

## Original Research Article

# Effect of combination of botulinum toxin and electromyographic biofeedback therapy on post-stroke patients with lower limb muscle spasticity

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### Abstract

**Purpose:** To investigate the clinical effect of combined use of botulinum toxin type A and electromyographic biofeedback therapy (EMGBFT) on post-stroke patients with lower limb muscle spasticity.

**Methods:** The data of 91 post-stroke patients with lower limb muscle spasticity who were admitted to Shanghai Seventh People's Hospital (January 2020 -January 2021) were retrospectively analyzed, and they were divided into control group (COG, n = 45) and study group (STG, n = 46) based on the treatments given. All patients received conventional rehabilitation and training. Patients in COG were treated with EMGBFT, whereas those in STG received botulinum toxin type A as well as EMGBFT. The parameters determined in the two groups were degree of spasticity, lower limb motor function [3m-Timed Up and Go (3m - TUG) and 10m - Walk Test (10 m - WT)], active range of motion (AROM) of ankle dorsiflexion, ability of daily living (based on Barthel Index, BI), and adverse reactions before and after treatment.

**Results:** The effectiveness of the treatments on spasticity was higher in STG than in COG ( $p < 0.05$ ). After treatment, the times taken for 3m-TUG and 10m-WT were significantly shorter in STG than in COG ( $p < 0.05$ ). The AROM of patients in both groups was expanded, but the expansion was significantly greater in STG than in COG ( $p < 0.05$ ).

**Conclusion:** Combined therapy using botulinum toxin and EMGBFT effectively relieved lower limb muscle spasticity of post-stroke patients, and also improved their lower limb motion function and daily living ability. Thus, the combined therapy provided better management of lower limb spasticity. However, further clinical trials are required prior to its adoption in clinical practice.

**Keywords:** Stroke, Lower limb muscle spasticity, Botulinum toxin, Electromyographic biofeedback therapy (EMGBFT)

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## INTRODUCTION

Post-stroke spasticity is an important factor that affects recovery of motor function in patients,

especially hemiplegic lower limb spasticity which easily leads to *pes varus* and foot drop, with adverse effects on standing and walking [1-3]. In clinical practice, spasticity is alleviated with oral

antispasmodics, local injection of botulinum toxin type A, and electromyographic biofeedback therapy (EMGBFT). Although botulinum toxin type A and EMDBFT are widely used in clinics, no studies have been carried out so far on the effect of their combined use.

Botulinum toxin type A is widely used in the clinic due to its limited adverse effects and low degree of complications. However, it is expensive, and cannot be re-injected within three months. Electromyographic biofeedback therapy (EMGBFT) is a modern physical rehabilitation technology which has been used in clinics. It applies electrical stimulation with low-frequency pulses of a certain intensity to make the muscle contract or relax. It enhances training, improves muscle function, and helps patients to reconstruct and recover normal motor function of the muscles. However, the application of EMGBFT alone has obvious limitations: better effects may be achieved when it is used in combination with other therapies [4-6].

For this reason, this study was carried out to determine the clinical effect of combining botulinum toxin type A with EMGBFT in treating post-stroke patients with lower limb muscle spasticity.

## METHODS

### Patients

The data of 91 post-stroke patients with lower limb muscle spasticity who were admitted to *Shanghai Seventh People's Hospital* (January 2020-January 2021), were retrospectively analyzed, and they were divided into control group (COG, n = 45) and study group (STG, n = 46) according to the type of treatment applied. This study was approved by the ethics committee of *Shanghai Seventh People's Hospital* (approval no. 20191150), in line with the criteria of the Declaration of Helsinki [7]. The patients or their family members signed informed consent indicating their willingness to participate in the study.

### Inclusion criteria

Patients in the following categories were enrolled in this study: patients who were diagnosed with stroke after brain CT or MRI and other examinations, those who had the disease for the first time, patients who presented lower limb spasticity and met the diagnosis criteria for lower limb spasticity, and those who did not have cognitive and communication disorders.

### Exclusion criteria

Patients in the following groups were excluded: patients with severe organic diseases or malignant tumors, those who were allergic to botulinum toxin type A, patients who were administered neuromuscular conduction-inhibiting drugs e.g., aminoglycoside in the previous one week, patients with disease duration of more than one year, those with joint deformity, and patients with low compliance or those who withdrew halfway during the study.

### Treatments

Patients in both groups received conventional medical treatments (anti-infection, anti-coagulation, rehydration, control of blood pressure and nourishing of the central nervous system), as well as limb rehabilitation training (improving range of motion, transfer exercises, balance exercises, weight loading exercises, stretching exercises, and ability of daily living exercises) [8-10].

For patients in COG, the multifunctional electromyographic biofeedback apparatus (model: AM800; Denmark) was used for neural rehabilitation treatment. The patients were informed about the therapeutic principle associated with the use of this apparatus, training methods, and uses of the apparatus. The patients were asked to stay focused and move the affected limbs in accordance with instructions. In the sitting or lying position, the affected limbs were degreased with alcohol, and electrodes were attached to the superficial skin of the tibialis anterior muscle of the affected limb. The settings of the apparatus were as follows: automatic mode, square wave, wave width of 200  $\mu$ s, frequency of 35 - 50 Hz, stimulation for 5-6 sec, interval of 10-15 sec, and self-triggered stimulation.

The intensity was gradually adjusted to a level that the patients could tolerate. The patients were instructed to make ankle dorsiflexion and pay attention to the electromyographic signal on the apparatus. When the patients were given the instruction, they actively contracted the relevant muscle groups, and the electrical stimulation was applied once the threshold was attained so as to cause contraction of the target muscle. As the patients' limb function improved, the threshold of the apparatus was increased to gradually enhance the strength of muscle contraction. The rehabilitation was performed once daily, each time for 20 - 30 min, and six times per week. The treatment cycle was 4 weeks.

For patients in STG, botulinum toxin type A (specification: 100 U/bottle; Lanzhou Institute of Biological Products Co. Ltd; NMPA approval no. S10970037) was injected in line with the guidance for treating adult muscle spasticity with botulinum toxin in China [11]. The muscles to be injected were selected according to the spasticity status of patients, and the injection dose was decided based on the degree of spasticity and muscle volume.

Taking the muscle belly as the center and according to the degree of muscle contraction, 4 - 6 injection points were selected for each muscle, and 1 - 5 muscles were injected each time. Botulinum toxin type A (100 U) was dissolved in 2 mL of normal saline, and 25 - 75 U was injected at each point after routine skin disinfection. The total dose for each patient did not exceed 400 U. The injected part was maintained dry 24 h after injection, and rehabilitation training and EMGBFT were not allowed. The other treatments were same as in COG.

## Evaluation of clinical indices/parameters

### Patients' profiles

The age, duration of disease, gender, stroke type, affected side, Brunnstrom staging, history of hypertension, diabetes, smoking and drinking, and other information on patients in both groups were recorded.

### Degrees of spasticity

Before and after treatment, the degree of effectiveness of treatment of lower limb spasticity in patients was evaluated with the Modified Ashworth Scale (MAS). On a scale of 0-5 levels, level 0 indicated *cured* status; decline of two or more levels indicated that the treatment was *markedly effective*, a decline of one level indicated *effective* treatment, while a situation where there was no change in MAS or where there was actually an increase in MAS level, indicated that the treatment was *ineffective*. Total treatment effectiveness (TE) was calculated as shown in Eq 1:

$$TE = \frac{(C + ME + E)}{T} \dots\dots\dots (1)$$

where *TE* = total effectiveness, *C* = number of cured cases, *ME* = number of markedly effective cases, *E* = number of effective cases, and *T* = total number of cases.

## Lower limb motor function

### 3m - Timed Up and Go (3m - TUG) test

The times that a patient spent getting up from a chair, walking 3 meters, turning around, walking back to the chair and sitting down, were recorded. Each test was conducted twice to obtain a mean value, and the interval between the two tests was 3 min.

### 10 m - Walk Test (10 m - WT)

Fourteen meters of pathway on a flat ground were cleared and marked with two points (at 2 m and 12 m). The time that a patient spent to walk from the 2-m point to the 12-m point was recorded. The test was conducted twice to obtain a mean value. The interval between the two tests was 3 min.

### Active range of motion (AROM) of ankle dorsiflexion

The AROM was measured with a special protractor for rehabilitation in line with the *Evaluation and Assessment for Rehabilitation Therapy*.

### Ability of daily living

The ability of patients to perform activities of daily living was evaluated with the Barthel indexes, and the maximum score was 100 points, with higher scores indicating better ability of daily living.

### Adverse reactions

The adverse reactions in patients during treatment were recorded.

### Statistical analysis

Between-group differences in data were calculated with SPSS 22.0, while Graphics/image analysis was carried out using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Enumeration data and measurement data are expressed as numbers and percentages [n (%)] and mean ± SD, respectively. Inter-group differences were determined with  $\chi^2$  test and *t*-test, respectively. Differences were considered statistically significant at  $p < 0.05$ .

## RESULTS

### General information on patients

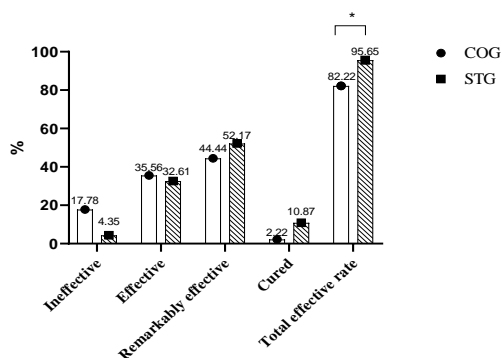
No statistical differences were observed in patients' general information between the two groups. These data are shown in Table 1.

**Table 1:** Patients' general information

Index	COG (n = 45)	STG (n = 46)	t/ $\chi^2$	P-value
Age (years)	51.71±8.36	50.96±8.14	0.4336	0.6656
Duration of disease (days)	57.02±18.59	56.54±18.32	0.1241	0.9016
Male/Female	28/17	28/18		
<b>Stroke types</b>			0.0890	0.756
Cerebral infarction	27 (60)	29 (63.04)		
Cerebral hemorrhage	18 (40)	17 (36.96)		
<b>Affected side</b>			0.0060	0.938
Left lower limb	16 (35.56)	16 (34.78)		
Right lower limb	29 (64.4)	30 (65.22)		
<b>Brunnstrom staging</b>			0.1047	0.746
I	14 (31.11)	13 (28.26)		
II	20 (44.44)	22 (47.83)		
III	11 (24.44)	11 (23.91)		
History of hypertension	23 (51.11)	21 (45.65)	0.2714	0.602
History of diabetes	18 (40)	16 (56.52)	0.2646	0.607
Smoking history	23 (57.5)	20 (43.48)	0.5317	0.466
Drinking history	28 (62.22)	31 (67.39)	0.2666	0.606

**Degree of spasticity**

As shown in Figure 1, total treatment effectiveness on spasticity was higher in STG than in COG ( $p < 0.05$ ).



**Figure 1:** Comparison of degree of spasticity (%). \* $P = 0.041$ , significant difference between the two groups ( $\chi^2 = 4.1945$ )

**Lower limb motor function**

The times taken for 3 m – TUG and 10 m – WT by patients after treatment were significantly shorter in STG than in COG ( $p < 0.05$ ). These results are shown in Figure 2 and Figure 3.

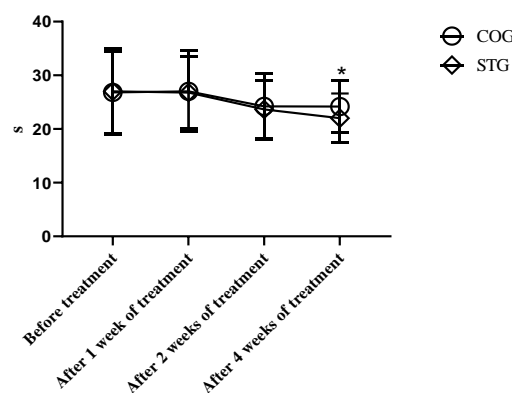
**AROM results**

After treatment, AROM was expanded in patients in both groups, but the expansion was greater in STG than in COG ( $p < 0.05$ ; Table 2).

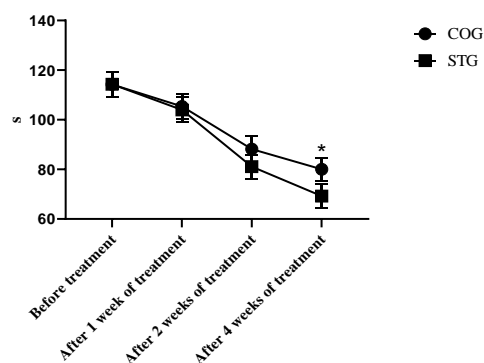
**Ability of daily living**

After treatment, there was improvement in ability of daily living of patients in both groups, but

scores on BI indexes were higher in STG than in COG ( $p < 0.05$ ).



**Figure 2:** Time taken for 3 m – TUG in each group (mean ± SD). \* $P < 0.05$ , time taken for 3 m – TUG in STG after 4 weeks of treatment, vs time taken for 3m-TUG in COG after 4 weeks of treatment



**Figure 3:** Time taken for 10 m - WT in each group (mean ± SD). \* $P < 0.05$ , time taken for 10 m - WT in STG after 4 weeks of treatment, vs time taken for 10 m - WT in COG after 4 weeks of treatment

**Table 2:** Comparison of AROM values (mean  $\pm$  SD)

Group	n	Before treatment	After treatment
COG	45	1.74 $\pm$ 1.18	8.24 $\pm$ 2.62
STG	46	1.83 $\pm$ 1.21	12.61 $\pm$ 3.05
<i>t</i>			7.3245
<i>P</i> -value			< 0.001

**Table 3:** Comparison of scores on BI indexes ( $\bar{x} \pm s$ )

Group	n	Before treatment	After treatment
COG	45	40.16 $\pm$ 6.62	70.20 $\pm$ 10.11
STG	46	40.25 $\pm$ 6.77	75.48 $\pm$ 10.26
<i>t</i>			2.4726
<i>P</i> -value			0.0153

### Adverse reactions

No obvious adverse drug reactions occurred in any of the patients in the two groups during the treatment.

## DISCUSSION

Spasticity is a relatively common complication after stroke. It occurs because stroke causes motor neuronal damage in patients, resulting in loss of regulation of stretch reflex in advanced central nervous system [12]. It has been reported in clinical studies that 60 % of stroke patients experience muscle spasticity at six months of onset, and that the level of disability in stroke patients with spasticity is higher than that in patients without spasticity [13]. Although several scholars worldwide have offered recommendations on the treatment of the disease, at present, there is no completely satisfactory and effective medical strategy for this condition in clinical practice. Thus, spasticity has become a problem in rehabilitation medicine.

Treating post-stroke lower extremity muscle spasticity mainly involves intrinsic recovery (the process of recovery of neurological control on the affected side) and adaptive therapy (the process of learning to use the healthy side). The two processes are conducted simultaneously, and they are inextricably linked to changes in the central nervous system (CNS) [14-16]. The EMGBFT, a promising and new modality adopted in recent years to treat post-stroke spasticity, is a rehabilitation technique that emphasizes subjective motility of the patients, and it incorporates physics, physiology and control. Usually, the patients are guided to do the autonomous training by recording and amplifying the weak electrical signal generated as the patient autonomously contracts the muscle, and then converting the signal into a perceptible auditive signal through associated devices.

However, its use alone for improving muscle spasticity in patients after stroke is still associated with some limitations. Therefore, in the clinics, it is used mostly in combination with acupuncture, exercise therapy, traditional Chinese medicine, and other methods.

Botulinum toxin, a neurotoxin protein produced during the propagation of botulinum and a highly selective neuro-inhibitor of macromolecular protein, is often used in clinical practice because of its high stability, strong toxicity, and ease of purification and production [17-19]. At present, not much has been reported on the combined use of botulinum toxin type A and EMGBFT in treating lower limb muscle spasticity after stroke, hence the present work.

In this study, total treatment effectiveness for spasticity was significantly higher in STG than in COG, which is consistent with a previous report [20]. Compared with COG, STG took shorter times for 3 m - TUG and 10 m - WT, greater expansion of AROM, better ability of daily living, and higher BI index. These results indicate that, compared with the use of EMGBFT alone, combined use of botulinum toxin type A with EMGBFT produced remarkably better effects on post-stroke lower limb muscle spasticity, and worked better in alleviating the degree of spasticity and improvement of lower limb motor function and ability of daily living in patients. Moreover, no obvious adverse drug reactions occurred in all patients during the treatment, implying that the combined therapy was safe.

The main reasons for the absence of adverse effects may be due to the fact that botulinum toxin type A selectively binds to glycoproteins at the nerve ending and hydrolyzes the zinc-dependent synaptic proteins of the presynaptic membrane, thereby indirectly inhibiting the stimulatory release and spontaneous quantal release of acetylcholine at the synapse: it blocks the conduction of nerve impulses, thereby relaxing the muscles. In addition, the combined use of botulinum toxin type A and EMGBFT produced synergistic and additive effects on post-stroke lower limb muscle spasticity due to the integration of body internal nerve and external stimulation. Botulinum toxin type A inhibited the release of neurotransmitters and promoted muscle relaxation through neuronal conduction, while EMGBFT enabled patients to fully feel their muscle contraction and improved their ability to actively contract their muscles.

### Limitations of this study

Firstly, the treatment cycle used was only four

weeks. Thus, the long-term mechanism of action of botulinum toxin type A was not elucidated. Secondly, this was a single-center, small-sample research, and investigation of the long-term mechanism of action was needed. Therefore, the treatment regimen for post-stroke lower limb muscle spasticity should be comprehensively optimized with more multi-center and large-sample studies.

## CONCLUSION

The combined therapy with botulinum toxin and EMGBFT significantly mitigates lower limb muscle spasticity in post-stroke patients, improves their lower limb motion function and ability of daily living, and produces higher treatment efficacy than the use of EMGBFT alone. However, further clinical trials are required to validate these findings.

## DECLARATIONS

### Acknowledgements

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### Funding

None provided.

### Ethical approval

None provided.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Honglin Wang and Changsheng Yu conceived and designed the study, and drafted the manuscript. Honglin Wang, Xueming Wang and Changsheng Yu collected, analyzed and interpreted the

experimental data. Xueming Wang and Changsheng Yu revised the manuscript for important intellectual contents. All authors read and approved the final manuscript.

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