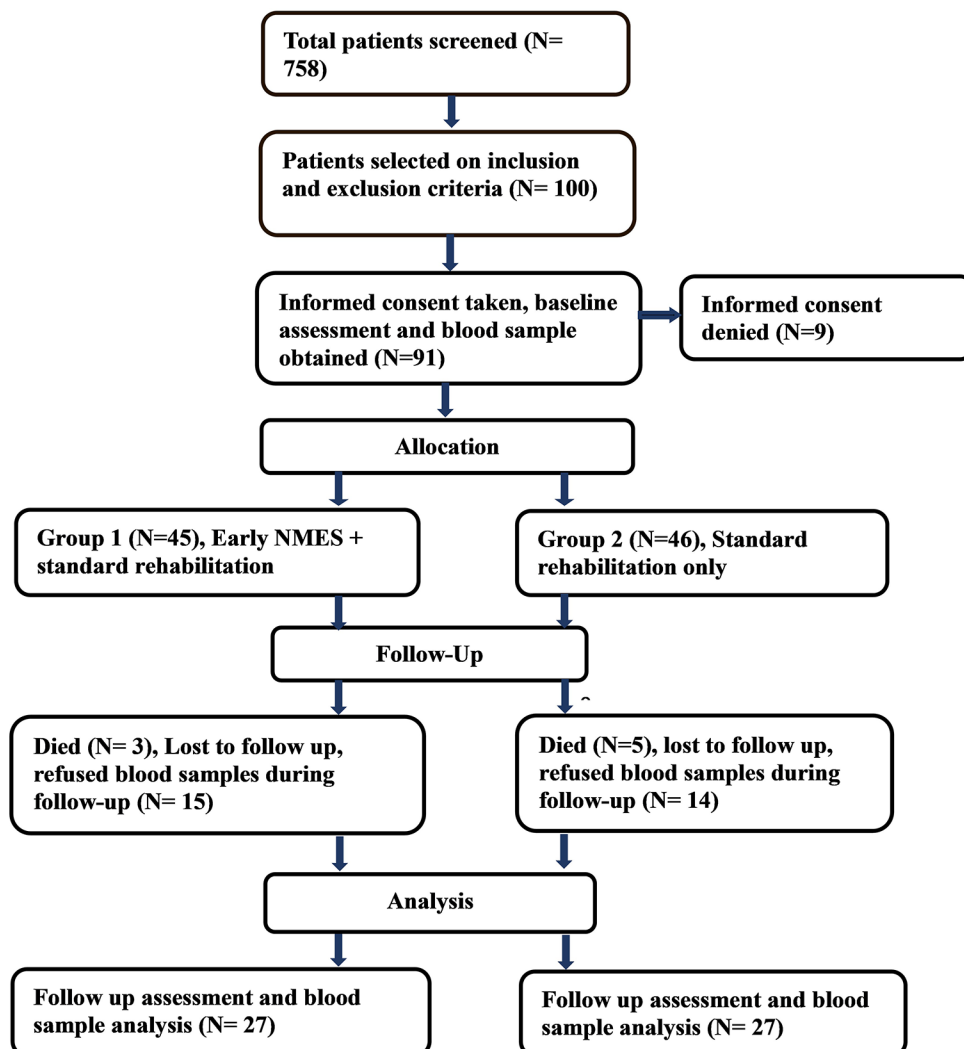


Figure 1: Study flow diagram. NMES: Neuromuscular electrical stimulation.

**Secondary outcomes**

Within-group analysis [Supplementary Table 2] showed a significant improvement in serum NFL and MMP-9 in both intervention and control groups.

Between-group analysis [Supplementary Table 3] showed non-significant differences between the groups; the median score of serum NFL in the intervention group was lower compared to the control group, which shows the effect of the intervention on biomarker levels.

**Table 1:** Baseline characteristics and baseline scores of participants of the intervention and control groups.

Demographic characteristics			
Variables	Group 1 (n=27)	Group 2 (n=27)	P-value
Age	60 (48–70)	55 (45–62)	0.064
Gender: Male/Female	14/13	19/8	N/A
Hand dominance: Right/Left	27/0	27/0	N/A
Onset of stroke (Days)	6 (5–7)	7 (6–7)	0.702
Clinical characteristics			
Side affected: Left/Right	13/14	11/16	N/A
Radiological features			
Anterior circulation	20	24	0.474
Posterior circulation	7	3	0.293
Outcome variables			
mRS	4 (3–4)	4 (3–4)	0.459
FMA-UE-A	15 (4–19)	4 (4–11)	0.118
FMA-UE-A-D	17 (4–29)	11 (4–27)	0.339
NFL (pg/mL)	94.18 (84.64, 99.18)	94.91 (93.36, 98.35)	0.634
MMP-9 (ng/mL)	22.4 (7.88, 31.17)	16.36 (6.6, 30.97)	0.762

NMES: Neuromuscular electrical stimulation, mRS: Modified Rankin scale, FMA-UE-A: Fugl–Meyer assessment upper extremity sub-scale A, FMA-UE A-D: Fugl–Meyer assessment upper extremity sub-scale A to D, NFL: Neurofilament light chain, MMP-9: Matrix metalloproteinase-9, N/A: Not applicable, P-value Significant at: P-value <0.05

**Hemiparetic side comparison**

The FMA-UE-A, FMA-UE-A-D, and serum NFL did not differ significantly between groups based on the hemiparetic side. However, there was a significant difference in MMP-9 levels in the intervention group (P = 0.04). However, the overall result suggests no substantial difference between the hemiparetic sides based on intervention [Supplementary Table 4].

**Regression analysis**

Regression analysis examined the impact of known hypertension, pre-stroke exercise, and risk factors (smoking and dyslipidemia) on outcomes. The analysis showed a positive but statistically non-significant effect of pre-stroke exercise on upper limb motor outcomes (FMA-UE A: B = 2.97, P = 0.12; FMA-UE A-D: B = 9.01, P = 0.14), with the latter showing a relatively larger effect size (R<sup>2</sup> = 0.21). Hypertension and risk factors were not significantly associated with motor outcomes (P > 0.40). The biomarkers (NFL and MMP-9) showed no significant effect, although hypertension showed a moderate negative trend on NFL (B = -10.96, P = 0.18). Overall, the regression analysis shows no strong associations [Supplementary Table 5].

**DISCUSSION**

This study is the first of its kind to evaluate the effects of early NMES on blood biomarkers and upper limb function 3 months post-stroke. The findings indicate that NMES applied within 10 days of an acute stroke has a positive influence on hand function compared to standard rehabilitation alone. Significant differences in mRS, FMA-UE-A, and FMA-UE A-D scores were observed in favor of the intervention group compared to the control group, which received only standard rehabilitation. These results align with earlier studies demonstrating the benefits of NMES in improving functional outcomes.<sup>[14,15]</sup>

NMES combined with standard rehabilitation proved more effective than standard rehabilitation alone. Conventional rehabilitation primarily includes body positioning, active

**Table 2:** Within-group analysis of primary outcomes.

Outcome Measures	Group 1 (n=27) (median, IQR)			Group 2 (n=27) (median, IQR)		
	BL	FU	P-value	BL	FU	P-value
mRS	4 (3–4)	1 (1–2)	<0.01	4 (3–4)	3 (2-3)	<0.01
FMA-UE-A	15 (4–19)	29 (19–32)	<0.01	4 (4–11)	15 (11–19)	<0.01
FMA-UE-A-D	17 (4–29)	53 (33–60)	<0.01	11 (4–27)	34 (25–49)	<0.01

Group 1: Intervention group, Group 2: Control group, BL: Baseline, FU: Follow-up, mRS: Modified rankin scale, FMA UE-A: Fugl–Meyer assessment upper extremity sub-scale A, FMA UE A-D: Fugl–meyer assessment upper extremity sub-scale A to D, IQR: Interquartile range, P-value Significant at: P-value <0.05

and passive movements, and proprioceptive neuromuscular facilitation. The observed improvements may result from increased presynaptic inhibition of muscle spindle reflexes, alterations in long-loop biofeedback control, and enhanced motor unit recruitment.<sup>[9]</sup> In addition, intramuscular electrical stimulation offers more precise targeting of specific muscles, further enhancing motor relearning.

Our study also demonstrated that NMES combined with active-assisted exercise improves motor control and promotes anabolic protein production. The previous research supports that NMES, when applied with voluntary contraction at a low ventilatory threshold, enhances outcomes.<sup>[16]</sup> A single session of NMES can increase phosphorylation of mTORC1 and S6K1, facilitating skeletal muscle protein synthesis and cell growth. Since stroke patients often exhibit reduced expression of mTOR and 4E-BP1, key regulators of protein phosphorylation, NMES may restore these pathways, thereby contributing to motor recovery.<sup>[6]</sup>

Despite these promising functional outcomes, statistical analysis revealed no significant differences in serum NFL and MMP-9 levels between the groups, questioning a direct relationship between NMES and these biomarkers. However, correlation analysis indicated a weak but a positive relationship between functional outcomes and MMP-9 levels in the intervention group, suggesting that additional biological or physiological factors may influence biomarker dynamics and recovery processes.

Peak concentrations of serum NFL and MMP-9 were observed around day seven, followed by a gradual decline over 3 months, consistent with previous studies.<sup>[17-19]</sup> NMES was applied at a lower frequency of biphasic current to stimulate slow-twitch muscle fibers, which contribute to sustained muscle activity. Mechanistically, NMES enhances acetylcholine receptor clustering at the neuromuscular junction by promoting postsynaptic receptor formation, which is regulated by activity-dependent proteins such as agrin and laminin.<sup>[5,20]</sup>

Serum NFL and MMP-9 levels have been shown to inversely correlate with cognitive function and the duration of physical activity before and after acute stroke.<sup>[21,22]</sup> MMP-9, a key mediator of blood-brain barrier disruption after stroke, exhibits reduced expression with pre-stroke exercise conditioning. Such conditioning improves blood-brain barrier integrity, reduces inflammatory damage, and limits neurological deficits by inhibiting MMP-9 through tissue inhibitors such as TIMP-1.<sup>[23-28]</sup> Furthermore, varying physical activity intensities (mild to high) have been associated with a 12–43% reduction in cognitive decline,<sup>[23]</sup> while improved white matter integrity over time corresponds to decreased NFL levels.<sup>[24]</sup> A single episode of exercise can also reduce NFL by rerouting the kynurenine pathway of tryptophan toward neuroprotective outcomes.<sup>[29]</sup>

A recent meta-analysis (2022) reported that NMES is more effective in subacute than chronic stroke cases, particularly for the upper limb. The benefits are more pronounced in severe paresis compared to moderate cases. However, improvements were more evident in activities of daily living scores than in direct motor function, likely because post-stroke recovery often reflects behavioral compensation rather than true physiological restoration.<sup>[30]</sup> This may explain why our study observed significant functional improvements (FMA-UE-A and FMA-UE-A-D) but no corresponding biomarker changes. While NMES may activate motor pathways, it might not sufficiently influence systemic biomarker levels within the given timeframe.

Despite demonstrated benefits in motor relearning, the lack of high-quality studies limits the generalizability of NMES-related findings.<sup>[11]</sup> Moreover, although several biomarkers have been proposed for post-stroke motor recovery, they remain underutilized in clinical rehabilitation protocols.<sup>[12]</sup>

Stroke recovery outcomes also vary with hemispheric involvement. Patients with right-hemisphere strokes tend to have greater awareness of their deficits and are more prone to depression due to higher rehabilitation demands and slower progress. Conversely, left-hemisphere stroke patients may exhibit impulsivity and memory deficits, often resulting in less favorable outcomes.<sup>[31]</sup> Our findings are consistent with these patterns and highlight the importance of tailoring rehabilitation strategies based on hemispheric involvement and individual patient characteristics.

### Limitation

Several limitations of our study should be acknowledged. First, the small sample size may limit the generalizability of the findings. Second, the NMES intervention was only given for 8 days, and home care settings may not be sufficient to generalize the results; the overall intervention duration may be insufficient to elicit clinically significant biomarker changes. The selection of the intervention session was based on the availability of the patient in the acute care setting. Third, variability in patient characteristics, such as pre-stroke physical activity levels and cognitive function, may have influenced outcomes. Fourth, the heterogeneity in stroke type (e.g., infarct size and location) was not accounted for, which could affect both functional and biochemical recovery. Finally, the absence of randomization in the quasi-experimental trial has the possibility of selection bias. Although efforts were made to match cases with controls and standardize the inclusion criteria, unmeasured cofounders may have influenced the results.

### CONCLUSION

Non-invasive early NMES, when applied within 10 days post-stroke, significantly improves hand function and

motor recovery, making it a valuable adjunct to standard rehabilitation. It may not directly influence biomarker levels, though the functional outcomes improved significantly, serum NFL and MMP-9 levels did not show strong inter-group differences, suggesting that NMES primarily enhances recovery through neuromuscular adaptations rather than direct biomarker modulation. Regular physical activity before a stroke may positively influence blood-brain barrier integrity, inflammation control, and axonal repair, reinforcing the importance of encouraging an active lifestyle for stroke prevention and recovery. NMES works best when combined with active-assisted exercise: The integration of NMES with voluntary movements enhances motor control, muscle recruitment, and synaptic plasticity, leading to better rehabilitation outcomes. Given the influence of physical activity on biomarker expression, further randomized controlled trials with optimized NMES protocols are needed to explore these relationships and develop personalized, biomarker-driven rehabilitation strategies.

**Ethical approval:** The research/study was approved by the Institutional Review Board at the Institute of Medical Sciences, Banaras Hindu University, approval number 2021/EC/2879, dated 31st August 2021.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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