Effect of a combined rehabilitation program with botulinum toxin type A injections on gross motor function scores in children with spastic cerebral palsy; a systematic review

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ABSTRACT

Cerebral palsy (CP) is primarily a disease of movement and posture. Spastic CP is the most common type of CP and is characterized by muscle spasticity. The management of CP aims to improve the function of the patients. Botulinum toxin type A (BTX-A) is one of the most effective therapies for focal spasticity for children with CP. Rehabilitation is also effective for CP when applied to children aged younger than 6 years. The study aimed to assess the effect of the combination of a rehabilitation program and BTX-A on spastic CP among children by reviewing the previous studies conducted on this subject. PubMed and Google Scholar databases were used for searching purposes to obtain articles related to the subjects of interest. The included searching terms were rehabilitation, physiotherapy, CP, children, spasticity, effect, combination, and BTX-A, which were used in several combinations to obtain all possible articles related to the current subject. A total of 340 articles were obtained; only six articles were eligible for the inclusion criteria. The six studies included 368 patients, and the longest duration of assessment was up to 13 months. The collected data from the included studies were summarized in one table. The combination of BTX-A therapy and rehabilitation for spastic CP children resulted in significant improvements in function, reduction in spasticity, improving strength compared to using BTX-A alone.

Keywords: Rehabilitation, BTX-A, spastic CP, gross motor function scores.

Introduction

Cerebral palsy (CP) is a neuromotor disease affecting the development of muscle, movement, and posture [1-3]. CP is a chronic disability of the central nervous system involving tone and posture occurring early in the life of an individual; it is the most common motor disability among children [4].

The incidence of CP is 7.5/1,000 live births in case of multiple births, whereas it is 2.1/1,000 live births in singletons; the incidence is much higher among children born 1,500 gm or less, and the incidence is 80/1,000 [4]. The prevalence of CP has increased as a result of the enhanced survival of very premature neonates weighing less than 1,000 gm who are more predisposed to develop CP with an increased risk of 15 per 100 live births [4].

The pathophysiology of CP is an injury to the developing brain during the prenatal through neonatal duration [1-3]. Children with CP might progress a range of...
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Secondary conditions over time that further affects their functional abilities [5,6]. There are various risk factors for CP, including low birth weight, multiple gestations, neonatal seizures, postnatal meninitis, preterm birth, pre-pregnancy obesity, and hypoxic-ischemic encephalopathy [7].

CP could be topographically classified into monoplegia, hemiplegia, diplegia, and quadriplegia. CP also could be classified based on the type of neuromuscular deficit into spastic, ataxic, hypotonic, mixed, and dyskinetic [4]. Spastic CP is the most common form of CP; it affects almost 70% of all cases with CP globally. Spastic CP is characterized by unique muscle tightness, and muscle spasticity could be experienced as the main impairment [8].

The classification of CP could be done through four functional classification systems, which are used to permit standardization for the assessment and therapy needs of the patients [9-14]. These systems, including the gross motor function classification system (GMFCS), which is used for the description of gross motor function, especially the ability of patients to walk, and is used for patients with age of 2-18 years. It is also used to describe movements assisted by devices and self-initiated movements [10,11].

The second classification system is the communication function classification system which is used for the description of the CP patients’ ability for daily routine communication, including manual signs, vocalization, and communication boards [13]. The manual ability classification system is another classification system used to describe the typical use of both upper extremities and hands of children from 4 to 18 years old [12]. The last classification system is the eating and drinking ability classification system which describes the function of eating and drinking for pediatrics with 3 years and older [14].

The management of CP involves increasing functions, sustaining health, and improving capabilities, not curing the patient. The management of spasticity is a major challenge for the treatment team [15]. Botulinum toxin type A (BTX-A) is one of the safest and effective therapy for focal spasticity for CP children [16] and for children with spasticity in general due to other causes as BTX-A reduces spasticity [16,17] and maintains a favorable range of motion in order to prevent vicious joint patterns [18,19]. The intramuscular injection of BTX-A was first introduced in the 1990s [20]. The use of BTX-A for CP is to reduce muscle overactivity, and as a result, reduce the risk of developing increased muscle stiffness [21]. BTX-A performs its effect by the inhibition of the neurotransmitter release of acetylcholine; its injection into a specific targeted muscle produces dose-dependent chemical denervation resulting in a reduction in over activity [22].

Physiotherapy and occupational therapy have shown more effective by the age of 4-5 years compared to its efficacy if started at a later age [23,24]. Rehabilitation interventions for the management of motor impairments in CP are mainly based on techniques aimed at repeatedly enhancing the paretic limb and, as a result, reducing spasticity [17,25].

There is heterogeneity regarding the adjunct therapies after BTX injection for optimization of the outcome. Rehabilitation programs were stated to be necessary after the injection of BTX [26]. Rehabilitation treatments including casting, strengthening exercise, movement training, stretch, and splinting are often provided in the context of normal activities. These therapies are thought to improve the range of motion and strength and, as a result, improve the function of patients [27]. There is little literature reported regarding the combination of BTX-A and rehabilitation programs for the management of children with spastic CP. So, this systematic review was performed to review the literature conducted on a combination of the rehabilitation program and BTX-A for the management of spastic CP in children.

Materials and Methods

The writing of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) checklist guidance [28]. The searching process involved revising electronic databases including, PubMed, and Google scholar databases. These two databases were explored for obtaining research articles with no specification of publication year.

Several keywords were used for the searching process, including rehabilitation, physiotherapy, CP, children, spasticity, effect, combination, and BTX-A. These keywords were used in various combinations to obtain all possible articles conducted on the subject of interest. All the titles obtained from this primary exploration were revised, and all titles which did not focus on the combination of rehabilitation and BTX-A injection in the treatment of CP were excluded.

The obtained articles were examined to choose only original research articles evaluating the rehabilitation programs combined with BTX-A for the treatment of spastic CP in the pediatric population. All articles were conducted on spastic CP and reported the combination of the two interventions, rehabilitation, and BTX-A injections, were included. Only articles in English and full-text articles were defined as articles of relevance for further steps.

The second step involved exploring abstracts manually to select the relevant studies for revision. All articles reported the combination of rehabilitation and BTX-A injection, spastic CP in children, full-text articles, and English articles were included. Duplicate articles, review articles, unavailable full-text articles, and studies that had incomplete or overlapped data were excluded (Figure 1).

A total of 340 articles were obtained; only 6 articles were eligible for the inclusion criteria. The 6 studies included 368 patients, and the longest duration of assessment was up to 13 months. All included articles underwent a preliminary review, and a specially designed excel sheet was used for data extraction. The extracted data was then
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Discussion

A total of six articles that met the eligibility criteria were included in this systematic review [29-34] (Table 1).

The included studies were published in different years; one study was published in 2018 [29], one study in 2017 [30], two studies in 2013 [31,32], one study in 2012 [33], and one study in 2009 [34]. Only two studies reported their design [29,31]; one study was prospective longitudinal [29], and the other was cross-comparison [31]. The remaining four studies did not report the study design [30,32-34]. The total number of patients in the included studies was 368, where the highest number was 244 patients [32], and the least number was 14 patients [33]. One study reported that their patients were ambulatory children [29], and another study reported that their patients were non-ambulatory children [30].

Three studies reported that their patients were suffering spastic diplegia CP [29-31], whereas one study reported that the patients only had spastic CP with no more classification [32], and two studies reported that children had hemiplegic CP [33,34]. The age range of patients was one to 23 years; however, only one study [32] included adult patients with the pediatric population, whereas the remaining studies included only the pediatric population [29-31,33,34]. Only three studies reported the level of CP [30,31,33]; one study reported GMFCS level IV [30], another study reported GMFCS level I-II [31], and the last study reported GMFCS level I [33]. Five studies reported the affected limb and/or complaints [29-32,34]; one study stated that all children had dynamic equines foot deformity [29], another study reported spasticity in two lower extremity muscle groups [30], one stated spasticity in lower limbs [31], another study reported high gastrocnemius and soleus muscle tension [32], and the last study reported affected upper arms [34].

Regarding the protocol of therapy, there were variations in the protocol therapy between studies; however, there was accordance between studies regarding using of physiotherapy and injection of BTX-A. There were four studies that divided patients into two groups [29,32,33,34], whereas the remaining two studies didn’t categorize patients [30,31]. One study divided patients into two groups; one received BTX-A only, and the other received BTX-A followed by additional 2 weeks of intensive physiotherapy [29]. The other study divided patients into two groups; the experimental group received ≥2 hours/day rehabilitation, and the control group received <2 hours/day rehabilitation after the injection of BTX-A [32]. One study divided patients into a control group that received physical rehabilitation without progressive resistant training after BTX-A injection, and the other group included patients who underwent physical rehabilitation with resistant training after BTX-A injection [33]. The last study divided patients into two groups; one group received BTX-A only, and the other group received modified constraint-induced movement therapy and BTX-A [34]. One of the other two studies that didn’t categorize patients reported injection of BTX-A, followed by stretching plaster casts, and then solid ankle-foot orthoses and knee extension braces, then received physiotherapy [30], whereas the other study reported injection of BTX-A for all patients followed by strength training either before or after BTX-A injection [31].

The follow-up or assessment of function varied between studies, and it ranged from assessment before intervention to assessment 1 year after the intervention. Also, various assessment tools were used in each study; these tools included MAS [30,32], MTS [30], GAS [31], GMFM [32,33], and PMAL [34].

The main findings of the studies showed that the addition of 2-week physiotherapy after the initial injection of BTX-A resulted in significant improvements in gross motor function scores [29]. Another study revealed that simultaneous use of BTX-A and strength training was successful in reducing spasticity and improving the strength and achieved functional goals compared to injection of BTX-A alone [31]. Also, another study reported that rehabilitation training after BTX-A injection resulted in greater improvements to motor function compared to BTX-A alone [32]. A combination of BTX-A and Modified Constraint-Induced Movement Therapy (mCIMT) enhanced the improvement of the function of the affected limbs and enhanced the effect of BTX-A [34]. Physical rehabilitation with resistant training after BTX-A injection resulted in increased maximal plantar flexion torque compared to physical rehabilitation without resistant training [33]. One study reported the effectiveness of multilevel BTX-A injection for non-ambulatory children with CP but didn’t report the impact of physiotherapy, although all patients underwent physiotherapy for 3 months with 3 times/week [30].

The management goal of CP is to improve capabilities, increase function, and sustain health in terms of cognitive development, independence, locomotion, and social interaction [15]. The best clinical outcomes results from early intensive management. Various forms of therapy are available for CP patients [15].

BTX-A injection could help the child improve his ability to walk and use the hands and allow better fitting orthotics by reducing spasticity [15]. The primary goal of using BTX-A is to reduce muscle over activity and, as a result, reduce the risk of developing muscle stiffness [21]. Following injection of BTX-A, muscle relaxations are evident within 48-72 hours and persist for a period of 3-6 months [15]. However, the reduction in muscle over-activity alone doesn’t lead to directly functional improvement [22]. One systematic review reported using adjunct therapies to improve the outcomes after injection of BTX-A. The review reported that rehabilitation programs after injection of BTX-A still need evaluation [26]. Therefore, this systematic review was conducted to evaluate the efficacy of rehabilitation combined with BTX-A injection for spastic CP children.
Spasticity is present among almost 80%-90% of CP children and results in abnormal motor function, contributes to reduced motor ability, and causes motor deficit [35-38]. Muscle spasticity in CP children might interfere with specific functions and services to facilitate others, so the reduction of spasticity should be considered within the context of its impact on function [7]. In most studies, diplegia is the most common form of CP, representing 30%-40%, whereas hemiplegia represents 20%-30% [4]. In the current review, spastic diplegia was the major type of CP reported in three studies [29-31], whereas hemiplegia was reported by only two studies [33,34].

It was found that the GMFM was the most commonly used in the included studies. The GMFCS is a recently developed system that classifies CP among children by age-specific gross motor activity. It describes the functional characteristics in five levels from level I through level V [1]. Of the six included studies, three studies [30] reported GMFCS level, and it was level IV [30], level I-II [31], and level I [33].

Physiotherapy has been found to improve muscle strength, joint range of movement, and local muscular endurance among CP children [39,40]. So, they could be a good adjunct therapy with BTX-A injection as it was stated that injection of BTX-A to reduce the over activity of muscles is not enough for the improvement of muscle strength. Increased muscle strength is achieved by performing regularly scheduled progressively increased resistive exercises [7]. The overall findings in this review as reported by the included studies revealed that the combination of rehabilitation programs with BTX-A injection resulted in improvement of the gross motor function, reduced the spasticity, improved the strength of muscles, achieved functional goals, and the effect of BTX-A was enhanced by combining rehabilitation programs in the treatment protocol. The outcomes of patients by combining rehabilitation programs with BTX-A injection were better compared to BTX-A alone.
Table 1. Description of the included articles in the review.

<table>
<thead>
<tr>
<th>Author and publication year</th>
<th>Study design</th>
<th>Population and affected organ</th>
<th>Protocol of therapy</th>
<th>Follow-up, assessment/tool of assessment</th>
<th>Results and main findings</th>
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</table>
| Flemban and Elsayed (2018) [29] | Prospective, longitudinal | -46 ambulatory children with spastic diplegia (Age = 25-154 months) | -Patients divided into two groups: Group 1: 18 children received BTX-A (6 units/kg) into the lower limb muscles, ankles were placed in plaster casts for 2 weeks and orthosis was prescribed after cast removal. A second BTX-A was given after 6 months. Group 2: 28 children received BTX-A (6 units/kg) into the lower limb muscles, ankles were placed in plaster casts for 2 weeks and orthosis was prescribed after cast removal. A second BTX-A was given after 6 months. | -The gross motor functions were recorded for both groups at baseline, 4, 6 and 52 weeks (1, 1.5, 13 months) | * There was an improvement from baseline in the mean gross motor function measure (GMFM) scores in both groups at the subsequent points of assessment with no significant difference.  
* The improvement in gross motor function scores was significant for Group 2 and non-significant for Group 1.  
* After 4, 6, and 52 weeks, Groups 1 and 2 showed 2.6% and 6.3% improvement, 4.8% and 12% improvement, and 5.5% and 19.4% improvement, respectively.  
* The addition of a 2-week physiotherapy program after the initial BTX-A injections produced significantly greater improvements in gross motor function scores. |
| Aydil et al. (2017) [30]     | —              | -17 non-ambulatory children with spastic diplegia (GMFCS) level IV (Age = 4-8 years) | -The muscles were injected at multiple sites with a maximum dose of 50 IU/muscle and maximum total dose of 110 IU/kg. Stretching plaster casts were applied up to the proximal parts of the lower extremities for 10 days. After removal of stretching casts, all patients had solid ankle foot orthoses and knee extension braces, and received physiotherapy. Physiotherapy was applied 3 times/week for 12 weeks (3 months), each session lasted 60 minutes. | -The gross motor function was assessed before, at first, third, and sixth month of BTX-A injection | * A statistically significant improvement was observed in fast angles of gastrocnemius and hamstring muscles at first and third months after BTX-A injection in non-ambulatory young children with CP.  
* Statistically significant improvement was found in MAS of gastrocnemius and hamstring muscles and slow angles of knee and ankle joint after first month of BTX-A injection.  
* Multilevel BTX-A injection, as part of an integrated approach, can be used for focal treatment of spasticity, especially of hamstring and gastrocnemius muscles, in non-ambulatory young children with CP gross function classification system level IV. |
| Williams et al. (2013) [31]  | Cross-comparison | -15 children with spastic diplegia CP (GMFCS) level I–II (Age = 5-12 years) | -All patients received two series of BTX-A for their lower extremity before the injection series of the study. All participants received BTX-A to bilateral medial gastrocnemius (30 legs injected; 2-6 U/kg), and five participants also received BTX-A to bilateral medial hamstrings (10 legs; 2-4 U/kg). Randomly allocated to 10 weeks of strength training either before or after BTX-A. | -Assessment was done over 6 months | * Spasticity was significantly reduced following BTX-A injection (p = 0.033).  
* Children made significant isokinetic strength gains in the intervention period compared to the control period irrespective of timing, significant strength improvements were seen immediately (10 weeks) and over 6 months for all children.  
* There were significant improvements in the GAS.  
* The simultaneous use of BTX-A and strength training was successful in spasticity reduction, improving strength and achieving functional goals, over and above treatment with botulinum toxin type-A (BoNT-A) alone. Muscles targeted for BTX-A injection should be included in strength training. |
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<th>Author and publication year</th>
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<tr>
<td>Jianjun et al. (2013) [32]</td>
<td>-----</td>
<td>-244 patients with spastic CP</td>
<td>-All patients received nerve block with BTX-A with a dose of 5-7 IU/kg or 7-9 IU/kg based on the degree of muscle tension and body weight, followed by: -in experimental group (120): ≥2 hours/day rehabilitation -in control group (124) &lt;2 hours/day rehabilitation</td>
<td>-The duration of action of BTX-A was assessed weekly -Motor function was assessed at 1 year post-block -MAS and GMFM were used</td>
<td>*There were no significant differences between the experimental group and the control group in age, body weight, pre-block MAS or GMFM, or BTX-A duration of Action. *MAS was significantly improved in both groups at 1 month post-block. *At 1 year post-block, GMFM was significantly improved in both groups, with a significantly greater improvement seen in the experimental group compared with the control group. *BTX-A block improved muscle tension and motor function. *Rehabilitation training, following the block, resulted in greater improvements to motor function than block alone.</td>
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<td>Bandholm et al. (2012) [33]</td>
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<td>-14 children with hemiplegic CP (GMFCS) level I</td>
<td>-All children received BTX-A treatment -Group 1 (7): underwent physical rehabilitation after BTX-A with resistant training 2/week for 12 weeks -Control group (7): received physical rehabilitation without progressive resistant training after BTX-A 2/week for 12 weeks</td>
<td>-At baseline, 4, 12 weeks (1, 3 months) after BTX-A -GMFM was used</td>
<td>*Submaximal torque control (torque steadiness) of isometric dorsiflexion improved similarly in the two groups, and the improvement was related to the reduction in antagonist (soleus) co-activity (p &lt; 0.05). *Maximal plantar flexion torque increased after physical rehabilitation with resistant training, whereas a reduction was seen after control (p &lt; 0.05). *No changes in function were observed. *Both types of physical rehabilitation in combination with BTX-A treatment improved antagonist (ankle dorsiflexion) torque-control to the same extent - which was related to the reduction in antagonist co-activity. *Only rehabilitation with PRT increased maximal plantar flexion torque.</td>
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<td>Park et al. (2009) [34]</td>
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<td>-32 children with hemiplegic CP</td>
<td>-All children received BTX-A into spastic upper limb muscles, where the dose was based on the weight, severity of spasticity and movement patterns -Group A (17): received combined therapy, Modified Constraint Induced Movement Therapy (mCIT) + BTX-A -Group B (15): received BTX-A only</td>
<td>-Assessment performed before and after 3 weeks of intervention -Pediatric motor activity log (PMAL) was used for the assessment of changes in the functional use of the affected arm</td>
<td>*There were significant improvements in the muscle tone and the movement patterns for both groups (p &lt; 0.05), and the changes were not significantly different between the two groups. *The How Often and the How Well scales in the revised PMAL were significantly improved in group A (p &lt; 0.05), but not in group B. *A combined therapy of mCIMT and BTX-A seems to be helpful to enhance the effects of the BTX-A injection in the functional use of the affected limb in children with hemiplegic CP.</td>
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</table>
It was reported in a systematic review that the resistance training could be an interesting adjunct therapy to avoid loss of strength following BTX-A injection [26]. Also, it could be concluded that rehabilitation programs with resistant training and BTX-A injection resulted in better outcomes compared to rehabilitation without resistant training and BTX-A injection.

**Conclusion**

The combination of BTX-A injection and rehabilitation for children with spastic CP showed significant improvements in function, reduction in spasticity, improving strength compared to using BTX-A alone; rehabilitation enhanced the effect of BTX-A. The effective application of rehabilitation is based on involving the affected muscles in physiotherapy.

**List of Abbreviations**

- BTX: Botulinum toxin
- BTX-A: Botulinum toxin type A
- CP: Cerebral palsy
- GAS: Goal Attainment Scale
- GMFCS: Gross motor function classification system
- GMFM: Gross motor function measure
- MAS: Modified Ashworth Scale
- MTS: Modified Tardieu Scale
- PMAL: Pediatric Motor Activity Log

**Conflict of interest**

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