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REVIEW

Latest Advances in the Treatment of Post-stroke Limb Spasm with Botulinum Neurotoxin

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ABSTRACT

Objective: To describe the latest progress in the use of botulinum neurotoxin for post-stroke limb spasm. Methods: This paper looks up the relevant research literatures in recent years in PubMed, Web of Science, Springer, Ovid, CNKI, WanFang databases and summarizes them. Results: The latest progress in the use of botulinum neurotoxin for post-stroke limb spasm was studied from the following aspects: the action mechanism of botulinum neurotoxin; efficacy evaluation; injection dose; target muscle selection; guiding technology; combination therapy. Conclusion: Botulinum neurotoxin is the first-line treatment for post-stroke limb spasm. We need to make continuous improvement and progress from the treatment period, injection dose, target muscle selection, guiding technology and efficacy evaluation to improve the quality of life of the majority of post-stroke survivors in China.

1. Introduction

Stroke is the leading cause of upper and lower limb spasm (the ratios are respectively about 66.2% and 62.1%), and the incidence of limb spasm in post-stroke survivors is 20-40%, which is a large part of the cause of disability.[1] Regarding the mechanism of post-stroke spasm, most researchers believe that excessive spinal cord excitement leads to spasm when the high-grade cortex is damaged. Some scholars have also suggested that the reticular spinal cord and the vestibular spinal cord mainly regulate excitation and inhibition. Under normal circumstances, it is in a state of equilibrium. When the nerve function is impaired, the balance is broken, and the cortex and spinal cord can be remodeled. The spasm is a milestone in the functional recovery process, since it will appear or disappear as the function recovers.[2] Post-stroke stroke Limb spasm can cause a serious decline in the quality of life of patients, increasing care and social and economic burden. For post-stroke spasm, treatment goals

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should aim to improve dysfunction, task performance, handling and self-care, reducing the burden of care and maintaining joint mobility, and avoiding skin complications. Botulinum neurotoxin (BoNT) is the focus of attention in the treatment of spasm in recent years. It began in 1989 when Das et al. successfully used botulinum neurotoxin for the treatment of spasm and myotonia after cerebral infarction. Subsequent randomized controlled trials have been reported. The results of recent studies on the use of BoNT for post-stroke spasm are summarized below.

2. The Pharmacology of Botulinum Neurotoxin

The botulinum neurotoxin consists of a 100kDa heavy (H) chain and a 50kDa light (L) chain linked by a disulfide bond, which mainly binds to cholinergic neuromuscular and blocks the endplate acetylcholine release causing paralysis. Botulinum neurotoxins are classified into seven types of A-G according to the serotype. The main types used in humans are type A and type B. There is no clear conversion formula between the dosage forms. Recently, the amino acid sequence of the new botulinum neurotoxin has been changed slightly but its activity and toxicity have changed greatly (study from rodents).[3] The botulinum neurotoxin currently used in clinical practice has the following three characteristics:

(1) Botulinum neurotoxins have a short duration and require repeated treatment every 3-4 months. In an attempt to solve this problem, researchers have extended their action time by using polyclonal antibodies to neural cell adhesion molecules.[4] And the botulinum neurotoxin is mixed with spheroidal chitosan,[5] although the above two studies are from animal experiments, it may provide some ideas for the development of botulinum neurotoxin stabilizer.

(2) Botulinum neurotoxin has the characteristic of being impossible to reverse, once the toxin has reached the cholinergic endplate, its activity cannot be reversed until it stops naturally.

(3) The botulinum neurotoxin only acts on the peripheral nerve muscles, and the existence of ultrastructural connections with the central nervous system has not been confirmed. Despite the findings of functional magnetic resonance studies, botulinum neurotoxins are used to treat post-stroke spasm, in terms of fMRI, the intensity of BOLD (blood oxygen level dependent) decreased significantly and increased cerebellar activity,[6,7] but the mechanism is unknown. Botulinum neurotoxin has been developed for 30 years, and its research field has gradually involved multiple disciplines. The power of function is obvious.

3. Post-stroke Upper Limb Spasm

The use of botulinum neurotoxin to treat post-stroke spasm is common in Europe and the United States. The investigation of the use of botulinum neurotoxin in Italy suggests that 80% of physicians use botulinum neurotoxin to treat adult spasm.[8] The 2016 US post-stroke spasm treatment guidelines also suggest that botulinum neurotoxin type A is effective in adult spasm (A grade evidence).[9] There are no relevant data reports in China. The main influencing factors of treatment outcome are as follows:

3.1 Treatment Period

The Early treatment is better. Fheodoroff et al.[10-12] found that the former was better in comparing the therapeutic effects in the two subacute and chronic phases. However, there are not many patients who actually get early treatment. Nalysnyk et al.[1] systematically reviewed 24 randomized controlled trials, 7 non-randomized, and 37 single-armed studies and found that the average time of upper limb spasm began to be treated after 46.9 months of onset, so there was a global delay in the treatment of post-stroke spasm.

3.2 Target Muscle Selection

The choice of muscle directly affects the therapeutic effect, and only the accurate positioning of the target muscle can be targeted. Nalysnyk et al.[1] conducted a systematic retrospective analysis to find the most frequently injected muscles: the radial flexor digitorum (64.0%) and the ulnar wrist flexor (59.1%), followed by the superficial flexor, the deep flexor, the biceps and the flexor hallucis longus. Spasm often causes severe joint deformities. Heikkila[13] boldly envisages the effect of intra-articular injection of botulinum neurotoxin, and studies the side effects of dogs as subjects. The results are not significantly different. Therefore, it is estimated that intra-articular injection of botulinum neurotoxin is not effective.

3.3 Dosage Requirement

If the dose is too small, the treatment is ineffective. If the dose is too large, it will cause toxic side effects. At present, there is still no research confirmed the safety of using the dosage range beyond the guideline. Nalysnyk et al.[1] obtained a systematic review of the average dose of upper limb spasm: shoulder muscles (40–100U), elbow flexors (41.1–95.4U), wrist flexors (23.8–72.8U), finger flexor (11.3–97.8U), forearm (5.0–33.3U), thumb muscle (18.9–30U), average total dose between 5-200U, it can be seen that there is a significant difference in the dose of each study. In order to determine whether dose differences affect treatment outcomes, Yablon et al.[14] included 7 randomized double-blind controlled studies

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for centralized data analysis: as measured by the greatest decrease in muscle tone (Ashworth drops by 1 point), the optimal dose for certain specific muscle groups: 22.5 U of the lateral flexor, 18.4 U of the ulnar flexor, 66.3 U of the superficial flexor, and 42.5 U of the deep flexor; there is a positive correlation between the dose effects within a certain range, and consistent with the results of Wissel et al.[15], Wissel will improve the total dose from 400U to 800U, better improvement in limb muscle tension and target achievement.

3.4 Efficacy Assessment

The most commonly used evaluation methods in clinical practice are MAS (Modified Ashworth Scale), SFS (Spasm Frequency Score), MTS (Modified Tardieu Scale), Brunnstrom, comprehensive spasm scale, and medial muscle tension scale. The assessment method is subjective, with a rough division, large individual differences, and lack of standardization. A large number of randomized controlled trials using MAS confirmed that BoNT can improve muscle tone, while decreased muscle tone only indicates improvement in passive function and does not explain the improvement in active function. Therefore, researchers began to use BI and FIM (Barthel Index and the Functional Independence Measure) to evaluate the efficacy, and the evaluation did not make a slight evaluation of the local function of the limb. For this reason, Fridman[16] designed the method of gripping the upper limbs. 8 patients with FIM scores of 126 were enrolled. The average total dose of 305 U (Botox) was injected by body surface markers and EMG guidance. The grasping speeds before and after injection were significantly different. However, there are shortcomings in the study that the control group is not established and the sample size is too small. The effect of the botulinum neurotoxin or the self-recovery of the patient itself cannot be judged. Therefore, the results need to be confirmed by more data, but this method is more detailed than BI and FIM evaluation, and it is worthy of clinical promotion. In addition, the researchers used the GAS (Goal attainment scaling) scoring initiative, a representative international, prospective; cohort study is the ULIS-II (the Upper Limb International Spasticity Study-II, ULIS-II for short), which was completed by 84 centers, 22 countries, and 355 patients, mainly referring to the long flexor as the target muscle, followed by the biceps and diaphragm, and the total dose range of BoNT-A (Dysport: 400-1900U; Botox: 50-500 U; Xeomin: 100-600 U), using EMG and electrical stimulation as a guiding method. During a follow-up period, the GAS score changed by an average of 17.6 (95% CI 16.4 to 18.8; $P < 0.001$),[17] Therefore, it is inferred that BoNT is beneficial to improve the active function. However, Fheodoroff et al.[18] subgroup analysis of the study found that the degree of hemiplegia, age, and post-stroke time all affected the GAS score, and each patient's target setting was inconsistent, so there are many defects in GAS evaluation. In order to make up for the above shortcomings, in the ULIS-III research plan (currently under study), a GAS-neous scale was designed to incorporate patient subjective feelings and look forward to relevant research results. Throughout the recent research on the upper limbs spasm after stroke, although the reduction of muscle tone after botulinum neurotoxin treatment makes the patient's movement more convenient and partially relieves the burden of care, however, the active function and muscle strength of the limbs have not been significantly improved. Maybe we need to find answers from the aspects of spasm mechanism, muscle positioning, dose selection, guiding technology, and evaluation methods.

4. Post-stroke Lower Limb Spasm

Compared with the post-stroke upper limb spasm, the study of post-stroke lower limb spasm is less, and the treatment is more challenging. The reasons are as follows:

(1) The lower limb muscles are deep and the range is large, so positioning is difficult.

(2) The dosage requirements are large, and the consideration of high dose safety is more than the treatment of the upper limbs.

(3) Lack of standardized evaluation methods: commonly used MAS, GAS and other scales, but subject to the evaluation of factors, and the degree of hemiplegia and post-stroke time, gait, pace measurement is subject to subjective factors, measurement is difficult.

(4) The improvement of active function is not clear: a multicenter randomized double-blind blank control study from Japan (120 patients in the group), the experimental group was injected with BoNTA300U in the ankle joint flexor, using MAS, gait mode, pace as an evaluation method, at 12 weeks of follow-up, the extent of MAS decline at 4, 6, and 8 weeks was significantly better in the test group than in the control group, while there was no significant difference in gait pattern and stride.[19] Another large multicenter, randomized, double-blind, blank-blind, controlled study (52 centers involved) selected 381 patients with limb spasm after half a year of stroke and set up 3 groups: Dysport1000U, 1500U and blank control group were injected. The treatment was repeated for 4 cycles and followed up for 1 year. It was found that a single treatment can only improve muscle tone, and the pace can be improved after one year of repeated treatment. Dashtipour et al.[20] confirmed the efficacy of muscle tension improve-

ment by meta-analysis, consistent with the results of these two multicenter studies. Gupta et al.[21] also confirmed by meta-analysis that there was no significant difference in walking speed and quality of life before and after injection of botulinum neurotoxin in patients with lower limb spasm. Therefore, it can be seen that the improvement of muscle tension is clear, but the active function and improvement are not clear.

For this reason, the researchers looked for the cause from the dose and concentration. 104 patients with spasm were randomly divided into four groups. The target muscles were the posterior tibial muscle and the soleus muscle. Two different doses (200U and 400U) and two different concentrations (50U/mL or 100U/mL) of botulinum neurotoxin were injected, which was evaluated by MAS and 10m speed. The follow-up of 12 weeks showed the effect, and the dose of 400U and the concentration of 50U/mL group was better.[22] Kim[23] found the main medial calf muscle affecting pace by healthy human studies, so it may be desirable to use the pace to evaluate the efficacy of this intramuscular injection. Analysis of the above studies: the current inclusion of assessment methods are inconsistent, botulinum neurotoxin treatment of lower extremity spasm after stroke to improve muscle tension is clear, repeated treatment effect and safety is affirmed, active function improvement is not clear. We also need to find the reasons from the evaluation methods, dose and concentration, target muscle positioning methods.

5. The Treatment Safety Botulinum Neurotoxin

It is safe for post-stroke spasm treatment according to the FDA-approved drug dose range of onabotulinumtoxinA/incobotulinumtoxinA 600U and abobotulinumtoxinA 1500U.[24] Severe adverse events were reported from the case (myasthenia gravis, Lambert-Eaton syndrome, anterior horn dysfunction).[25,26] According to the data analysis, the probability of antibody production is very small: 0.5% (Botox), 0 (Abobotulinumtoxin A, Incobotulinumtoxin A, Rimabotulinumtoxin B).[27] To understand the high-dose effects and side effects, Santamato et al.[28] reviewed eight studies that found that treatments beyond the recommended dose of 300 U were more effective in treating spasm with no significant side effects. At present, there are no clear big data confirmations about the adverse effects beyond the scope of the guidelines. However, as can be seen from the above description, botulinum neurotoxin is highly safe, and the clinician does not have to worry too much about the adverse reaction as long as it is within the prescribed dosage range and skillful operation.

6. Guiding Methods

The existing guiding methods include sports endplate area, palpation, manual needle marking, electromyography, electrical stimulation, and ultrasound guidance. In theory, the endplate region is the best method, but it is difficult to accurately position the endplate region on the living body. There are few studies on the comparison of different guiding techniques. The muscles with clear body signs are usually palpated, manual needles or EMGs are quickly and accurately positioned. For deep muscles with difficult positioning (such as piriformis), ultrasound positioning is more accurate to reduce peripheral vascular damage. Electrical stimulation is suitable for thinner and superficial muscles, in order to compare the accuracy of different positioning methods, a prospective study of 81 patients compared manual needle localization, electrical stimulation localization, and ultrasound localization. It was found that electrical stimulation was more accurate for the lateral muscle of the gastrocnemius than for the medial muscle of the gastrocnemius. Because the lateral muscle is thinner than the medial muscle, ultrasound alignment was found to be the most accurate after comparison of the three methods.[29] Therefore, different positioning methods should be selected clinically according to different muscles.

7. Combination Therapy

Existing rehabilitation methods include electrical stimulation, magnetic stimulation, bioelectric stimulation, acupuncture, shock wave therapy, adhesives, splinting, exercise therapy, and robotic rehabilitation. In a randomized, single-blind, crossover study of electro-assisted exercise therapy, 11 patients who underwent severe stroke for the first half of the year participated in 90 minutes of follow-up and 18 weeks of follow-up. The results showed an increase in the number of upper limb activities in daily life.[30] Functional electrical stimulation improves the spasm state of the hemiplegic wrist and finger flexor.[31] Station-sitting alternating action combined with percutaneous electrical stimulation can improve the spasm state and balance function of the limb.[32] Studies have found that peripheral magnetic stimulation does not improve spasm status, but can improve sensory function.[33] Extracorporeal shock wave therapy can improve the spasm state of the plantar flexor digitorum after stroke and improve the passive movement of the ankle joint dorsiflexion.[34] Compared with the above methods, robotic rehabilitation combined with botulinum neurotoxin treatment can obtain better clinical efficacy [35,36], but the cost is too high and it is difficult to popularize. Splint fixation and adhesive combination with botulinum neurotoxin treatment can improve the symptoms of spasm. In contrast, the adhesive is even better. A single-blind randomized

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controlled trial enrolled 70 patients with upper extremity spasm after stroke. After injection of botulinum neurotoxin into the flexor digitorum of the wrist, they were divided into two groups, Group A and Group B. Group A was treated with adhesive and schedule muscles, and Group B was fixed with splint. Both groups were able to reduce the excessive activity of spasm, and the efficacy of Group A was better than that of Group B.[37] Exercise therapy is also effective, especially in children, a randomized controlled trial of perinatal stroke children showed that botulinum neurotoxin combined with early intensive leg function training improved walking ability.[38] In the use of botulinum neurotoxin, it is necessary to combine rehabilitation exercise training to maximize the treatment effect.

8. Challenges Ahead

Although botulinum neurotoxin is recommended as a first-line treatment for post-stroke spasm, there are still many difficulties for clinicians, mainly as follows:

8.1 The Prediction of Spasm

Whether it is based on the degree of hemiplegia and deep sensory disturbance, or using MAS, GAS score and robot evaluation, the subject and the tester are subjective and lack quantitative measurement methods, which ignore the patient's subjective perception to assess the extent of spasm. Zorowitz et al.[39] considered that a 13-item spasm screening scale could make up for the shortcomings.

8.2 Clinical Efficacy Evaluation

All clinical studies found that passive function improvement and active function improvement were not clear. Perhaps the mechanism of spasm and the mechanism of recovery of motor function are not the same.[40] Some questionnaires found that cold, fatigue, stress, and anxiety can increase the severity of spasm status,[41] but our assessment often ignores these contents.

8.3 Individualized Treatment

Patient satisfaction is gradually reduced with factors such as treatment cycle, peak incidence, and low-efficiency treatment, so the same patient needs individualized strategies at the beginning of treatment and during treatment,[42] however, the formulation of individualization is a very big problem.

8.4 Invalid Treatment Attribution

How to identify whether it is caused by antibody production, injection methods, interval time, disease outcomes, dosage forms, etc. and how to convert different dosage forms.[43]

9. Future Prospects

The number of strokes is still rising, and the number of disabled people is increasing year by year. In the face of post-stroke spasm, botulinum neurotoxin is a safe and effective local injection treatment, and should be carried out as soon as possible. Compared with foreign countries, China's use and understanding of botulinum neurotoxins is still insufficient, so there is still a large amount of clinical data to be explored. Based on reasonable spasm prediction and efficacy evaluation methods, a comprehensive treatment with botulinum neurotoxin as a core drug and functional physiotherapy can be established to bring more benefits to patients with post-stroke spasm disability.

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