REVIEW
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Systematic evaluation of the efficacy and safety of botulinum toxin type A in the treatment of spastic cerebral palsy

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Author contributions

Yu Jiang and Gang Liu conceived this study, carried out this study, and drafted the manuscript. Yu Jiang designed the study, collected and analyzed the data. Jing-Pei Ren and Yi Zhao directed the charts and pictures drawing and reviewed the article critically. Hiu-Zhong Bai and Tuo Zhao helped accomplish the conception and design of the study. Lin Xu and Xiao-Hong Mu were responsible for this manuscript and reviewed the article critically. All authors read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

BTX-A, botulinum toxin type A; SCP, spastic cerebral palsy; MAS, modified Ashworth scale; PRS, Physician Rating Scale; GMFCS, Gross Motor Function Classification System.

Citation

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Abstract

Background: Botulinum toxin type A (BTX-A) is a neuromuscular blocking agent. BTX-A inhibits acetylcholine release, causes neuromuscular transmission impairment, and decreases muscle spasms. **Objective:** To explore the efficacy and safety of BTX-A injection in the treatment of spastic cerebral palsy through systematic evaluation and to provide a reference for the clinical use of BTX-A. **Methods:** We used "Cerebral palsy" and "BTX-A" as the subject terms and used a combination of subject terms and free words for the search. We searched 7 databases, including CNKI, Wanfang, VIP, Sinomed, PubMed, Embase, and Web of science. Based on the inclusion and exclusion criteria, we screened the articles by reading their titles, abstracts, and full texts and finally included relevant literature for systematic evaluation. **Result:** A total of 93 papers were systematically evaluated, revealing that BTX-A injection treatment can effectively reduce muscle tone, increase joint mobility, improve gait and motor posture, and enhance gross motor movements in patients with spastic cerebral palsy. The benefits of BTX-A treatment can be sustained for 3–6 months, with motor ability improvement lasting up to 1 year. Combining BTX-A treatment with rehabilitation or external fixation therapy can enhance its efficacy. However, the effectiveness of BTX-A treatment is influenced by several factors, such as the dosage, number of injections, and patient age. Adverse reactions to BTX-A treatment are typically mild and can be relieved within 1–2 weeks. **Conclusion:** BTX-A injection is relatively safe but reversible.

Keywords: spastic cerebral palsy; botulinum toxin type A; systematic evaluation

Introduction

Cerebral palsy is a non-progressive brain injury caused by damage during the immature stage of brain development, such as premature birth, difficult birth, asphyxia, jaundice, etc.

There are numerous subtypes, with the spastic type being the most common, accounting for about 60%–70% of cases. Injury to the cone system of the brain, especially after damage to the cerebral cortex, causes elevated limb tone, hyper-retentive reflexes, muscle spasms, and stiffness [1, 2]. Spasticity leads to motor deficits and postural abnormalities that severely affect the patient's ability to live, participate, and quality of life. Spasticity hinders the development of the expected movement in children and causes contractures, deformities, pain and other complications [3]. How to relieve spasticity has been an essential topic in rehabilitating patients with spastic cerebral palsy. The management of cerebral palsy spasticity can be summarized into physiotherapy, medication, and surgical treatment. Botulinum toxin type A (BTX-A) is a neuromuscular blocking agent [4]. BTX-A acts on the presynaptic membrane of motor nerve endings to inhibit acetylcholine release and leads to neuromuscular conduction disorders. Chemical muscle denervation reduces muscle tone and muscle spasms. In 1989, Das and Park used BTX-A for the first time in treating spasticity. Six patients with hemiplegia had improved muscle spasms after directly injecting botulinum toxin into skeletal muscles after the stroke. And no significant side effects were found [5]. In 1992, BTX-A began to be used in the clinical treatment of cerebral palsy [6]. In the following 30 years, BTX-A injections have been widely used in clinical practice as one of the essential adjunctive treatments to relieve muscle spasticity in patients with spastic cerebral palsy. However, there is no standard dose for clinical use of BTX-A injections, the duration of efficacy is unclear, and the phenomenon of rebound or even aggravation of the efficacy of injections has been observed clinically. Therefore, this paper summarizes the existing literature on treating spastic cerebral palsy with BTX-A. A systematic evaluation of the efficacy and safety of BTX-A was conducted to provide clinical guidance.

Methods

Inclusion criteria

1. The type of study is a pilot study on clinical; 2. The study language is restricted to Chinese and English; 3. The study subjects are patients diagnosed with spastic cerebral palsy (SCP), and their gender, age, disease duration, race, and nationality are not limited; 4. Interventions should include BTX-A injection therapy; 5. The outcome indicators should report the improvement of SCP, including gross motor function scale scores, modified Ashworth scale (MAS) scores, total effective rate, etc. and adverse effects.

Exclusion criteria

1. studies in which the subjects were combined with other diseases, such as epilepsy; 2. studies without full text, missing data, or duplicate reports; 3. types of articles such as theoretical discussions, basic experiments, conference abstracts, reviews, and Meta-analyses; 4. Research with missing data.

Search strategy

A computerized search of seven databases, PubMed, Embase, Web of Science, SinoMed, CNKI, WanFang Data, and VIP, was conducted to collect literature on BTX-A for SCP. The search time frame was from database creation to November 30, 2022. Search terms include: "Cerebral Palsy", "Atonic Cerebral Palsy", "Congenital Cerebral Palsy", "Dystonic-Rigid Cerebral Palsy", "Diplegic Infantile Cerebral Palsy", "Quadriplegic Infantile Cerebral Palsy", "Spastic Cerebral Palsy", "Monoplegic Cerebral Palsy", "Botulinum Toxin Type A", "Botulinum toxin" and so on. Take PubMed as an example, and its specific search strategy is shown in Figure 1.

Information extraction

Two evaluators independently screened the literature, extracted data, and cross-checked them; in case of disagreement, a complete discussion was held to reach a consensus, or a third party was consulted to assist in judgment. The data extraction included: title, year, study type, the sample size of the injectable treatment, presence or absence of a combination of other drugs and treatments, outcome indicators, and adverse events.

Results

Literature search and screening

A total of 1561 relevant literature was initially detected, and after the screening, 93 pieces of related literature were finally included. The literature screening process and results are shown in Figure 2

Essential characteristics of the included literature

The essential characteristics of the included studies are shown in Table 1. The occurrence of adverse reactions is shown in Table 2.

Evaluation of the efficacy of BTX-A alone in the treatment of SCP

Reduces muscle tone and increases joint mobility. BTX-A can reduce muscle tone and increase joint mobility; the effect can last 3-4 months. A single injection of BTX-A treatment at 7 days, 14 days, one month, two months, and three months follow-up studies revealed

#1[Title/Abstract]"Cerebral Palsy" or "Atonic Cerebral Palsy" or "Congenital Cerebral Palsy" or "Dystonic-Rigid Cerebral Palsy" or "Diplegic Infantile Cerebral Palsy" or "Quadriplegic Infantile Cerebral Palsy" or "Spastic Cerebral Palsy" or "Monoplegic Cerebral Palsy"

#2[Title/Abstract]"Clostridium botulinum A Toxin" or "Botulinum Toxin A"or"Botulinum Neurotoxin A" or "Botulinum A Toxin" or "Botulinum Toxin Type A" or "Botulinum Neurotoxin Type A" or "Clostridium Botulinum Toxin Type A" or "Botox"

#3 #1AND#2

Figure 1 Search strategy

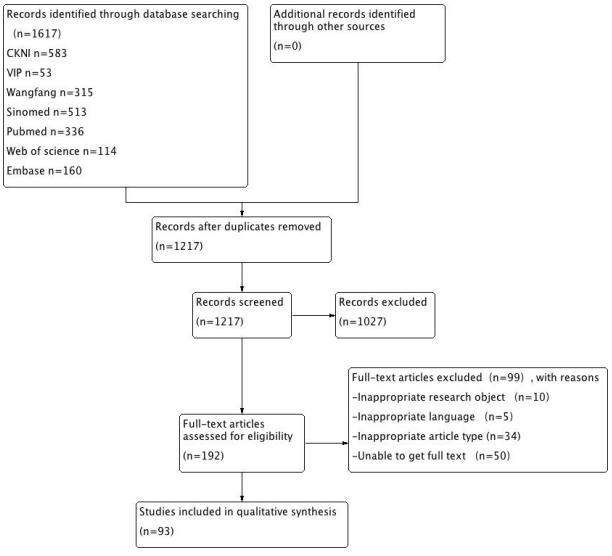

Figure 2 Flow chart of literature screening

Table 1 Basic characteristics of included documents

Study	Type	Participants	Other Interventions	Assessments
Chen Fang, 2010	RCT	40	–	MAS
Du Fengzhen, 2003	RCT	32	–	PRS, ADL
Gao Baoqin, 2001	single arm study	30	–	PRS
Gao Baoqin, 2005	single arm study	1000	–	PRS
Gao Baoqin, 2003	RCT	120	–	PRS
Huang Dongfeng, 2001	single arm study	23	–	MAS, ROM, Gait analysis
Liang Huiying, 1999	single arm study	9	–	PRS
Lin Bo, 2013	single arm study	10	Rehabilitation treatment	MAS, ROM
Lv Juanfen, 2001	single arm study	8	Rehabilitation treatment	ROM
Wan Guolan, 2003	single arm study	46	–	–
Wang Yajie, 2001	single arm study	45	–	MAS, PRS
Wang Yajie, 2002	RCT	58	–	MAS
Wang Yajie, 2007	RCT	150	–	MAS, PRS
Xu Qingling, 2004	RCT	34	–	ADL, PRS
Zhang Meiyu, 2011	single arm study	2006	–	PRS
Braendvik S. M., 2017	RCT	48	Comprehensive therapy	Gait analysis
Camargo C. H., 2009	single arm study	20	–	MAS, PRS
Choi J. Y., 2016	single arm study	25	Rehabilitation treatment	MAS, MTS, Gait analysis
Choi J. Y., 2019	single arm study	591	–	MAS, GMFM, MTS
Dabrowski E., 2021	RCT	350	–	GIFCS
De Beukelaer N., 2022	cohort study	25	–	Ultrasonic
Degelaen M., 2013	single arm study	14	–	Gait analysis
Du F., 2007	RCT	45	–	Gait analysis, PRS
Dursun N., 2020	RCT	114	–	OGS
Eek M. N., 2016	single arm study	20	–	ROM, Gait analysis
García Ruiz P. J., 1996	single arm study	6	–	Gait analysis
Kim K., 2010	RCT	59	–	PRS, ROM, GMFM
Linder M., 2001	single arm study	25	–	GMFM, ROM
Liu J. J., 2022	single arm study	52	–	PRS, GMFM
Niu G. H., 2014	RCT	256	–	MAS, GMFM
Mirska A., 2014	single arm study	41	–	ROM
Mirska A., 2019	single arm study	60	–	MAS, PRS, ROM
Maanum G., 2011	RCT	33	–	SF-36, Gait analysis
Read F. A., 2017	single arm study	17	–	Gait analysis
Schless S. H., 2019	case-control study	19	–	Ultrasonic
Schless S. H., 2017	case-control study	15	–	Ultrasonic
Wang Yajie, 2005	single arm study	30	–	MAS, PRS
Sutherland D. H., 1999	RCT	10	–	ROM
Valentine J., 2013	RCT	4	–	Muscle biopsy
Van Campenhout A., 2015	RCT	27	–	Electromyogram, MAS
Wang Y., 2008	RCT	150	–	MAS, PRS
Wang Y. J., 2013	single arm study	52	–	MAS, PRS
Williams S., 2011	single arm study	15	–	MRI
Wong A. M. K., 2005	RCT	22	–	Gait analysis
Wong V., 1997	single arm study	17	–	ROM, Gait analysis
Yang T. F., 2008	single arm study	35	–	MAS, ROM
Yang T. F., 2003	single arm study	15	–	MAS
Zelnik N., 1997	single arm study	14	–	Gait analysis
Xu Dehe, 2014	RCT	43	Rehabilitation treatment	CSS, GMFM, ADL
Feng Yunyun, 2005	RCT	67	Comprehensive therapy	–
Li Na, 2012	RCT	25	Rehabilitation treatment	FMQ, MAS
Li Zhiyong, 2002	single arm study	28	Orthosis	MAS, ROM, Gait analysis
Liao Wei, 2003	RCT	18	Rehabilitation treatment	PRS, MAS
Ma Caiyun, 2003	single arm study	65	Rehabilitation treatment	MAS
Ma Jinguang, 2002	single arm study	68	Vojta, Bobath therapy	GMFM
Ren Xingqin, 2006	single arm study	66	VitB1, VitB12 injection	ROM
Song Meiju, 2008	RCT	18	Vojta, Bobath therapy	GMFM
Wang Yafei, 2003	single arm study	20	Rehabilitation treatment	ROM
Xu Lianxiang, 2004	RCT	66	Bobath therapy	WeeFIM
Zhang Guibin, 2003	single arm study	20	Vojta, Bobath therapy	MAS, ROM, GMFM

Table 1 Basic characteristics of included documents (*continued*)

Study	Type	Participants	Other Interventions	Assessments
Zhou Taocheng, 2018	RCT	20	Medicated bath	MAS, GMFM
Boyaci A., 2014	single arm study	16	Rehabilitation treatment, Orthosis	Ultrasonic
Desloovere K., 2007	case-controlstudy	30	Rehabilitation treatment, Orthosis	Gait analysis
Dursun N, 2021	RCT	28	Plaster fixation	PROM, MAS, MTS
Flemban A., 2016	single arm study	23	Physiotherapy, Plaster fixation	GMF
Galen S., 2012	single arm study	31	Electrostimulation therapy	ROM
Lee S. J., 2012	RCT	26	Plaster fixation	MAS, PRS
Liang S., 2004	RCT	25	Rehabilitation treatment, Tuina, Orthosis	PROM
Lidman G. R. M., 2020	RCT	10	Rehabilitation treatment, Orthosis	AHA, ICF
Peeters N., 2018	RCT	12	Plaster fixation	Ultrasonic
Peeters N., 2020	single arm study	31	Plaster fixation	Ultrasonic
Ploypetch T., 2015	single arm study	98	–	UE, GMFC
Reddihough D. S., 2002	RCT	25	Physiotherapy	GMFM, VAB, ROM, MAS
Schasfoort F., 2018	RCT	41	Comprehensive therapy	ROM, Gait analysis, Muscle strength
Schasfoort F. C., 2017	RCT	41	Physiotherapy	Gait analysis
Scholtes V. A., 2006	RCT	23	Comprehensive therapy	GMFM-66
Scholtes V. A., 2007	RCT	42	Physiotherapy, Orthosis	Gait analysis
Selimoglu E., 2015	single arm study	29	Orthosis	MAS
Willoughby K., 2012	RCT	46	Orthosis	Gait analysis
Zwick E. B., 2009	single arm study	10	Plaster fixation	Gait analysis
Liu Jianjun, 2005	single arm study	39	–	MAS
Zhu Xiaojun, 2006	single arm study	20	–	MAS, CSS, MOA
Liu Jianjun., 2013	RCT	8	Rehabilitation treatment	MAS, GMFM
Guo Wenying, 2018	RCT	94	–	MAS, GMFM
Yang Zhaohui, 2004	single arm study	16	–	MAS, MTS, PF50, GAS, COPM
Balbaloglu O., 2010	single arm study	16	Rehabilitation treatment	Gait analysis, MAS
Jacobson D., 2021	RCT	8	–	VAS
Kaushik P., 2018	RCT	14	–	MAS, GMFM-66
Kim S. K., 2020	single arm study	31	–	GMFM, MAS, MTS, Gait analysis
Lidman G, 2015	RCT	10	Rehabilitation treatment	AHA, ROM, ICF
Misra A. K., 2010	single arm study	63	–	MAS, PRS, VAS
Picelli A, 2017	RCT	5	Electrostimulation therapy	Ultrasonic, MAS, TMS
Wallen M. A., 2004	single arm study	16	–	MAS, ROM

Table 2 The occurrence of adverse events

Study	Adverse event
Yang T. F., 2008	6 cases of pain; 5 cases of ecchymosis; 3 case of limb weakness; 2 cases of gait instability
Yang T. F., 2003	2 cases of limb weakness
Gao Baoqin, 2001	1 case of limb weakness
Gao Baoqin, 2005	5 cases of limb weakness
Wang Yajie, 2001	10 cases of limb weakness; 2 cases of pain
Wang Yajie, 2002	16 cases of pain and limb weakness
Wang Yajie, 2007	21 cases of pain; 1 case of limb weakness; 1 case of gait instability
Camargo C. H., 2009	3 cases of limb weakness; 1 case fell
Dabrowski E., 2021	23 cases of Nasopharyngitis; 13 cases of Bronchitis; 3 cases of dermatitis
Dursun N., 2020	3 cases of limb weakness; 2 cases of pain
Eek M. N., 2016	1 case of limb weakness
Kim K., 2010	3 cases of Nasopharyngitis; 5 cases of fever; 2 cases of hemoptysis and joint contracture
Yang T. F., 2008	6 cases of pain; 5 cases of ecchymosis; 3 case of limb weakness; 2 cases of gait instability
Yang T. F., 2003	2 cases of limb weakness
Lee S. J., 2012	3 cases of pressure sore; Reduced calf circumference
Guo Wenying, 2018	2 cases of fever; 4 cases of pain;2 cases of dermatitis
Jacobson D., 2021	5 cases of pain; 2 cases of limb weakness
Misra A. K., 2010	5 cases of pain; 2 cases of ecchymosis

significant reductions in lower extremity muscle tone, increases in joint mobility, significant reductions in MAS and MTS scores compared to pre-treatment, and significant increases in ROM [7–17]. Some studies noted improved muscle tone and joint mobility slowed with longer injection times. For example, 1–4 months follow-up still improved compared to pre-treatment or control group, but no significant difference between follow-up data [18–21]. Similar results were observed in injection therapy targeting spastic muscles in the upper extremities [22].

Study shows single injection of BTX-A for the lower extremity lasts up to 6 months [15]. Most studies show a decreasing trend in efficacy maintenance with increasing follow-up time after a single injection of

BTX-A treatment. At the 6-month follow-up, muscle tone and joint mobility may no longer improve significantly or return to pre-injection levels, or may even rebound [23–25]. In studies targeting spastic muscle groups in the upper extremities, the results are similar [26].

Improve gait, exercise posture. The effect for gait is generally maintained for a long time, most up to 6 months [27]. After a single injection of botulinum toxin types A treatment, each Physician Rating Scale (PRS) efficacy index: ankle flexion, foot turn, knee turn, gait speed, and gait are improved compared with the pre-treatment or control group, and PRS score can significantly increase, and the efficacy can last for 1 month, 2 months or 3 to 10 months [28–31]. Similarly, some of the studies observe similar parameters to pre-treatment at an interim follow-up of 6 months, and the efficacy in terms of PRS scores does not persist for long. Only a tiny percentage of patients can walk without any support after treatment.

In terms of improving gait and motor posture, BTX-A injections can reduce the patient's lower extremity adduction angle, increase the ankle dorsiflexion angle, and improve gait quality [31, 32]. Patients can walk with their feet on the ground and change their gait posture from "toe-toe" to a constant or occasional "heel-toe" gait [25, 33]. In addition to visual observation, computerized gait analysis is available. Significant changes in ankle kinematic data such as maximum ankle dorsiflexion, mean dorsiflexion, and foot contact pattern during the stance phase after BTX-A injection when assessed by the F-scan system [19]. When 3D gait recording is evaluated, there are significant changes in the coronal and sagittal trunk range of motion and significant changes in the lower extremity coordination model in the barefoot state of the patient after injection. The efficacy can last about 1 month, 4 months, 6 months, or 9 months [19, 31, 32, 34].

A few studies report that BTX-A injections alone were ineffective in improving gait in the short term. Only an improvement in the degree of muscle spasticity in patients could indicate a positive effect of BTX-A [35].

Improve coarse movement. BTX-A has shown long-term positive implications in improving gross motor activity. After a single injection treatment, there were significant improvements in gross motor function scale scores at short-term follow-up (1–4 months) and mid-term (6 months) follow-up, indicating that injection treatment can improve the overall motor ability of patients with SCP [20, 23]. Continuous follow-up revealed that even though the improvement effect of muscle tone and muscle spasm after injection treatment disappeared at 5–6 months, the patient's motor ability improved significantly at long-term one-year and two years follow-ups [14, 36].

Analysis of the efficacy of BTX-A in combination with other therapies

Analysis of the efficacy of combined rehabilitation therapy. BTX-A injection can further improve the efficacy of the rehabilitation treatment. The overall treatment efficacy of rehabilitation combined with BTX-A injection is significantly better than that of the rehabilitation control group alone. Rehabilitation can extend the duration of BTX-A treatment, and studies show that reduced muscle tone can be maintained for up to 6 months [18, 37, 38]. However, the combination of botulinum toxin A and rehabilitation therapy still does not reverse the unsustainable efficacy of BTX-A. In some studies, myospasm and muscle tone returned to pre-treatment at 6 and 7 months after combined rehabilitation. However, gait and motor ability did not reverse with muscle tone recovery can be maintained for 6 months or even 1 year [39–42].

A few studies find no significant differences between the effects of rehabilitation with injection therapy and rehabilitation alone at short-term (1–3 months) and mid-term (3–6 months) follow-up [43]. It may suggest that treatment with BTX-A does not increase the clinical outcome of rehabilitation, which is inconsistent with most experimental results.

Efficacy analysis of combined orthosis or cast fixation. BTX-A injection therapy combined with external limb immobilization can further improve muscle tone, joint mobility, and gait compared to injection therapy alone, and the effect can maintain for 3–6 months [44, 45]. However, a few studies find no significant difference between orthotic brace fixation combined with injection and fixation therapy alone [46]. It may suggest that treatment with BTX-A does not increase the clinical effect of rehabilitation.

Factors influencing the efficacy of BTX-A injection therapy

Relationship between BTX-A injection dose and efficacy. Several studies show that relatively higher doses of BTX-A over a range of injections can improve overall treatment efficacy [13, 47]. The efficacy of higher doses, such as 3 U/kg, 4 U/kg, and 5 U/kg, is higher than that of lower doses, such as 1 U/kg and 2 U/kg. Relatively high-dose injections allow for more prolonged maintenance of efficacy in muscle tone, gait, etc., for up to 6 months [48]. However, few studies do not find a correlation between the dose of BTX-A injection and improvement in limb muscle tone, reduction in muscle spasticity, and motor ability [9].

Relationship between the number of BTX-A injections and efficacy. Repeated injections of BTX-A, such as two or more injections at 2, 3, or 4-month intervals, are a way to make the treatment last [11, 49–51]. This approach maintains the effect for about 6 months after a single injection [23, 50]. However, the overall efficacy in terms of muscle tone and gait continued to decrease with increasing duration of follow-up [11, 23]. Efficacy remains poor at long-term 1-year follow-up after discontinuation of injections [51, 52].

Relationship between precise injection of BTX-A and efficacy. The precise selection of injection sites can be made clinically with the help of EMG, ultrasound, or electrical stimulation guidance, which can help improve the BTX-A treatment's efficacy. The MAS score and GMFM scale of patients treated with EMG-guided injection at the same dose are better than those of the traditional freehand group, with significant efficacy [53]. However, other studies find that ultrasound-guided injection therapy has no significant advantage in terms of efficacy over traditional freehand localization methods [54].

Relationship between other factors and the efficacy of BTX-A

Age. The younger the age, the better the outcome. The rate of improvement in gait and muscle tone after botulinum toxin type A injection treatment increases with decreasing patient age, and the duration of efficacy is prolonged [55]. Some of the older patients show ineffective performance after injection [45]. The current study can be administered at a minimum of 1.5 years of age for longer-term efficacy [28].

Type of cerebral palsy. The types of SCP can be classified as monoplegic or diplegic. Multiple studies find superior efficacy of injection therapy in patients with unilateral paralysis compared to patients with bilateral paralysis [34, 55]. The improvement in muscle tone, joint mobility, and trunk motor coordination is more pronounced in patients with unilateral paralysis [34].

Gross Motor Function Classification System (GMFCS) grading. The degree of cerebral palsy injury, such as the GMFCS, is associated with efficacy. The lower the grade, the better the treatment efficacy. Patients with a GMFCS grading of less than or equal to 3 have better clinical efficacy [36]. Patients with grade I at GMFCS grading get the best results [55]. However, some studies have also shown that BTX-A is most effective in the GMFM Class II patient population [20].

Muscle strength. Pre-treatment muscle strength of patients is related to the efficacy of injection therapy [28]. The greater the muscle strength level, the better the treatment effect. If the muscle strength is insufficient, the weakness of the affected limb is even more apparent after the injection than before the treatment.

Safety analysis of BTX-A treatment

Most of the adverse events reported in the article following BTX-A injections are mild and generally resolved independently within 1–2 weeks. Common adverse reactions include temporary and mild pain at the injection site [49, 50, 53, 56, 57]. It is also common to feel muscle weakness after injection, and there are cases of falling due to weakness [13, 28, 30, 49, 57, 58]. Temporary gait instability also occurs [17]. Various types of inflammation, rhinitis, bronchitis, dermatitis, fever after injection, and local bruising at the injection site may also occur [20, 50, 53, 59, 60]. Severe adverse reactions can interfere with everyday life due to muscle weakness after injection, worsening hemoptysis, joint contractures, and even requiring hospitalization [20, 57].

Adverse reactions may increase with higher injection doses but are equally mild. The incidence of adverse events, such as injection site pain and spontaneous weakness of the injected limb, in the high-dose injection group is higher than in the low-dose group. However, the two groups have no statistical difference [12].

Precise positioning of the treatment reduces the incidence of adverse effects. The incidence of adverse reactions was lower with electromyography EMG-guided injections than freehand localization injections, but there was no statistical difference between groups for comparison [53].

Combined plaster immobilization of the limb can result in pressure sores, mainly at the heel, with grade 1 or 2 [44]. The general reduction in calf circumference after treatment in patients with combined cast immobilization (-1.7 ± 1.9 cm) [44].

Injectable treatment may have long-term side effects on the patient's body shape, which are not apparent in the short term of injectable treatment. If only the gastrocnemius and posterior tibialis muscles of patients with lower limb SCP, the reduction of muscle tone near the ankle joint, the patient can improve the pointed foot gait. However, the muscle strength near the ankle joint will be reduced, resulting in the need for more hip extensor strength, which will affect hip flexion, and other deformities will occur in the gait over time [19].

Some studies have evaluated the efficacy of botulinum toxin at the microscopic level with the help of imaging. BTX-A has a certain degree of damage to the injected muscles. Ultrasound assessment of lower limb muscle growth 6 months after injection [19]. The muscle growth rate slows, the cross-sectional area of the muscle belly reduces, and the muscle echogenic intensity increases, significantly different from normal children's muscle development progress. BTX-A injections can harm average muscle growth and development, muscle integrity, and poor recovery of muscle status 6 months after injection. At follow-up 1 year after injection, the parameters related to lower limb muscles detected under ultrasound are still more defective than uninjected muscles [61]. Repeated interventions with BTX-A may further inhibit muscle growth and alter muscle morphology. Ultrasound testing reveals a positive correlation between muscle echo intensity after botulinum toxin types A injection and the number of previous interventions [62]. Muscle biopsies after multiple injections of BTX-A reveal neurogenic muscle atrophy in some patients. Changes in gastrocnemius fiber type distribution after injection, loss of type 1 fibers, and a shift to type 2 fiber predominance may decrease muscle endurance and are significantly associated with the number of interventions [63].

Discussion

Muscle spasm results from upper motor neuron injury and is one of the leading clinical manifestations of cerebral palsy. Spasticity is an essential factor in the delayed motor development and abnormal motor posture of patients with cerebral palsy. The mechanism of muscle spasm is due to damage to the cerebral cortex and downstream inhibitory conduction pathways in the brain, which weakens the inhibitory effect on gamma motor neurons, increases the excitability of gamma motor fibers, increases the sensitivity of the muscle shuttle, produces abnormal discharge, and excites alpha motor neurons, resulting in muscle spasm [64]. BTX-A is a protein produced by anaerobic Clostridium botulinum, which is neurotropic. BTX-A can inhibit the release of acetylcholine, leading to flaccid muscle paralysis and reduced muscle tone [65].

This systematic evaluation included 93 publications, including 7,288 patients. The results of this system show that after one intramuscular injection, the muscle spasm showed different degrees of release, the muscle tone showed different degrees of decrease, and the joint mobility also increased to different degrees. However, it cannot reduce to normal muscle tone after injection, and the short-term efficacy is exact, usually lasting 3–4 months. Most of them show ineffective or even rebound in muscle tone and joint mobility after 6 months of treatment. BTX-A only improves muscle tone and gait for a certain period in children with SCP. However, gross motor function (GMFM score) increases gradually with the treatment time and does not regress significantly due to muscle tone recovery, which maintains for up to 1 year. BTX-A only improves muscle tone and gait for a certain period in patients with SCP. The adverse effects of injection therapy are mild and most resolve independently in about 1–2 weeks. The most common adverse reaction is pain at the injection site, followed by transient muscle weakness, but it is also important to be alert for serious adverse events.

Clinically, BTX-A injections are often combined with rehabilitation training to promote recovery of limb motor function. For SCP, commonly used rehabilitation therapies include the Bobath and Vojta methods, which include active muscle contraction, strengthening of antagonist's muscles, and slow and continuous stretching of spastic muscles. BTX-A injections can be used as an adjunct to rehabilitation treatment. The most significant value of the injections is that they provide a treatment window of approximately 6 months, creating conditions conducive to muscle relaxation and reduced muscle tone for rehabilitation. The spasticity of the active muscles is relieved, which was conducive to strengthening the functional training of the antagonist's muscles, improving the range of motion of the joints, enhancing motor function and improving postural abnormalities, and promoting the further improvement of the overall efficacy of the rehabilitation training. The ability to move can be maintained for up to 1 year, helping patients achieve their desire to live and work usually. For the long-term maintenance of motor function, the researchers believe that children with rehabilitation based on the release of spasticity have the opportunity to learn to control the spastic muscles. In contrast, the antagonist muscles improve their strength through exercise and can become familiar with the correct motor posture and movements. The correct movement pattern can be formed in the brain so that abnormal movements and postures can be corrected, and the movement pattern will be improved even if the spasm is restored [14, 23].

BTX-A injections are often combined with foot and ankle orthoses, braces, and casts to immobilize the limb, with casts used most often. External fixation produces a low-loading, long-duration force on the stretched tissue, which causes specific physiological changes in the stretched tissue, including remodeling of connective tissue and muscle [66]. When the muscle is fixed in an elongated state, it increases the number and length of muscle segments, which reduces muscle spasms. Plaster immobilization of the lower extremity ankle joint can also increase the dorsiflexion angle and help improve the deformity of the lower extremity [67, 68]. Combining BTX-A with external fixation also improves the overall efficacy, which can be maintained for about 3–6 months. The use of plaster immobilization for standard pressure sores requires special care.

Several factors influence the effectiveness of BTX-A injection. Within a specific range, the higher the injectable dose, the better the clinical efficacy, up to 5 U/kg in a single dose. However, some studies conclude that the difference in effect between large and small doses is insignificant. Whether there is a dose-response relationship between the injected dose of BTX-A and the effects produced is controversial and needs to be verified in numerous studies. The effectiveness of the treatment is also related to the number of repeated injections. By repeating the injections at intervals of several months, the effect of a

single treatment can be stably maintained for 6 months. However, there is no accepted optimal dosage, concentration standard, or standard injection interval for BTX-A injection therapy. The current clinical single injection dose varies from 1–5 U/kg, and the injection interval varies from 1-6 months. The current study finds that adverse reaction incidence increases with higher injection concentrations. High-dose or repeated multiple injections may be favorable for botulinum toxin antibodies in the patient's body, producing drug resistance and affecting the therapeutic effect [20]. Imaging observations show that each injection of BTX-A produces some damage to the muscle and affects average muscle growth and development. It takes some time to recover after each injection, so waiting at least 6 months before the subsequent injection treatment is recommended. Therefore, exploring the best injection protocol for BTX-A should continue.

The choice of injection method can also affect the efficacy of the treatment. The existing injection localization methods are divided into four categories, freehand localization, EMG-guided localization, ultrasound-guided localization, and electrical stimulation-guided localization. In the freehand positioning method, the physician pulls the muscle along its long axis in the opposite direction, repeatedly causing excessive dorsiflexion of the affected limb to induce increased muscle tone or spasm. The physician presses the spastic muscle by touching it with his or her hand and administers the injection treatment at the site where the muscle spasm is most apparent [53]. This method is the most commonly used in clinical practice and has the advantages of being simple, quick, and inexpensive, and it is suitable for superficial and large muscles. It is difficult to accurately locate small or deeply located muscles with bare hands. Sometimes spasticity can be caused by a combination of different muscles, and severely spastic muscles can mask the motor deficits caused by less spastic muscles, making them difficult to distinguish with bare hands [28]. The electromyography-guided localization method is used to identify the selected muscle and then use a probe to pierce the area, determine the degree of spasm according to the muscle discharge, and determine the injection site [69]. The EMG localization injection method suits muscles with large muscle volumes and shallow locations. This invasive procedure is challenging to perform on patients under 6 years of age. The electrical stimulation-guided localization method requires using an electrical stimulator and a disposable nerve block insulated injection needle to find the location where the minimum stimulation current can cause the maximum contraction of the corresponding muscle, which is the injection site [70]. Ultrasound is the most accurate and readily accepted by the child, but it is more expensive and less clinically convenient [28]. Most of these methods are designed for precise injection site selection to further improve efficacy and reduce the incidence of adverse effects. However, some studies question its usefulness, and the improvement of clinical efficacy is not apparent, but it increases the cost of treatment and wastes human and material resources. Current studies are insufficient; for example, there are no articles exploring the efficacy of electrical stimulation, and further studies should be conducted in the future with larger sample sizes.

Meanwhile, in the future, the clinic can classify the injected muscles according to their location and volume and choose the injection method reasonably. The gastrocnemius muscle is a superficial, large-volume muscle, and precise injection is not meaningful. The ability to precisely apply BTX-A to smaller muscles would be more clinically helpful [54].

This systematic evaluation found individual differences in clinical treatment outcomes. The efficacy of the treatment may be related to the patient's factors. The younger the age, the better the outcome; currently, the youngest to receive treatment is 1.5 years. Patients at a young age have muscles in the power spasm stage without developing fixed contractures, which emphasizes the need for early intervention. In older patients, muscle contracture and joint deformities develop into fixed structures, affecting the injection effect. If the patient is too young, the motor function is immature, and the muscle strength is weak, affecting the injection effect [45].

Regarding the type of cerebral palsy, unilateral palsy is more effective than bilateral palsy. Patients with less severe symptoms have better outcomes than those with more severe symptoms regarding GFMF grading, muscle tone, and muscle strength before injection. Most of the current studies are influenced by these confounding factors and cannot accurately assess the efficacy of BTX-A injections. Therefore, further patient classification studies are needed to determine the optimal population for BTX-A injection treatment.

Conclusions

BTX-A injection is a relatively safe but reversible treatment for patients with SCP. BTX-A injection reduces muscle tone, joint mobility, and gait improvement, creating the conditions for improved motor function. Overall efficacy is maintained for 3–6 months, and improvement in motor ability can be maintained for up to 1 year. However, no method can reverse the fact that the efficacy of BTX-A is not sustainable. BTX-A injection treatment can only be used as one of the auxiliary means to relieve spasticity and promote rehabilitation in patients with SCP and cannot achieve the purpose of cure. Some studies also question the efficacy of BTX-A. Therefore, other safe and effective treatments need to be explored for the clinical management of SCP.

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