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A systematic review and meta-analysis of neuromuscular electrical stimulation post-botulinum toxin injection in children with cerebral palsy

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The aim of our study is to investigate whether adjunct neuromuscular electrical stimulation (NMES) therapy improves functional performance outcomes in children with cerebral palsy (CP) who have received botulinum toxin (BTX) injections. We searched the PubMed, Cochrane Library, CINAHL, EMBASE, and Scopus databases for randomized controlled trials studying the effects of NMES after BTX injection in children with CP from database inception to July 3, 2024. Two independent reviewers extracted data, and risks of bias were assessed using the PEDro scale for randomized controlled trials. We included 5 randomized controlled trials in this meta-analysis. NMES treatment following BTX injection resulted in greater functional performance outcomes compared with BTX injections alone (standardized mean difference = 0.57; 95% CI = 0.22 to 0.92). However, NMES following BTX injections did not significantly improve spasticity outcomes (standardized mean difference = 0.28; 95% CI = – 0.21 to 0.76). Despite including only a small number of trials, the present analysis demonstrated that NMES is an effective adjunct to BTX injections for managing CP in children. Further research must be conducted to refine these therapies, ensure better outcomes, and alleviate the burdens faced by individuals with CP.

Keywords Cerebral palsy, Electrical stimulation, Botulinum toxin, Meta-analysis, Spasticity.

Cerebral palsy (CP) is a complex neurological disorder characterized by abnormalities of muscle tone and motor functions[1]. The disorder is caused by damage to the brain that occurs before the brain has matured[2]. CP is nonprogressive but leads to a range of physical and developmental challenges[3]. Spasticity is the most prevalent motor impairment among individuals with CP—80% of children with CP have spasticity[3]. CP is typically accompanied by sensory, perceptual, cognitive, communicative, and behavioral problems[4]. The burden of CP is profound, affecting not only the afflicted individual but also their families and caregivers.

A common therapeutic approach for managing spasticity in individuals with CP is the use of botulinum toxin (BTX) injections[5]. Focal injection of BTX effectively reduces muscle spasticity while giving clinical symptoms similar to myasthenia gravis[6]. Another common approach for managing spasticity is neuromuscular electrical stimulation (NMES), a technique that involves using electrical impulses to stimulate nerves and muscles[7]. NMES has been proven effective in enhancing functional performance, coordination, and muscle strength[8,9], and the technique is increasingly being employed as an adjuvant treatment to enhance the efficacy of BTX injections[10]. BTX plus NMES combined treatment approaches involve the targeted administration of BTX injections to alleviate spasticity in specific muscles, followed by the application of NMES[11]. BTX injections provide a brief

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window of reduced spasticity, during which NMES can be applied to facilitate muscle strengthening and coordination improvements[10].

Several studies have examined the efficacy of combined BTX and NMES therapies for treating spasticity and functional performance, particularly in patients with CP[12]. The present systematic review and meta-analysis was conducted to examine the efficacy of combined BTX and NMES treatment on functional performance in children with CP.

Methods

This meta-analysis and systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42024559545) on June 29, 2024. The PRISMA checklist is presented in Supplementary Appendix A.

We analyzed randomized controlled trials that examined functional performance outcomes in children with CP following the use of NMES as an adjunct to BTX injections. The following Patient, Intervention, Comparison, and Outcome criteria were applied to determine which randomized controlled trials were to be included for analysis:

P: Children with CP.

I: NMES after BTX injection to treat spasticity.

C: BTX injection to treat spasticity without the use of NMES.

O: Reporting functional performance.

We excluded trials that were not peer reviewed, such as conference papers, letters to editors, and trials that only presented protocols. We also excluded review articles and trials that lacked sufficient data. No restrictions on language or journal type were applied.

We searched the PubMed, Cochrane Library, CINAHL, EMBASE, and Scopus databases for relevant trials published between database inception and July 3, 2024. The search was conducted using the following keywords and synonyms: ("cerebral palsy" or CP or (cerebral palsy [MeSH])) AND (BTX OR "botox" OR BoNT OR botulinum) AND ("electrical and stimulation" or "electric and stimulation" or electrostimulation or ES or FES or NMES). Only randomized controlled trials were included, and only 1 count was made for articles from a series or duplications in the same or different journals.

Two reviewers independently screened the titles and abstracts of retrieved articles. Full texts were reviewed when necessary. Disagreements regarding the Patient, Intervention, Comparison, and Outcome criteria were resolved by achieving a consensus with a third reviewer.

Two reviewers independently assessed risks of bias by using the Physiotherapy Evidence Database (PEDro) scale for randomized controlled trials[14]. Discrepancies in domain scores between the 2 reviewers were resolved through discussion with a third reviewer until a consensus was reached with a two-thirds majority. Total PEDro scale scores are between 0 and 10 and are classified as poor (0 to 3), fair (4 to 5), good (6 to 8), or excellent (9 to 10)[14]. The PEDro scores did not influence article inclusion or exclusion decisions.

Two authors independently extracted data from each included trial. The following parameters were extracted from each trial: patient number, age, gender, CP type, treatment duration, and follow-up duration. The NMES waveform, location, frequency, intensity, pulse width, and session frequency and duration were assessed. The primary and secondary outcomes were functional performance and spasticity, respectively. For each included study, the outcomes at the last follow-up were assessed. Discrepancies were identified and resolved through discussion with a third reviewer. Unclear or missing data were addressed by contacting the study authors via email.

Statistical analyses were conducted using RevMan 5.4 software (Cochrane Collaboration), which is available at https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download. This study followed guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[15]. All continuous data were converted to the same scale by using standardized mean differences (SMDs) with 95% CIs. Pooled data were analyzed using a random-effects model. Statistical heterogeneity was assessed using an I^2 test, with I^2 scores of more than 50% indicating high heterogeneity. In the case of high heterogeneity, a sensitivity analysis was performed to validate the effect. Statistical significance was indicated by $P \leq .05$. Cohen's d-based SMDs were used as follows to gauge the likely clinical significance of relationships: <0.2 (*clinically meaningless effect*), 0.2 to 0.5 (*small effect*), 0.5 to 0.8 (*moderate effect*), and >0.8 (*large effect*)[16].

The Grading of Recommendations, Assessment, Development, and Evaluation approach was employed to assess the quality of evidence and confidence in effect estimates[17]. This approach involves evaluating the quality of publications by considering study design (randomized vs. nonrandomized study design), risk of bias, inconsistency, imprecision, and indirectness. Size and trend in the effect were also considered during the evaluation process[17].

Results

The article inclusion process is presented in Fig. 1. Initially, 84 articles were retrieved, and 40 duplicates were excluded. After title and abstract screening, 27 articles were excluded for irrelevance, leaving 17 articles remaining for full-text assessment. Among these articles, 8 were review articles, 2 were conference papers, 1 was a study protocol, and 1 lacked sufficient data. Finally, 5 articles met al.l inclusion criteria and were included in this systematic review and meta-analysis[11,18–21].

The 5 included trials were published between 2015 and 2021[11,18–21], involved 131 children (NMES group, $n=65$; control group, $n=66$) with spastic CP after BTX injections, and reported outcomes associated with functional performance. Because each included study used different measurements for motor and functional

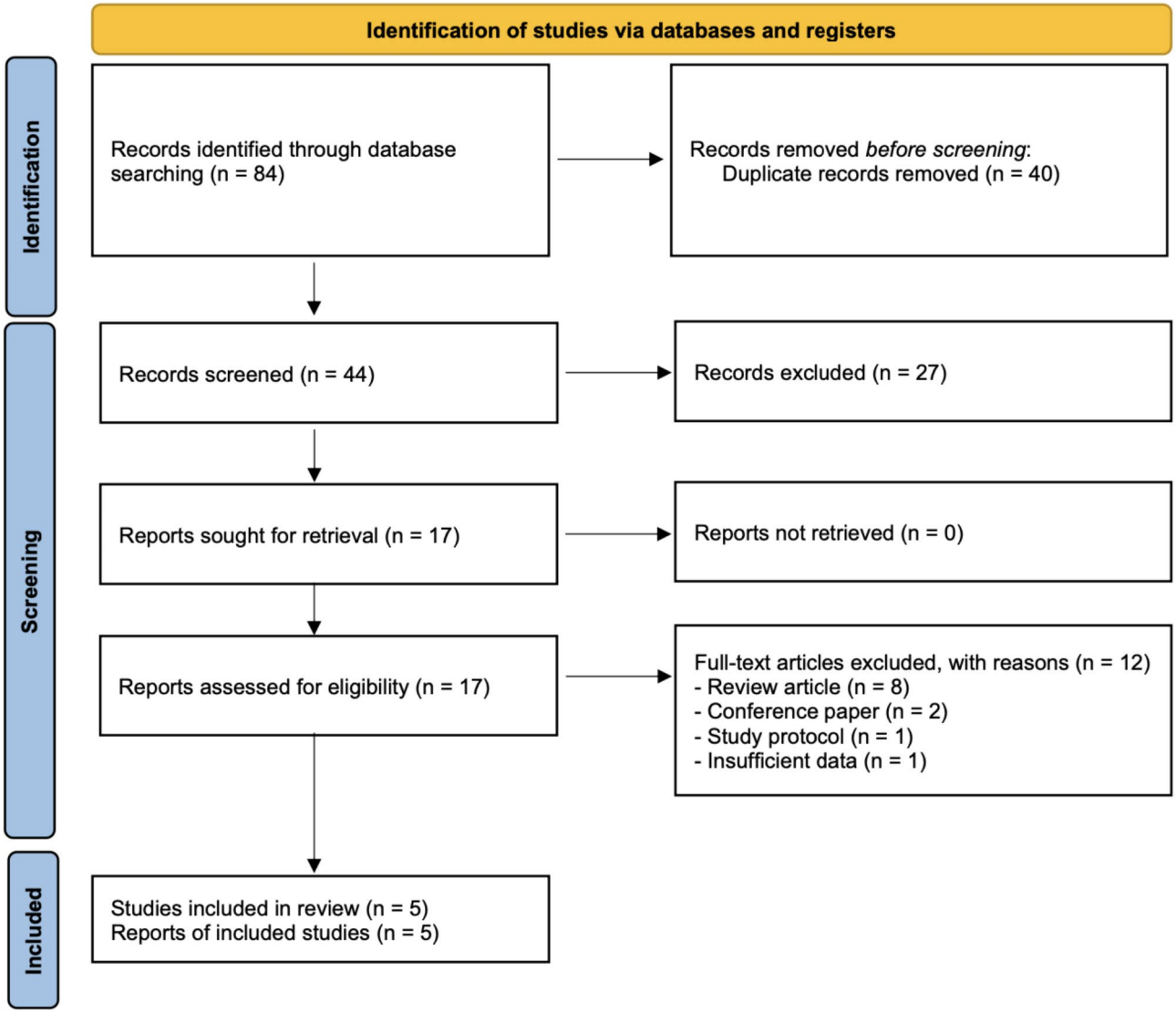

Fig. 1. Article selection process.

performance—such as the Gross Motor Function Measure-88, the Melbourne Assessment, passive hamstring extensibility, and dynamic limits of postural stability—we combined the primary or main outcome from each study to illustrate overall changes in motor and functional performance. Three trials reported spasticity outcomes, which were assessed using the Modified Tardieu Scale and Modified Ashworth Scale[11,20,21].

The effects of NMES were compared to those of a placebo or a combination with the baseline treatment. Özen et al.[21] included patients who had already received BTX injections and subsequently received either NMES plus standard treatment, sham NMES plus standard treatment, or standard treatment alone. We included only the NMES plus standard treatment and the sham NMES plus standard treatment groups in our meta-analysis. Furthermore, the study focused on functional electrical stimulation (FES), a targeted application of NMES designed to facilitate specific functional movements. Elnaggar et al.[18] classified participants into BTX, NMES, combined BTX plus NMES, and control groups. We included only the BTX and the combined BTX plus NMES groups, both of which had standard physical rehabilitation as a baseline treatment. Mudge et al.[20] randomly assigned one leg of each of the participants in their trial into an experimental group, with the other leg of each participant being assigned to a control group. All legs received BTX injections and underwent a stretching program. The legs in the experimental group received adjunct NMES stimulation. Elnaggar et al.[19] divided participants into NEMS, BTX, and integrated NMES plus BTX groups and applied a regular exercise rehabilitation program. Of these groups, we included only the BTX and the integrated NMES plus BTX groups. Yiğitoğlu et al.[11] had a BTX-only control group and a combined BTX plus NMES group, both of which underwent a home-based exercise program. The characteristics of the included trials are detailed in Table 1.

Three of the included trials adjusted the intensity of the electrical stimulator to elicit muscle contractions[11,18,19]. One trial had a maximum stimulus intensity of 100 mA[21], and one trial did not report the intensity of stimulation used on the patients[20]. Botulinum toxin-A was used in all 5 trials to reduce spasticity[11,18–21]. In 2 trials, the BTX

Study	Group	Protocol	Protocol of exercise	Type of CP	Participants	Age (years), Mean (SD)	Treatment duration	Follow-up duration	GMFCS I/II/III	Outcomes included in meta-analysis
Özen et al., 2021[21]	NMES	BTX, FES, and standard treatment	Range of motion exercises, stretching, balance training, neurophysiologic exercises, resistance training, gait training, and occupational therapy.	Diplegic CP	9	6 (1.7)	4 weeks, 5 times/week	At the end of the intervention	N/A	MTS and GMFM-88
	Control	BTX, sham FES, and standard treatment			9					
Elnaggar et al., 2020[18]	NMES	BTX, NMES, and standard treatment	Unimanual and bimanual functional activities, functional strength training, hand weight-bearing exercises, stretching exercises, and bilateral-arm and inter-arm coordination exercises.	Hemiplegic CP	15	7.67 (1.23)	One-time treatment	6 months	N/A	MA and AHA
	Control	BTX and standard treatment			16	7.57 (1.29)				
Mudge et al., 2015[20]	NMES	BTX, NMES, and daily stretch program	Stretch the hamstring muscles of both legs.	Diplegic CP	5	9.1 (N/A)	12 weeks, 5 times/week	6 months	N/A	MTS and passive hamstring extensibility
	Control	BTX and daily stretch program			5					
Elnaggar et al., 2019[19]	NMES	BTX, NMES, and standard treatment	Neurodevelopmental training, balance training, functional training, range of motion exercises, and functional stretching exercises.	Diplegic CP	17	5.35 (1.22)	12 weeks, 3 times/week	6 months	0/5/12	Overall dynamic limits of postural stability
	Control	BTX and standard treatment			17	6.23 (0.70)			0/11/6	
Yiğitoğlu et al., 2019[11]	NMES	BTX, NMES, and home-based exercise program	Calf stretching, ankle dorsiflexor muscle strengthening, and walking exercises.	Diplegic CP	19	6.1 (2.2)	10 days, 20 min/day	3 months	5/5/9	MAS and GMFM-88 (Dimensions D and E)
	Control	BTX alone and home-based exercise program			19	6.5 (2.1)			4/4/11	

Table 1. Characteristics of selected trials. *AHA* assisting hand assessment, *CP* cerebral palsy, *GMFCS* gross motor function classification system, *GMFM-88* gross motor function measure-88, *MA* Melbourne assessment, *MAS* modified Ashworth scale, *MTS* modified Tardieu scale, *NMES* neuromuscular electrical stimulation, *FES* functional electrical stimulation, *N/A* not applicable.

	NMES intervention group						BTX in both intervention and control group		
Study	Waveform	Location	Protocol	Frequency	Intensity	Pulse width	BTX type	Injection sites	BTX dosage
Özen et al., 2021[21]	Biphasic rectangular	Both sides of the quadriceps, hamstring, tibialis anterior, and gastrocnemius muscles	30 min a time, 5 times per week for 4 weeks	30–45 Hz	Maximum of 100 mA	250–300 μs	BTX-A	Hamstring and gastrocnemius muscles	N/A
Elnaggar et al., 2020[18]	Symmetrical biphasic square	Wrist flexor and extensor muscles	15 min a time, 3 times per week for 3 months	30 Hz	Visible contraction	300 μs	BTX-A	Determined using ultrasound-guided injection procedure	Maximum dose of 12 $U{\cdot}kg^{-1}$ bodyweight or 400 U; 0.5-2 $U{\cdot}kg^{-1}$ muscle group
Mudge et al., 2015[20]	N/A	Hamstring muscles	30 min a time, 5 times per week for 12 weeks	50 Hz	N/A	260 μs	BTX-A	Hamstring muscles	N/A
Elnaggar et al., 2019[19]	Symmetrical biphasic rectangular	Ankle dorsi and plantar flexors	30 min a time, 3 times per week for 12 weeks	30 Hz	Visible contraction and within tolerance	250 μs	BTX-A	Medial and lateral gastrocnemius and soleus muscles	Maximum dose of 12 $U{\cdot}kg^{-1}$ bodyweight or 400 U; 0.5-2 U per injection site
Yiğitoğlu et al., 2019[11]	N/A	Gastrocnemius muscle	20 min a time, once per day for 10 days	40 Hz	Visible contraction and within tolerance (7.5–22 mA)	350 μs	BTX-A	Gastrocnemius and soleus muscles	10 $U{\cdot}kg^{-1}$ bodyweight

Table 2. NMES and BTX intervention parameters. *NMES* neuromuscular electrical stimulation, *N/A* not applicable, *BTX* botulinum toxin.

dosage was 0.5 to 2 $U{\cdot}kg^{-1}$ muscle group, with a maximum dose of 12 $U{\cdot}kg^{-1}$ bodyweight or 400 U[18,19]. One study administered 10 $U{\cdot}kg^{-1}$ bodyweight to each participant[11]. Two studies did not report BTX dosages[20,21]. The intervention parameters are detailed in Table 2.

The results of risk-of-bias assessments are presented in Table 3. The risk-of-bias scores for each trial ranged from 5 to 7. Three trials had good scores[19–21], and two trials had fair scores[11,18]. All the trials adhered to random

Criteria	Özen et al., 2021[21]	Elnaggar et al., 2020[18]	Mudge et al., 2015[20]	Elnaggar et al., 2019[19]	Yiğitoğlu et al., 2019[11]
Random allocation	V	V	V	V	V
Concealed allocation	V		V		
Baseline comparability	V	V	V	V	V
Blind participants					
Blind therapists					
Blind assessors			V	V	
Adequate follow-up	V	V		V	V
Intention-to-treat analysis			V		
Between-group comparisons	V	V	V	V	V
Point estimates and variability	V	V	V	V	V
Overall (Points)	6	5	7	6	5
Quality	Good	Fair	Good	Good	Fair

Table 3. PEDro scale evaluations. *Not included in the calculation of the total score. **Methodological quality: excellent, 9–10 points; good, 6–8 points; fair, 4–5 points; poor, 0–3 points.

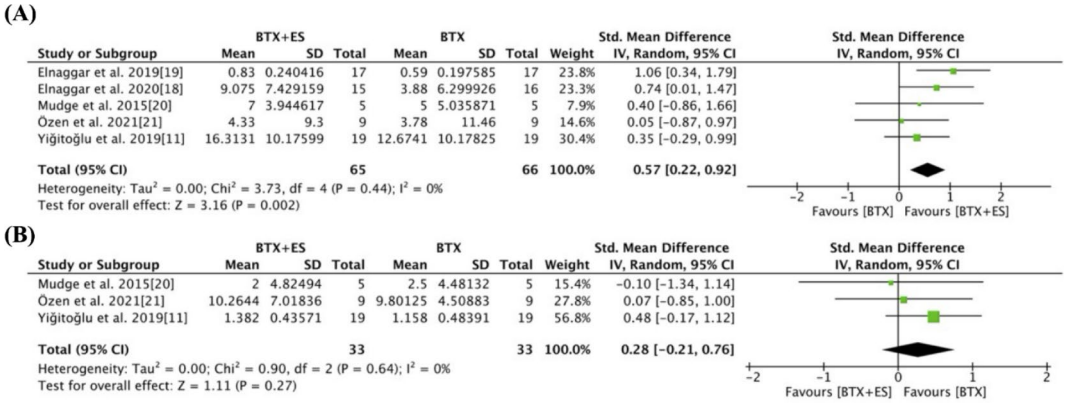

Fig. 2. Improvements in (**A**) motor and functional performance outcomes and (**B**) spasticity outcomes. *BTX* botulinum toxin, *ES* electrical stimulation.

allocation, baseline comparability, between-group comparison, and point estimate and variability standards. Three studies did not employ allocation concealment[11,18,19]. Intention-to-treat analysis was reported only in the study by Mudge et al.[20] None of the studies reported blinding of participants or therapists.

The NMES group exhibited significantly higher levels of improvement in motor and functional performance than did the control group (SMD = 0.57; 95% CI = 0.22 to 0.92; $P = .002$; $n = 66$; $I^2 = 0\%$). A forest plot illustrating motor and functional performance improvements is presented in Fig. 2A.

Two studies assessed spasticity by using the Modified Tardieu Scale[20,21], and one study assessed spasticity by using the Modified Ashworth Scale[11]. The NMES group did not exhibit a significant improvement in spasticity relative to the control group (SMD = 0.28; 95% CI = − 0.21 to 0.76, $P = .27$; $n = 33$; $I^2 = 0\%$). A forest plot illustrating muscle tone spasticity improvement is shown in Fig. 2B.

The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation approach. The quality of evidence was considered moderate for motor and functional performance outcomes and low for spasticity outcomes (Table 4).

Of the five included RCTs[11,18–21], three studies examined adverse events[19–21]—one focused on BTX injection[19] and two on NMES[20,21]. None of these studies reported any adverse events throughout the procedures, suggesting that the interventions were well tolerated by the participants.

Discussion

CP is a complex condition that affects an individual's functional abilities and overall quality of life[22]. Its effects extend beyond physical challenges to psychological and societal dimensions, affecting both patients with CP and relatives[1,2,23]. BTX injections are frequently used to manage spasticity. BTX injections increase muscle tone and stiffness[24]. Although BTX can improve mobility by temporarily paralyzing overactive muscles, its effectiveness varies[25]. This variability underscores the need for personalized treatment approaches[25]. Combining BTX with other therapies, including physical and occupational therapies, has proven to be effective for improving outcomes in CP[26]. NMES appears to be a more reliable treatment for CP[8]. Its efficacy has been definitively established. NMES is particularly effective at enhancing functional performance, coordination, and muscle strength[8]. The

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Experimental group	Control group	Relative (95% CI)	Absolute (95% CI)		
Motor and Functional Performance												
5	Randomized controlled trial	Severe[a]	Not severe	Not severe	Not severe	None	65	66	-	SMD 0.57 higher (0.22 higher to 0.92 higher)	⨁⨁⨁◯ Moderate	Important
Spasticity												
3	Randomized controlled trial	Severe[a]	Not severe	Not severe	Not severe	None	33	33	-	SMD 0.28 higher (−0.21 higher to 0.76 higher)	⨁⨁◯◯ Low	Important

Table 4. Grading of recommendations, assessment, development, and evaluation approach. *SMD* standardized mean difference. a. Blinding of the participants and therapists was difficult because of the nature of the intervention.

present systematic review and meta-analysis investigated the effect of combined BTX injections and NMES treatment on functional performance in children with CP.

The rationale for combining BTX injections with other therapies for the treatment of CP lies in the unique postinjection period of denervation[5]. BTX injections control spasticity and allow affected muscles to be stretched[5,6]. In the postinjection period, when spasticity is reduced, patients with CP can benefit from additional interventions[27]. The use of NMES alongside physical exercises can enhance the effects of BTX injections[21]. NMES helps to direct muscle responses toward a more organized activation pattern. NMES targets both spastic and antispastic muscles[11,19,28]. A combined approach facilitates learning of new, more functional motor patterns, ultimately improving motor function and quality of life for children with CP[18]. Integrative therapies effectively address the complexity of CP and can involve combinations of pharmacological and rehabilitative techniques[21]. Such approaches reduce spasticity and improve motor control and functional abilities[21].

In our analyses, significant improvement was observed in motor and functional performance outcomes when NMES was applied together with BTX injections. The improvement in motor and functional performance was clinically meaningful, indicating a moderate effect, according to Cohen's statistic[16]. This improvement can be attributed to the aforementioned rationale, whereby the reduction in spasticity following BTX injections provides a therapeutic window[5]. During this period, NMES and physical exercises help children learn and develop new motor patterns[10]. This process stimulates central neuroplasticity, which is crucial for adapting and reorganizing neural pathways to improve motor function[19]. By leveraging the temporary reduction in spasticity, this combined therapeutic approach facilitates more effective muscle re-education and functional gains[18,19]. Regarding the exercise protocols, one study focused on the upper limbs[18], while the others focused on the lower limbs[11,19–21]. For upper limb training, exercises included functional activities, functional strength training, hand weight-bearing exercises, and coordination exercises[18]. For lower limb training, protocols included range of motion exercises, balance training, gait training, and resistance training[11,19–21]. Therefore, we recommend that children with CP undergo NMES following BTX injection, combined with a concurrent exercise training, to facilitate improved functional recovery.

In Novak et al.'s study, they conducted a comprehensive systematic review to summarize the best available evidence on interventions for preventing and managing CP[29]. NMES following BTX was suggested as a potentially effective intervention in the domain of motor function[29]. Another study investigated various adjunct therapies to improve outcomes after BTX injection in children with CP[30]. Different adjunct interventions were assessed[30]. Only four studies were included in the analysis of ES, with two focusing on NMES and two on FES[30]. The review concluded that neither intervention provided additional benefits compared to BTX alone in terms of reducing spasticity or improving gait[30]. Furthermore, the number of participants was relatively small, and the included studies were not exclusively RCTs[30]. In contrast, our study included only RCTs, which allowed for more robust analyses. We identified significant improvements in motor and functional performance measures following NMES after BTX injection. Additionally, we thoroughly reviewed the potential mechanisms underlying the effects of NMES after BTX injection to enhance the conceptual understanding of its benefits. Moreover, we summarized the exercise protocols implemented alongside these interventions, providing practical insights based on the included studies.

This study has several strengths. First, the obtained results were clinically meaningful. Second, the study employed broad inclusion criteria and used multiple major databases without language restrictions. Last, the included studies had a low risk of bias, enhancing the credibility and reliability of the findings.

The study also has several limitations. First, the population of individuals with CP was diverse and included those of different ages and with different severities and symptoms. This posed a challenge to drawing universally applicable conclusions. Furthermore, because of the heterogeneity among the included patients, the results may not be generalizable to all individuals with CP. Second, variations in the amount, number, and location of BTX injections and the duration and intensity of NMES differed between the trials, potentially leading to inconsistent outcomes. Third, the follow-up durations varied between the trials, affecting this study's long-term assessments of intervention effectiveness. Individual response variations also contribute to the complexity of interpreting the results. Fourth, the included studies exhibited variability in the outcome measures used to assess motor and functional performance, with each study selecting a different primary outcome. To address this inconsistency, our analysis focused on the primary outcomes reported in each study, which may have introduced heterogeneity. Furthermore, spasticity assessments varied across studies, with some using the Modified Tardieu Scale and others the Modified Ashworth Scale, each offering distinct strengths and limitations. These inconsistencies highlight the need for standardized assessment tools to enable more reliable and comparable evaluations of treatment outcomes in children with CP. Future studies should address these limitations, and the results should be cautiously interpreted. Larger-scale and better-designed randomized controlled trials are warranted to overcome these challenges and provide more robust evidence on the effectiveness of NMES following BTX injection in children with CP. Such trials should aim for standardized protocols regarding BTX dosage, injection sites, NMES parameters, and follow-up durations to enhance the reliability and comparability of the findings.

Conclusion

BTX injections and NMES hold promise in enhancing the lives of individuals with CP; however, a more nuanced understanding of their effects must be obtained. This study highlighted the need for personalized, comprehensive treatment plans that consider the multifaceted nature of CP. Further research is vital for refining these therapies, ensuring better outcomes, and alleviating the burdens faced by individuals with CP.

Data availability

All data generated or analyzed in this study are included in this published article (and its Supplementary Information files).

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Author contributions

Fu-An Yang and Jie-Ren Mi Le conceptualized and designed the study and drafted the manuscript. Hung-Chou Chen critically revised the manuscript for intellectual content. Chia-Hsiang Lu and Chao-Chun Huang conducted a comprehensive search for articles that met the eligibility criteria. Fu-An Yang and Jie-Ren Mi Le extracted the relevant data and assessed the quality of the selected trials. Fu-An Yang and Hung-Chou Chen provided statistical expertise, analyzed and interpreted the data, and submitted the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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