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Physical Exercises in Combination with Botulinum Toxin in Treating Children with Cerebral Palsy: A Literature Review

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Background: Botulinum Toxin type-A (BoNT-A) is a safe and effective treatment for reducing spasticity in children with cerebral palsy (CP). BoNT-A injection into the muscles alleviate spasticity by interrupting neurotransmission at motor endplate (MEP). Physical activities combined with botulinum injections can help children with CP to become physically independent and improve their health-related quality of life.

Methods: 'Botulinum toxin' and 'Physical exercises' for children and adolescents, were searched in three major online databases (PubMed, Science Direct, and Scopus). Through the inclusion and exclusion processes from total 1,233, nine articles were selected for review.

Results: All studies included were experimental trials including various interventions. Botulinum toxins when paired with physical exercises to treat hypertonia, a condition in which a little change in tone can affect a child's balance, strength and motor function, as well as secondary concerns such as malalignment and repair contractures.

Conclusion: BoNT and physical exercises are two promising therapeutic techniques for treating children with CP that enable them for enhancing use and function of their afflicted limb.

Key Words: Botulinum toxins, Cerebral palsy, Physical exercises, Physical activity, Child, Quality of life

INTRODUCTION

Botulin neurotoxins is formed by toxins of the micro-organisms like *Clostridium botulinum* and *Clostridium barati*. Botulin neurotoxins are divided into seven distinguishable forms of animal antisera and selected in alphabetical order from A to G. Mechanism of action of botulin neurotoxin classified as: (1) Bond formation with nerve terminals (2) Abatement in bond of interchain disulphide [1]. Botulin act on nerve end plates to inhibit the release of neuropeptide and plays as an anti-inflammatory one [2]. Botulin injections are injected in neurological conditions like stroke, multiple sclerosis, amyotrophic lateral sclerosis, cervical dystonia, head and brain injuries it is effective in reduction of muscle spasticity by inhibiting the effect of acetylcholine and block the synapse transmission [3].

Apart from neurological conditions botulin injections are also administered in several health conditions such as congenital torticollis, myofascial pain syndrome, knee osteoarthritis, myofascial pelvic pain, stroke, burn and Cerebral Palsy (CP) [4]. Botulin neurotoxin is considered to be a safe invasive treatment for humans as it has restricted diffusion

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time period when injected locally, with high potentiality and reversible action [1]. The soul benefit of botulin administration in any condition is to reduce spasm, pain and inflammation and ameliorate patient condition [5]. Where administered in conditions like, burns botulin help in reduction from burn itching and prevent development of contracture [6].

CP is a series of permanent mobility and posture development abnormalities resulting in reduced functioning caused by non-progressive disruptions in the growing brain of the foetus or child. Sensation, perception, cognition, communication, and behaviour issues, as well as epilepsy and secondary musculoskeletal problems are frequently associated with motor function impairments [7]. CP occurs in 2-2.5 occurrences per 1,000 live births [8]. Spasticity is the most presentable symptom in CP. It is a sign of upper motor neuron injury, characterised by poor sensory-motor modulation of muscle tone exhibited by involuntary increase in muscular activity on a regular or fixed basis [9]. It inhibits motor function in children with CP at first and contributes to the growth of osteoarticular abnormalities over time. Botulinum Toxin type A (BoNT-A) injection is choice of treatments for reducing spasticity. It was first used to treat CP of gastrocnemius muscular stiffness. Since then its use has expanded to other lower limb muscles and upper extremity muscles. Unless a fixed contracture is developed in a pertinent joints, it is preferred therapeutic interventions in aberrant gait patterns reported in children with CP. BoNT-A prevents release of acetylcholine from the presynaptic terminal, blocking signal transmission at the neuromuscular junction [1]. This intervention has shown its potential by being both safe and successful in the treatment of spasticity in children with CP [10].

It is becoming evident that muscle deficits, such as spasticity and reduced strength, should be evaluated joint wise during assessment of CP children [11]. A multidisciplinary strategy to control spasticity and particular muscle strength in therapy of children has been advocated in previous studies. However there is a lack of data supportting this approach [12]. Presuming the same, the goal of the present study was to explore major internet databases (PubMed, Science Direct, and Scopus) for original papers on the effectiveness of physical exercise combined with botulinum toxin in rehabilitating children with CP.

METHODS

The present review was planned and commissioned by exploring major online databases such as PubMed, Science Direct, and Scopus for the key terms (botulinum toxin) AND (Physical exercise) with the following search terms: (Exercise intervention) AND (Botulinum injections), (CP) AND (children), (CP) AND (Botox) AND (Physical exercise), (CP) AND (Botox). Articles were chosen following fulfilment of inclusion criteria. The following criteria were used to determine inclusion of studies for review: scientific research articles based on the terms mentioned, studies involving children with CP, articles involving physical exercises and botox in the rehabilitation of children with CP, studies with a methodological quality score of more than 5 on the PEDro scale, randomized control/clinical trial study design. The following were the exclusion criteria: case studies, review articles, meta-analysis articles, letters to editors, proceedings, master's or doctorate unpublished theses, research on surgical management and non-clinical/non-human studies were excluded from analysis.

1. Selection of articles

Reviewers individually evaluated and analysed titles and abstracts acquired from the searches to explore if they met the inclusion criteria (PICOS). Full text of all titles and abstracts that satisfied the inclusion criteria were extracted. Three independent reviewers (SA, CA, and VS) examined the full-text papers to establish eligibility. To address differences among reviewers, the consensus method was adopted. Data was extracted from the included studies by two reviewers (SA and AC), and the results were double-checked by the third reviwer (VS). All point estimations were double-checked at the RCT level. Only children received botulinum injections and underwent exercise session were included in the study. Each RCT conclusion was extracted to give an overall estimation of the evidence.

RESULTS

A total of 1,233 articles were retrieved from various databases based on the keywords and carefully filtered for the title to avoid overlap. Necessary, additional filtering such as year of publication, randomized controlled/clinical trial was done by reading the abstracts and main text of the articles. Every possible article was thoroughly examined. Complete content of 26 articles were examined to ensure inclusion criteria along with their research intervention and subjects were met. 19 publications dealing with surgical intervention were excluded. Finally, the present review comprise of total 9 articles with their detailed analysis. All selected articles are randomized controlled/clinical trials with total of 277 patients (Fig. 1).

Demographic characteristics of studies included in the review are as shown in Table 1. Study article presentation with objective, intervention, conclusion with methodological quality assessment using PEDro scale is shown in Table 2. RCT's included in review are of high quality.

DISCUSSION

To begin with, functional improvement is the principal objective behind treating spasticity in CP. In addition, preventing muscular contractures is another key goal. Botulinum toxins pose specified effect when used for children and adults [10]. Unlike adults, who are relatively static organisms, children have two distinct processes of childhood, growth and development, overlaid on the underlying hypertonic condition [13]. Although botulinum toxins treat hypertonia, the small change in tone supports a child's balance, strength, and motor function, as well as secondary issues like malalignment and repairing contractures [14].

Koman et al. [15] reported the very first safe and success-

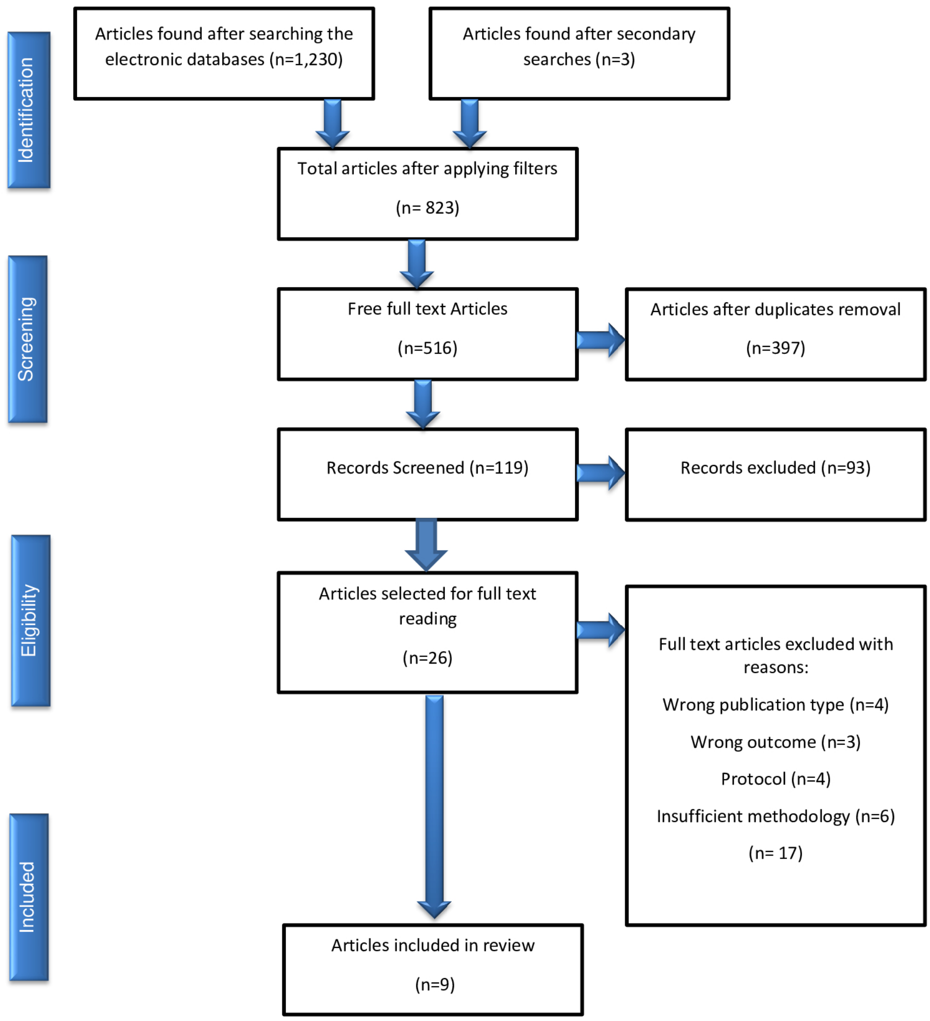

Fig. 1. Flow chart for selecting studies for review.

Table 1. Demographic characteristics of the included articles for review

Author (year)	Country	Research outline	Total participants (males, females)	Age of patients (years)*
Williams et al. (2013)	Australia	Randomized controlled clinical trial	15 patients	8 y 5 m ± 1 y 10 m
Elvrum et al. (2012)	Norway	Pre-post intervention study	10 patients	Group B = 12 ± 3.3 y Group BT = 14.8 ± 3.0 y
Hoare et al. (2013)	Australia	A randomized trial	34 patients	3 y ± 1 y 4 m
Lidman et al.(2015)	Sweden	A randomized controlled trial	14 patients	Median age - 3 y 1 m
Speth et al. (2015)	Netherlands	A Clinical trial	35 patients	7.4 ± 2.63 y
Desloovere et al. (2012)	Belgium	Randomized controlled study	38 patients	BTX-A+NDT group = 3 y 1 m ± 15 y 5 m BTX-A+ Conventional Physiotherapy group = 2 y 9 m ± 14 y 7 m
Park et al. (2009)	South Korea	Randomized controlled trial	32 patients	Median age Group A = 3 y 5 m Group B = 4 y 8 m
Kaishou et al. (2009)	China	Randomized controlled trial	65 patients	BTXA-E group = 55.3 ± 11.5 BTXA-P group = 59.4 ± 22.7 Physiotherapy group = 51.7 ± 8.6
Thomas et al. (2016)	Australia	A single-blind randomized comparison trial	34 patients	Group Physiotherapy = 7 y 8 m ± 2.0 Individual Physiotherapy group = 8 y 7 m ± 2.0

BTXA-E: botulinum toxin A injection guided by electrical stimulation plus physiotherapy, BTXA-P: botulinum toxin A injection guided by palpation plus physiotherapy, NDT: neurodevelopment treatment.
*y: years, m: months.

ful use of BoNT-A in infants with CP in 1993. Following this study, other clinical trials with the aim of considerable reduction in spasticity following BoNT-A injection were published [16]. However, it has recently been stressed that functional improvement is more significant than focussing reduction in muscle tone and an increase in joint range of motion. Spastic muscles fail to grow as quickly as nearby structures as the child grows, leading to dynamic abnormalities to become fixed deformities or contractures. Stretching, development, and contracture prevention are all made easier by relaxing spastic muscles. It also permits weak antagonist muscles to be strengthened. These enhancements result in increased functionality [10,17].

Dynamic development have been noticed in both, healthy children and children with spastic movement disorders during the first six years of life. As a result, all therapeutic interventions in the early stage of life are assessed in the context of a rapidly developing and changing motor system. Early intervention necessary to maximize a child's developmental potential and extract maximal therapeutic outcome [18]. Cosgrove and Graham et al. [19] verified association between spasticity and reduced muscle growth in a randomised controlled trial among inherited spastic mouse model showing injecting of botulinum toxin in gastrocnemius muscle earlier in the growth period to pose favourable effect.

BoNT-A is still recommended as a supplementary method in young children with spastic CP. Stretching exercises and orthotics are recommended for younger children since greater mobilisation and contracture reduction are still possible. It's crucial to choose the right patients [19]. There are high chances of an early surgery to impose deteriorating effect on spasticity in children up to the age of six [20].

Scholtes et al. [21] studied effect of multiple levels BoNT-A injections on gait pattern and spasticity in 46 children with spastic CP as part of a comprehensive therapy. They discovered following 6 week of injections, spasticity of hamstrings, soleus, and gastrocnemius muscles decreased

Table 2. Presentation of articles according to the objectives, intervention methods, conclusion with PEDro scoring.

Authors (year)	Objective	Intervention	Results	Conclusion	PEDro Score
Williams et al. (2013)	Effects of strength training and Botulinum Toxin Type-A (BoNT-A) in children with Cerebral Palsy on muscular strength and morphology	Participants performed a 10-week home-based strength training programme that included three sessions per week. Manual and passive stretching of the lower limb muscle groups were incorporated in each training session. Progressive strengthening exercises were given with repetitions and loading levels as the child's strength increased.	Spasticity was reduced significantly ($p = 0.033$) post BoNT-A injection. In the intervention phase, children improved their isokinetic strength significantly (mean $p = 0.022$, ES = 0.57) compared to the control period (mean $p = 0.15$, ES = 0.56)	Treatment with BoNT-A alone, the combination of BoNT-A and strength training was effective in reducing spasticity, enhancing strength, and reaching functional goals	8/10
Elvrum et al. (2013)	To investigate effects of additional resistance training on the upper limbs in children with CP after using Botulinum Toxin-A (BoNT-A)	BoNT-A injections in the pronator teres were given to all individuals in Groups B (BONT-A therapy) and BT (BONT-A injection with eight-week resistance training). BoNT-A injections in biceps brachii and brachialis were also given to three subjects in Group B and two in group BT	Short-term treatment benefits in favorgroup BT for muscular strength in injected muscles (elbow flexor strength, $p = 0.08$) and non-injected regions (elbow extension and supination strength, both $p = 0.05$) were significant or near to significant,. Both groups improved their active supination range, but group BT improved more ($p = 0.09$)	Without increasing muscular tone, resistance training temporarily strengthens non-injected muscles and may decrease short-term strength loss caused by BoNT-A injections	6/10
Hoare et al. (2013)	Examine the effects of modified mCIMT with a carefully specified, standard BOT programme on bimanual upper limb performance in young children with unilateral CP after upper limb injections of BoNT-A	BoNT-A and mCIMT to the experimental group ($n = 17$). BoNT-A and BOT were given to the comparison group ($n = 17$)	BONT-A + mCIMT: EMD 2.7, 95% confidence interval 0.7-5.2; BONT-A + BOT: Estimated mean difference 95% confidence interval 2.1–8.6) showed improvement with time	In young children with unilateral CP, there was no evidence that mCIMT was superior than a structured BOT programme in terms of bimanual upper limb performance, functional skills, occupational performance, or goal attainment outcomes after injection of BoNT-A	8/10

Table 2. Continued 1

Authors (year)	Objective	Intervention	Results	Conclusion	PEDro Score
Lidman et al. (2015)	In children with unilateral spastic cerebral palsy, the effects of repeated botulinum toxin A (BoNT-A) injections combined with occupational therapy, including a splint, were compared to the effects of occupational therapy alone on hand function in all international classifications of functioning, disability, and health domains	Both groups got two 8-week therapy blocks that included the establishment of a home programme as well as a weekly consultation with an occupational therapist. Manual stretch (once a day) and the use of a static circular splint were used in conjunction with bimanual training (56 hours in 8 weeks) of repeated task practise and goal-directed exercises (8 h per night). The splint was created with the elbow flexed, the forearm in supination, and the thumb in radial and volar abduction on an individual basis	At 12 months, the BoNT-A/OT group had a better effect on hand assessment: 6 out of 10 in the occupational therapy group improved, compared to 1 out of 10 in the control group ($p < 0.03$)	In young children with unilateral spastic CP, repeated BoNT-A/OT proved to be superior to occupational therapy alone for bimanual performance. Both groups improved their active ROM and goal performance	7/10
Speth et al. (2015)	Effects of botulinum toxin Injections in the upper extremity along with bimanual task-oriented therapy or each treatment method administered independently in children with unilateral Cerebral Palsy	For 12 weeks, the Bimanual task focused therapy programme comprised of half an hour of physiotherapy (PT) and one hour of occupational therapy (OT). Two times a week, children in the outpatient clinic got PT and OT (12 hours) following each other	The quality scores,posture during grasping and holding, notably in the younger children, improved significantly in the BoNT-A group. At 12 and 24 weeks, the BITT group improved greatly on the AK and much more on the COPM's performance and satisfaction scores on various goals	During the three months of work, BoNT-A has a beneficial influence on the quality of mobility and amount of use of the affected upper extrimity. Bimanual performance and achievement of goals are unaffected by BoNT-A	6/10
Desloovere et al. (2012)	To compare the effects of various physiotherapeutic programmes in children with Cerebral Palsy after treatment with BTX-A.	First group received BTX-A on multiple levels, followed by NDT Second group - Multilevel BTX-A injections, followed by conventional physiotherapy (muscle strengthening, stretching,). All patients got multilevel BoNT	Overall treatment efficacy was attained in 76 % of the targets in the NDT group, compared to 67 % in the conventional physiotherapy group	The short-term benefits of a NDT approach are more evident in a post-BTX-A regimen than those of a traditional physiotherapy technique	6/10
Park et al. (2009)	To see if using modified constraint-induced movement therapy (mCIMT) after a BoNT-A toxin (BoNT-A) injection in the spastic upper extremity of children having hemiplegic cerebral palsy improves the effects of the BoNT-A injection	Group A - BoNT-A and mCIMT Group B - BoNT-A injections	Both groups showed significant improvements in muscle tone and movement patterns ($p < 0.05$)	In children with hemiplegic CP, combined mCIMT and BoNT-A therapy generally improves the effect of the BoNT-A injection in the functional use of the affected limb	5/10

Table 2. Continued 2

Authors (year)	Objective	Intervention	Results	Conclusion	PEDro Score
Kaishou et al. (2009)	To compare the effectiveness of different types of botulinum toxin to treat ankle plantar flexor spasticity, an injection guided by several localising techniques, electrical stimulation, and palpation is used	Group A - Botulinum toxin A injection group guided by electrical stimulation plus physiotherapy Group B - Botulinum toxin A injection group guided by palpation plus physiotherapy Group C - Physiotherapy	Three groups showed a substantial improvement ($p < 0.05$). In the botulinum toxin group guided by electrical stimulation injection plus physiotherapy, the mean improvements between baseline and the end of follow-up were respectively 20, 16.2 and 11.9 degrees for passive ROM, 1.9, 1.4 and 0.7 for modified Ashworth Scale scores, 5.8, 4.2 and 2.3 for Composite Spasticity Scale scores, 18.6, 11.3 and 6.9 for Gross Motor Function Measure scores, and 0.2, 0.1 and 0.1 m/s for walking velocity	In children with cerebral palsy, botulinum toxin injections combined with electrical stimulation and physiotherapy are most likely to improve spasticity and functional performance	7/10
Thomas et al. (2016)	The goal of this study was to compare the efficacy of groupindividual physiotherapy rehabilitation for ambulant children with cerebral palsy after lower limb intramuscular injections of Botulinum Toxin-Type A (BoNT-A)	Total treatment time (six hours, six weekly 60-minute sessions). The only difference between the two groups was the therapeutic delivery technique. Both groups got the same direct dosage and content of the treatment based on the groups and individual groups	Both groups showed clinically major improvements in COPM performance, but only a slight improvement in gait quality (EVGS). Following lower limb BoNT-A injections, six hours of direct physiotherapy were combined with an additional indirect dose (median 16 episodes) of personalised home programme exercises	After lower limb injections of BoNT-A, this pragmatic randomised comparative trial demonstrated no clinically relevant changes in any primary or secondary outcomes between group and individually provided physiotherapy	8/10

significantly which was maintained for 12 weeks and also sustained till 24th week. While patients in their study were ambulatory with Gross Motor Function Classification System (GMFCS) levels I-III, patients were non-ambulatory at GMFCS level IV and exhibited considerable reduction in spasticity. These findings, are critical in demonstrating efficacy of the BTX-A injections in non-ambulatory young infants with CP GMFCS level IV.

It is becoming increasingly evident that muscle deficits of spasticity and strength should be evaluated together while planning treatment of children with CP. A multi-disciplinary approach to spasticity reduction and particularly muscle strength for children with CP has been supported by various researchers [22]. Williams et al. [12] investigated effect of strength training and BoNT-A on muscular strength and morphology in children with CP. Hence, concluded combination of BoNT-A and strength training to be more effective than BoNT-A alone in reducing spasticity, improving strength, and achieving functional goals. Thus suggesting strength training to involve muscle targeted with BoNT-A injection [12].

Following injecting BoNT-A in upper extremities, Elvrum et al. [11] investigated effects of extra resistance training in CP children. Without raising muscular tone, resistance training temporarily strengthens non-injected muscles and decreased short-term strength loss caused by BoNT-A injections. Furthermore, resistance training improved active range of motion more effectively than BoNT-A alone. Hardly any improvement in neuromuscular deficits improved in the hand and arm. Larger clinical trials are needed to determine whether resistance training offer counter strength loss incurred by BoNT-A, whether combination of BoNT-A and resistance training were beneficial compared to either BoNT-A or resistance training alone in getting better active range of motion, and whether increased task-related training is a more effective way to improve active range of motion and whether increasing task-related training is a better way to improve hand and arm usage in children with CP [10].

According to Hoare et al. [23] BoNT-A paired with occupational therapy improves upper limb outcomes in children with unilateral CP. In young children with unilateral CP, the significantly higher intensity of the home programme produced a superior benefit across a variety of outcomes when compared to a structured program of bimanual occupational therapy.

Lidman et al. [24] examined effect of repeated BoNT-A injection combined with occupational therapy with hand splint on physical functioning in children with unilateral spastic CP in comparison with occupational therapy alone in all International Classification of Functioning, Disability and Health domains. In early children with unilateral spastic CP, repeated BoNT-A/Occupational therapy posed superior to occupational therapy alone for bimanual performance. Both groups improved for their active ROM and goal performance.

Speth et al. [25] evaluated effect of BoNT-A injection on muscles of upper limbs in children with unilateral CP already received either Bimanual Task oriented Therapy (BITT) or each treatment modality separately. During the three months of its action, BoNT-A showed beneficial impact on the quality of motion and load accepted by the affected UE. Bimanual performance and achievement of goals are unaffected by BoNT-A. Even up to 6 weeks after therapy, BITT refelected positive influence on achieving objectives and bimanual performance. Desloovere et al. [26] evaluated impact of several physiotherapeutic programmes in a post-BTX-A regime for children with CP. To them the short-term effects of an NDT method proved more pronounced in post-BTX-A regime than those of a traditional physiotherapy technique.

Following a BoNT-A injection, Park et al. [27] studied if modified constraint-induced movement therapy (mCIMT) could help in improving upper limb functions. Asa result of BoNT-A injection to the spastic upper limb of children having hemiplegic CP was found to be improved. Combination of mCIMT and BoNT-A therapy appears to improve the functional effects of the BoNT-A injection in children with hemiplegia. With aim to treat spasticity of ankle plantar flexors, Kaishou et al. [28] tested efficacy of BoNT-A injection guided by different localising techniques, electrical stimulation, and palpation. They concluded that botulinum toxin injection combined with physiotherapy and electrical stimulation are likely to be effective in reducing spasticity and functional performance in children with CP.

Both group and individual physiotherapy models displayed excellent acceptability and practicality, giving physiotherapists a choice to offer rehabilitation towards ambulanting children with CP after lower extremity intramuscular BoNT-A injections to optimize occupational performance results. Future research is needed to isolate dose (direct and indirect) and delivery of physiotherapy to achieve functional lower limb change following BoNT-A injections [29]. Physical exercises improves endurance, functional ability, inspiratory muscular strength, and delays disease progression. The practise should be made available to the rural, suburban, and metropolitan populations, thus catering to all socioeconomic groups [30]. Children with CP require ongoing education that satisfies the needs of both the children and their parents or caregivers. Independent ambulation is more difficult to come by, especially in resource-strapped settings [31].

CONCLUSIONS

Botulinum toxin injection and physical exercises are two promising therapeutic approaches for treating children with CP that help them utilise their affected limb more easily and enhance their functions. Tone reduction and functional improvements can be achieved by injecting BoNT-A into spastic limb muscles. As a result, combining these two interventions in children with CP would result in improved functional gains in the affected limbs.

CONFLICTS OF INTEREST

None to declare. No funding received for this study.

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