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Therapeutic Effect of Botulinum Toxin a on Children with Spastic Cerebral Palsy: Meta-analysis

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Abstract: To systematically evaluate the clinical effect of botulinum toxin A (BXT-A) on children with spastic cerebral palsy. All clinical randomized controlled trials (RCTs) of BXT-A in children with spastic cerebral palsy were collected from the database establishment to April 20, 2021. Meta-analysis was performed on the extracted data using Review Manager 5.4 and R 4.0 software. A total of 21 studies met the inclusion criteria, including 1357 cases of spastic cerebral palsy and 704 cases in the BTX-A+ rehabilitation group. Meta-analysis results showed that: MAS score [MD=-0.83, 95%CI (-0.86, -0.80), Z=51.03, P<0.05] and GMFM-88 score [MD=5.50, 95%CI (4.40, 6.59), Z=9.85, P<0.05] in BTX-A+ rehabilitation treatment group, GMFM-D score [MD=8.51, 95%CI (5.24, 11.78), Z=5.09, P<0.05], GMFM-E score [MD=8.44, 95%CI (5.16, 11.72), Z=5.04, P<0.05], CSS score [MD=-1.86, 95%CI (-3.07, -0.66), Z=3.03, P<0.05], PRS score [MD=0.85, 95%CI (0.26, 1.44), Z=2.83, P<0.05] were better than the rehabilitation treatment group in these aspects, and the diversity between the two groups was statistically (P<0.05). BTX-A can effectively enhance motor function, and is an effective method for the treatment of children with spastic cerebral palsy.

Pediatric cerebral palsy is also known as pediatric cerebral palsy, commonly known as cerebral palsy. Among the incidence types of children with cerebral palsy, spasticity is the most common, accounting for 70% [1].

Since 1997, Botulinum toxin A (BTX-A) has been studied in the treatment of spastic cerebral palsy. This artical conducted a meta-analysis based on all the randomized controlled trials (RCT) comparing the effectiveness of BTX-A , in the hope of providing evidence-based medical evidence

for clinical medicine and better guidance for clinical application.

1. Makings and Methods

1.1. General Information

Study Type: Randomized controlled trials (RCTs) of all BTX-A, regardless of whether the trials were blind or not.2. Inclusion criteria of subjects: confirmed to have cerebral palsy. The diagnosis of cerebral palsy conforms to the standards specified by the national pediatric cerebral palsy symposium in 2004 [2]. Exclusion criteria for subjects included neurological diseases such as motor neurone disease and the presence of muscular atrophy. 3. Intervention measures: the experimental group received conventional rehabilitation therapy combined with BTX-A injection treatment; The control group only received conventional treatment, such as physical therapy, occupational therapy, etc. 4. Modified Ashworth Scale (MAS) score for outcome indicators; Cross Motor Function measure-88 (GMFM-88) score; Compopsite Spasticity Scale (CSS) score; Physician Rating Scale (PRS) 5. Exclusion criteria: repeated publications; inconsistent interventions; outcome indicators do not meet the requirements, data is incomplete, not in Chinese and English literature.

1.2. Methods

Retrieval strategy: PubMed, EMbase, Cochrane Library, CNKI and Wan Fang Data were sought by computer. The time is from the establishment to April 20, 2021, in Chinese and English only. The Chinese search keywords were "botulinum toxin" OR "type A botulinum toxin" AND "cerebral palsy" OR "spastic cerebral palsy". The key words of English search were: "Botox" OR "botulinum toxin A" OR "botulinum toxin" OR "BTX-A" AND "spastic cerebral palsy". 2. Literature screening: two reviewers screened the articles, extracted the data and cross-checked them. For the repeatedly published articles, updated and more comprehensive studies were selected; for the data with differences and difficult to extract, a third party was consulted to solve the problem. Firstly, the thesis title and abstract were read to screen the articles. After excluding the obviously inconsistent articles, the full text was further read to determine whether the articles were finally included or not. 3. Quality assessment: quality assessment was carried out using the Cochrane System Evaluator's Manual 5.1.0 quality assessment criteria, which included: generation of random assignment scheme; Concealment of distribution schemes; The implementer of the treatment plan and the study subjects were blinded; The results of the study were measured by blindness; Integrity of the resulting data; Selective reporting of research results; Other biases.

1.3. Statistical Analysis

Statistical analysis was performed with Review Manager 5.4 and R 4.0 software. Heterogeneity was evaluated by Q test and I2 statistics. If $P \geq 0.01$ and $I2 \leq 50\%$, it was indicated that there was homogeneity among the studies, and used the fixed-effect model for analysis. If $P < 0.01$ and $I2 > 50\%$, it was considered that there was a large heterogeneity among studies, and used the random effects model for analysis, and subgroup analysis was conducted according to the possible heterogeneity factors.

2. Results

2.1. Literature Retrieval Results

A total of 889 relevant articles were retrieved, including Wan Fang Data (169), CNKI (178), Cochrane Library (24), PubMed (461) and EMbase (57). After preliminary reading of the titles and abstracts, 476 articles were eliminated, leaving 413 articles remaining. After reading the full text by 2 researchers according to the inclusion and exclusion criteria, 393 articles were further removed, and 20 qualified articles [3-22] were finally included, including 2 English articles [14-15] and 19 Chinese articles [3-13,16-22].

Table 1: Basic literature information

The author	Published year	Number of patients		Rating scale
		Experimental group (Rehabilitation +BTX-A)	Control group (Rehabilitation therapy)	
Liu Jianjun	2013	17	20	MAS GMFM-88
Gao Yongqiang	2017	49	49	GMFM-88
Li Jinling	2015	108	105	MAS GMFM-88 PRS
Tian Zhaoxia	2010	33	30	PRS
Xu Ling	2008	22	20	GMFM-88 CSS
Shao Yinjin	2018	28	28	GMFM-88 CSS
Wang Liang	2014	34	34	MAS GMFM-88
Hou Yujin	2017	33	33	GMFM-88
Yan Hua	2010	60	46	GMFM-88 CSS
Liang Tianjia	2012	30	30	MAS GMFM-88
Dong Xiaoli	2008	50	50	MAS
Nigar Dursun	2017	36	18	MAS
M.A. El-Etribi	2004	20	20	MAS PRS
Guan Lijun	2011	30	30	GMFM-88
Zhang Yanjiao	2016	21	21	MAS GMFM-88
Yi Aiwen	2016	40	40	GMFM-88 CSS
Zheng Zhihong	2020	27	26	MAS CSS
He Feiping	2012	28	17	MAS GMFM-88
Jiang Hong	2008	22	20	CSS GMFM-88

Wu Suying	2011	16	16	MAS GMFM-88

2.2. Basic Literature Information

A total of 20 articles were included, including 1357 cases of spastic cerebral palsy and 704 cases in the BTX-A+ rehabilitation treatment group. The detailed information is shown in Table 1.

2.3. Evaluation of Included Studies

One study was Grade A in quality [6], and 21 studies were Grade B in quality [3-5, 7-22]. The quality assessment was shown in Figure 1. The included articles were all of high quality, with one study showing high risk of blindness between regimen implementer and study subject and outcome measure, and one study showing high risk of blindness between regimen implementer and study subject and other bias.

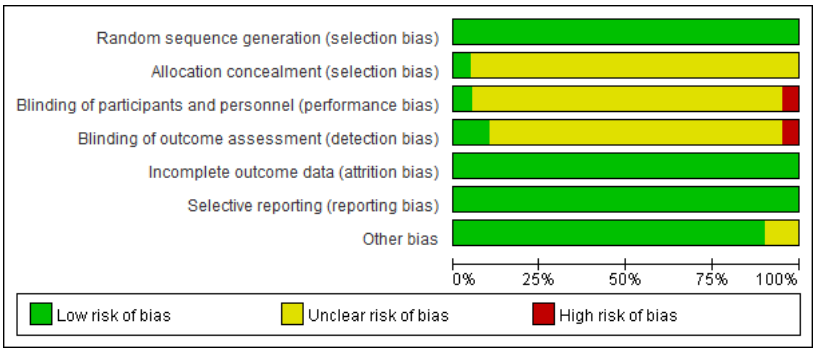

Figure 1: Literature quality assessment

2.4. Meta-analysis Results

(1) MAS score

Among the included articles,11 reported MAS scores after treatment [3, 5, 9, 12-15, 17, 19-20, 22]. There was no heterogeneity in clinical studies among articles (P=0.05, I2=45%), and used the fixed-effect model. The results revealed that the diversity between the two groups was statistically [MD=-0.83, 95%CI (-0.86, -0.80), Z=51.03, P<0.05]. This indicated that the degree of muscle spasm after BTX-A treatment was lower than that of the control group. As shown in figure 2.

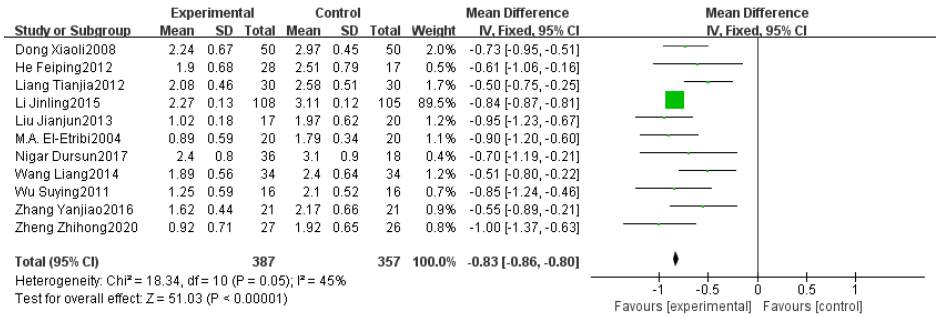

Figure 2: Forest diagram of MAS score

(2) GMFM-88 score

Among the included articles, 10 reported GMFM-88 score after treatment [3-5, 7-8, 12, 16-17, 22], and three reported GMFM-D region (standing) and GMFM-E region (walking, running and jumping) [10,11,21]. Among the 10 studies that reported GMFM-88, there was no clinical heterogeneity (P=0.07, I2=44%), and used the fixed-effect model. The results revealed that the diversity between the two groups was statistically [MD=5.50, 95%CI (4.40, 6.59), Z=9.85, P<0.05]. It indicated that the motor function after BTX-A treatment was better than that of the control group. As shown in figure 3.

The results showed that there was no heterogeneity between GMFM-D area (P=0.16, I2=46%) and GMFM-E area (P=0.81, I2=0%), and used the fixed-effect model for both of them. The results revealed that the differences between the two groups were statistically in area D and E [MD=8.51, 95%CI (5.24, 11.78), Z=5.09, P<0.05] and [MD=8.44, 95%CI (5.16, 11.72), Z=5.04, P<0.05]. It indicated that the motor function of D and E area after BTX-A treatment was better than that of the control group. See Figures 4 and 5.

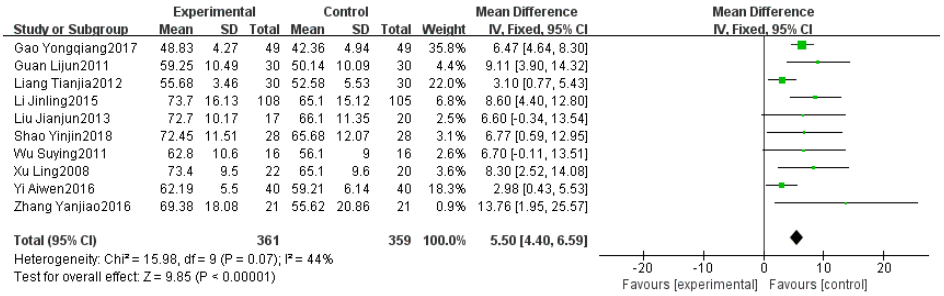

Figure 3: Forest diagram of GMFM-88 score

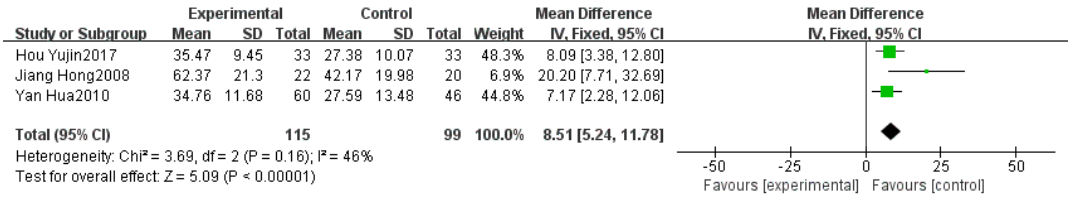

Figure 4: Forest map of GMFM-D score

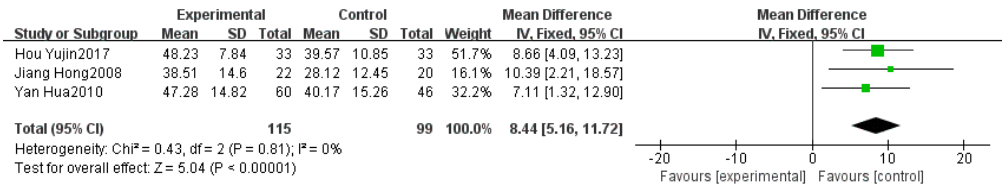

Figure 5: Forest diagram of GMFM-E score

(3) CSS score

Among the included articles, 6 reported the CSS scores after treatment [7-8,17,18-19,21]. The clinical studies among the articles showed high heterogeneity (P<0.00001, I2=96%), and used the random effects model. The results revealed that the diversity between the two groups was statistically [MD=-1.86, 95%CI (-3.07, -0.66), Z=3.03, P<0.05]. This indicated that the degree of muscle spasm after BTX-A treatment was lower than that of the control group. As shown in figure 6.

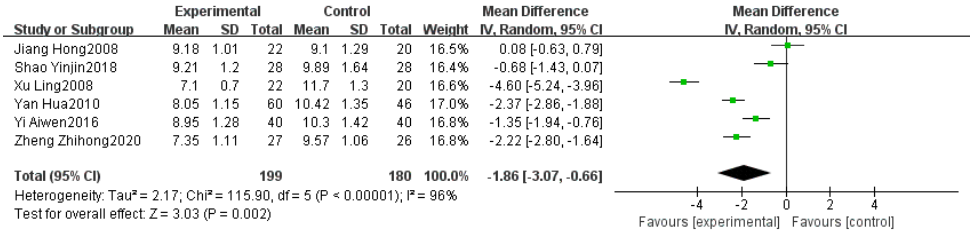

Figure 6: Forest diagram of CSS score

(4) PRS score

Three of the included articles reported PRS scores after treatment [5,6,15], and there was high heterogeneity in clinical studies among articles (P=0.001, I2=85%), and used the random-effects model. The results revealed that the diversity between the two groups was statistically [MD=0.85, 95%CI (0.26, 1.44), Z=2.83, P<0.05]. It indicated that the motor function after BTX-A treatment was higher than that of the control group. As shown in figure 7.

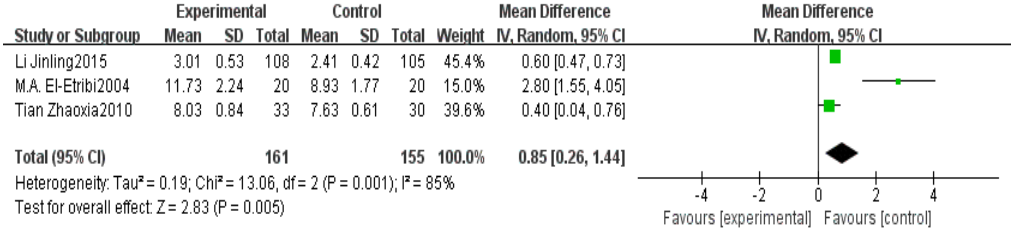

Figure 7: Forest diagram of PRS score

(5) Publication bias

The funnel plots of MAS scoring index and GMFM scoring index were symmetrical. The Egger's test of publication bias was P=8793 and P=0.9328, respectively, indicating that there was no publication bias. The funnel plots of CSS scoring criteria were asymmetric, and the Egger's test of publication bias was P=0.2722, indicating that there was certain publication bias.

3. Discussion

3.1. Validity Analysis

Since its clinical application in 1977, BTX-A has become the main drug for the treatment of muscular diseases such as handwriting spasm [23], facial spasm [24] and blepharospasm [25].

Malgorzata Field et al. [26] studied the effects of Dysport, Botox and Xeomin, and the results showed that the content of active neurotoxin in Dysport was significantly higher than that in Botox and Xeomin. Larger doses of active neurotoxins may prolong the blockage of neurotransmitter release at the neuromuscular junction and may result in longer clinical action. Li Xuewei et al. [27] injected different concentrations of BTX-A (experimental group: 3.33U/ml, control group: 2.5 U/ml) into 100 patients with hemifacial spasm (HFS), and the results showed that high concentration of botulinum toxin was safe and more effective in the treatment of HFS, with short onset time, long relieving time of spasm, and also alleviating anxiety of patients.

3.2. Safety Analysis

BTX is one of the most toxic biological toxins at present. Therefore, the dosage must be strictly controlled in clinical use. If the dosage is too small, it will fail to achieve the expected therapeutic effect; if the dosage is too large, it will cause some complications [28, 29]; if the dosage is too large, it will lead to death. Maanum G et al. [30] studied 66 adults with spastic cerebral palsy, in which 16 patients had adverse reactions, such as injection site pain, headache, nausea, fatigue, etc.

3.3. Research Limitations

The 21 included clinical research articles all described the basic information of the research object in detail. Due to various factors, there were still the following limitations: 1. Limited clinical research literature included; 2. The evaluation index of RCT in some English articles is non-mean ± variance, and there are some systematic errors in the conversion process;3. Not every RCT test can obtain the required evaluation indexes and data. 4. In the included literature, different rehabilitation treatment methods were adopted.

In conclusion, BTX-A can effectively enhance motor function, and is an effective method for the treatment of children with spastic cerebral palsy. But in the process of clinical application must be comprehensive consideration of various possible factors, strict and reasonable grasp of the dose of treatment, in order to achieve the best treatment effect.

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