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Review

Effectiveness of Integrating Botulinum Toxin Type A with Rehabilitative Strategies for Managing Spastic Diplegia in Children: Scope Review

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Abstract

This review examines the effectiveness of integrating botulinum toxin type A (BONT-A) with various rehabilitative strategies in treating spastic diplegia in children. The studies analyzed consistently demonstrate significant reductions in spasticity and improvements in gait when BONT-A is combined with interventions such as intensive physical therapy, serial casting, electrical stimulation, physiotherapy, occupational therapy, and robotic-assisted gait training. The findings underscore the importance of personalized rehabilitation plans tailored to each child's needs. Early intervention is particularly effective in preventing spasticity and related complications, leading to better long-term outcomes. Despite the robust results, limitations such as heterogeneity in rehabilitative approaches, small sample sizes, and varying follow-up durations necessitate further research. Future studies should focus on larger, multicenter randomized controlled trials with standardized outcome measures and more extended follow-up periods to validate these findings and assess the long-term sustainability of treatment benefits. The review highlights the necessity of interdisciplinary collaboration among healthcare professionals to ensure comprehensive care, which is crucial for optimizing therapeutic outcomes. The consistent improvements in both spasticity reduction and gait functionality emphasize the critical role of integrated treatment approaches in enhancing the quality of life for pediatric patients with cerebral palsy. The evidence supports the implementation of comprehensive, personalized rehabilitation strategies in clinical practice, promoting early and proactive management to achieve the best possible outcomes for children with spastic diplegia. This review provides a foundation for developing best practices and guiding future research in pediatric neurorehabilitation.

Keywords

Cerebral palsy; spastic diplegia; botulinum toxin type A; rehabilitation; physical therapy

1. Introduction

Cerebral palsy (CP) is a complex neurological condition affecting approximately 2-3.5 per thousand live births in Western countries. One of the most common clinical variants of CP is spastic diplegia, which primarily manifests as spasticity in the lower limbs, with less severe involvement of the upper limbs [1, 2]. Managing spasticity is critical, as this condition significantly impairs mobility and overall quality of life in affected patients [3-6]. The literature widely recognizes botulinum toxin type A (BONT-A) as one of the most effective treatments for focal spasticity. BONT-A works by temporarily weakening targeted muscles, reducing spasticity, and improving functional outcomes such as gait. However, despite its efficacy in reducing muscle tone, there remains a lack of clarity regarding the optimal rehabilitative strategies to be employed following BONT-A injection [7-9]. This gap in knowledge poses a significant challenge for clinicians seeking to maximize the therapeutic benefits of BONT-A treatment. Several studies have explored various post-injection rehabilitation approaches, yet no consensus exists on the most effective methods [4, 10-13]. This uncertainty can lead to inconsistent treatment protocols and potentially suboptimal patient outcomes. The need for a comprehensive synthesis of existing evidence is evident to guide clinical practice and improve patient care [14-19]. To address this gap, the present literature review aims to examine and synthesize the scientific evidence regarding rehabilitative strategies following BONT-A injections in children with spastic diplegia. The research involved systematic searches of relevant biomedical databases, using specific keywords to identify pertinent studies. The primary objective of this review is to identify and evaluate the rehabilitative interventions that have proven effective in enhancing outcomes such as spasticity reduction and gait improvement in children with spastic diplegia treated with BONT-A. By critically analyzing the selected studies, this review seeks to provide evidence-based recommendations that can inform clinical practice, ultimately aiming to enhance the quality of life for pediatric patients with this condition. Moreover, the findings may highlight areas where further research is needed, contributing to the ongoing development of best practices in the management of spastic diplegia [14, 20].

2. Methods

The present scoping review was conducted following the JBI methodology [21] for scoping reviews. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [22] Checklist for reporting was used.

2.1 Review Question

We formulated the following research question: "What are the most effective rehabilitative strategies to enhance outcomes such as spasticity reduction and gait improvement in children with spastic diplegia following treatment with botulinum toxin type A (BONT-A)?".

2.2 Eligibility Criteria

Studies were considered for inclusion based on the following criteria related to Population, Concept, and Context (PCC):

2.2.1 Population

Children aged 0-18 years diagnosed with cerebral palsy, specifically those with spastic diplegia who, have undergone treatment with botulinum toxin type A (BONT-A).

2.2.2 Concept

Rehabilitative strategies employed post-BONT-A treatment aimed at improving outcomes such as spasticity reduction and gait enhancement. This includes various physiotherapeutic and adjunctive interventions designed to maximize the benefits of BONT-A.

2.2.3 Context

Clinical settings where children with spastic diplegia receive post-BONT-A rehabilitative care. Studies included must be randomized controlled trials (RCTs), available in English, and accessible through online biomedical databases.

2.3 Exclusion Criteria

Studies that did not align with the defined Population, Concept, and Context (PCC) criteria were excluded from the review. This exclusion applied to research that either did not focus on the specified age group or condition, lacked relevant rehabilitative interventions post-BoNT-A treatment, or failed to assess outcomes in clinical rehabilitation settings.

2.4 Search Strategy

A preliminary search of MEDLINE was carried out using the PubMed platform to locate relevant articles. The search terms and indexing used in the initial articles helped shape a broader search strategy, which was then applied to other databases such as Cochrane Central, Scopus, and PEDro. Additionally, grey literature sources (including Google Scholar and consultations with field experts) and the reference lists of key studies were reviewed. The comprehensive search, conducted on March 23, 2024, did not impose any restrictions on the publication date.

("Diplegic children" AND "Cerebral palsy" AND "Botulinum toxin type A" AND "Spasticity reduction" AND "Rehabilitative strategies" AND "Physical therapy" AND "Functional outcomes" AND "Gait improvement" AND "Randomized controlled trials").

2.5 Study Selection

The process used for study selection in the scoping review followed a systematic and structured method. Initially, search results were compiled and refined using Zotero, eliminating duplicates. The screening process was conducted in two phases: first, by reviewing titles and abstracts and then by assessing the full texts. Two authors independently performed both stages, with any disagreements resolved through consultation with a third reviewer. This procedure adhered strictly to the PRISMA 2020 guidelines to ensure accuracy and transparency. The aim was to identify articles highly relevant to the research question, providing a thorough and systematic review process.

2.6 Data Extraction and Data Synthesis

For this scoping review, data extraction was performed using a customized form based on the JBI tool, designed to capture essential information such as authorship, country and year of publication, study design, patient demographics, interventions, outcomes, procedures, and other key details. Descriptive analyses were then carried out, with numerical data used to illustrate the distribution of studies. The entire review process was carefully documented to ensure transparency, and the extracted data were organized into tables, facilitating easy comparison and interpretation of the core findings across different studies.

3. Results

As presented in the PRISMA 2020 flow diagram (Figure 1), from 60 records identified by the initial literature searches, 45 were excluded, and five articles were included (Table 1). The quality of the studies was assessed using the al PEDro scale (Table 2).

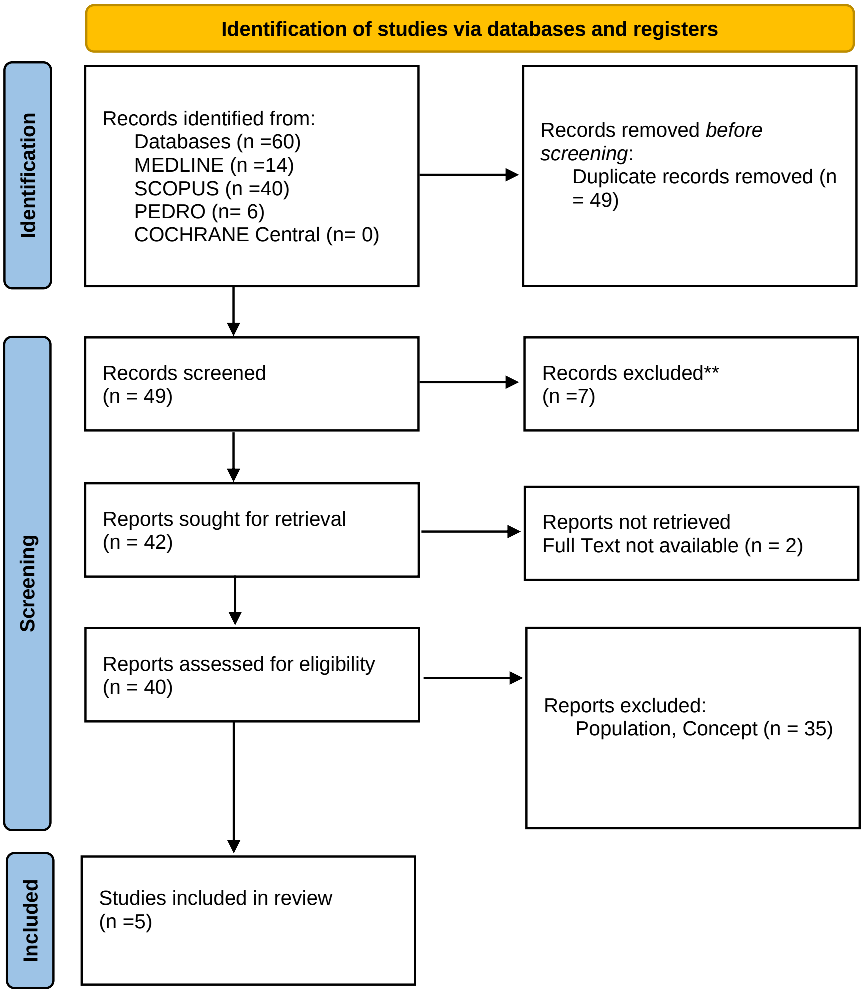

Figure 1 Preferred reporting items for systematic reviews and meta-analyses 2020 (PRISMA) flow diagram.

Table 1 Main characteristics of included studies.

Study	Objective	Target Population	Interventions	Outcomes	Results
Ragab K. Elnaggar et al. "Evaluation of independent versus integrated effects of reciprocal electrical stimulation and botulinum toxin-A on dynamic limits of postural stability and ankle kinematics in spastic diplegia: a single-blinded randomized trial" (European Journal of Physical and Rehabilitation Medicine, 2019) [11]	To analyze the effects of reciprocal electrical stimulation and botulinum toxin type A, both independently and combined, on dynamic limits of postural stability and ankle kinematics in spastic diplegia.	53 children with spastic diplegia, aged 4-7 years, GMFCS levels II/III, MAS of triceps surae 1+/2, with "independent equinus" or "crouch gait," height over one meter, and intact cognitive, visual, and auditory functions. Randomized into three groups: RES (19), BONT-A (17), and RES+BONT-A (17).	- **RES Group:** Alternating electrical stimulation to ankle dorsiflexors and plantarflexors for 30 minutes, 3 times a week for 12 weeks. - **BONT-A Group:** Injections bilaterally in gastrocnemius and soleus muscles. - **RES+BONT-A Group:** Both treatments combined. - **Concurrent Physiotherapy Program:** Functional goal-based therapy including neuromotor training, functional training, balance training, functional stretching, and exercises to improve ROM, 1 hour per	- **Primary:** Dynamic limits of postural stability (AP-LOS, ML-LOS, O-LOS). - **Secondary:** Ankle kinematics (misalignment at initial contact, maximum dorsiflexion during stance, peak dorsiflexion during swing). Evaluations before treatment and after 12 weeks.	- **Intergroup Analysis:** The RES+BONT-A group showed significant improvements in all outcomes compared to the RES group. The RES+BONT-A group also improved significantly over the BONT-A group in maximum dorsiflexion during stance and O-LOS. The BONT-A group had significant improvements over the RES group in AP-LOS and ML-LOS.

			session, 3 times a week.		
Nigar Dursun et al. "Randomized controlled trial on effectiveness of intermittent serial casting on spastic equinus foot in children with cerebral palsy after botulinum toxin-A treatment" (American Journal of Physical Medicine and Rehabilitation, 2017) [4]	To demonstrate the effect of intermittent serial casting in addition to standard treatment on outcomes such as spasticity, passive ROM, and gait.	51 children with CP, GMFCS I/II/III, aged 3-17 years (mean age 6 years 4 months), with unilateral or bilateral spastic equinus foot deformity, ankle plantarflexor shortening preventing dorsiflexion beyond 80°, MAS score of 3 for ankle plantarflexors, scheduled BONT-A (Dysport) treatment. Randomized into two groups: serial casting (34 children: 25 diplegic, 9 hemiplegic) and control (17 children: 12 diplegic, 5 hemiplegic).	- **Serial Casting Group:** Cast applied after BONT-A treatment, maintained for 72 hours, reapplied the next weekend with adjusted ankle position for 3 consecutive weekends. - **Control Group:** Received only BONT-A (Dysport). - **Concurrent Physiotherapy Program:** 1 hour daily, 5 days a week for 3 weeks, including stretching, weight-bearing exercises, balance, proprioception, and gait training.	- **Primary:** Passive ROM (PROM), spasticity (MAS). - **Secondary:** Spasticity (Tardieu Scale), gait (OGS), treatment response (PGA). Evaluations before treatment, at week 4, and at week 12.	- **Intergroup Analysis:** The serial casting group showed significantly better mean PROM and MAS scores at weeks 4 and 12. Improvements in XV3, X, and Y were significantly better in the casting group at different time points. OGS and PGA scores were also significantly better in the casting group at weeks 4 and 12.
Sian A. Williams et al. "Combining strength training and botulinum neurotoxin intervention	To investigate the effects of muscle strengthening physiotherapy	15 children (10 males, 5 females, mean age 8 years 5 months) with spastic diplegia, GMFCS	- **PRE BONT-A Group:** Muscle strengthening before BONT-A	- Objectives (GAS), spasticity (MAS), motor control (SCALE), muscle strength	- **Intergroup Analysis:** No significant differences in muscle strength or volume

in children with cerebral palsy: the impact on muscle morphology and strength" (Disability & Rehabilitation, 2013) [12]	combined with botulinum toxin type A treatment in children with CP.	I/II, randomized by age, gender, GMFCS level into PRE BONT-A and POST BONT-A groups. The PRE BONT-A group served as the control for the POST BONT-A group before starting muscle strengthening.	injections (between A1 and A2). - **POST BONT-A Group:** Muscle strengthening after BONT-A injections (between A3 and A4). All received BONT-A (Botox) bilaterally in the medial gastrocnemius, hamstrings, soleus, adductors, posterior tibialis, and rectus femoris, with no more than three injections per leg. - **Concurrent Physiotherapy Program:** Progressive home-based muscle strengthening, 3 times a week for 10 weeks, supervised bi-weekly by a physiologist, including lower limb passive stretching.	(dynamometer), muscle volume (MRI). Evaluations: A1 (12 weeks pre-BONT-A), A2 (2 weeks pre-BONT-A), A3 (5 weeks post-BONT-A), A4 (14 weeks post-BONT-A).	between groups over six months, except for quadriceps volume favoring POST group. No significant differences in SCALE scores or spasticity changes during muscle strengthening, but both groups showed decreased spasticity post-BONT-A. Both groups increased GAS scores.
Pembe Yigitoglu et al. "Effectiveness of	To investigate the effectiveness of	38 children with spastic diplegia, able to walk	- **Group 1:** Electrical stimulation of the	- **Primary:** Spasticity (MAS).	- **Intergroup Analysis:** No statistically

electrical stimulation after administration of botulinum toxin in children with spastic diplegic cerebral palsy: A prospective, randomized clinical study" (Turkish Journal of Physical Medicine and Rehabilitation, 2019) [13]	electrical stimulation of agonist muscles after BONT-A injection in children with spastic diplegia.	independently or with minimal assistance, aged 4-10 years, with equinus foot and triceps surae spasticity (MAS 1+ to 3), GMFCS I/II/III. Randomized into two groups: BONT-A and electrical stimulation (Group 1), and BONT-A only (Group 2).	gastrocnemius starting the day after BONT-A injection (Allergan), once daily for 20 minutes for 10 days, with intensity adjusted for visible muscle contraction. - **Group 2:** BONT-A injection and concurrent physiotherapy without electrical stimulation. - **Concurrent Physiotherapy Program:** Home-based exercises including triceps surae stretching, ankle dorsiflexor strengthening, and gait exercises, instructed by a physiatrist.	- **Secondary:** Muscle spasms (PSFS), standing (GMFM-88 Dimension D), gait, running, and jumping (GMFM-88 Dimension E), walking speed (maximum distance walked in one minute). Evaluations before treatment, at 2 weeks, and at 3 months.	significant differences between groups for any outcomes.
Bottos et al. "Botulinum toxin with and without casting in ambulant children with spastic diplegia: a clinical and	To compare clinical and functional outcomes with or without casting following BONT-A	10 children (7 males, 3 females, mean age 6 years 4 months) with spastic diplegia, aged 4-11 years, independent	- **Group 1:** BONT-A (Dysport) bilaterally in triceps surae, followed by ankle-foot orthosis and physiotherapy.	- **Clinical Outcomes:** PROM, spasticity (Ashworth), standing and walking (GMFM, items 52-74).	- **Intergroup Analysis:** Significant differences in spasticity at 4 months and GMFM walking items favoring

functional assessment" (Developmental Medicine & Child Neurology, 2003) [10]	treatment in children with spastic diplegia and dynamic equinus foot.	walking, equinus foot, no structural contractures, bone or joint deformities, no orthopedic surgeries in the last 12 months. Randomized into two groups: BONT-A with orthosis (Group 1), and BONT-A with fixed cast for 3 weeks (Group 2).	- **Group 2:** BONT-A bilaterally in triceps surae, followed by inhibitory casting for 3 weeks, then physiotherapy. - **Concurrent Physiotherapy Program:** Progressive stretching of gastrocnemius, active tibialis anterior contractions, orthostatic and gait training introduced progressively.	Evaluations before treatment, at 1 month, 4 months, and 12 months. - **Gait Analysis:** Temporal-distance parameters, ankle kinematics and kinetics, dynamic EMG. Evaluations up to 4-month follow-up.	Group 2. Significant differences in walking speed favoring Group 2 at 4-month follow-up. No significant differences in ankle kinematics, kinetics, or dynamic EMG. No significant improvements in ankle ROM or GMFM standing items.

Legend: **AP-LOS:** Anterior-Posterior Limits of Stability, **BONT-A:** Botulinum Toxin Type A, **CP:** Cerebral Palsy, **GAS:** Goal Attainment Scaling, **GMFM-88:** Gross Motor Function Measure-88, **GMFCS:** Gross Motor Function Classification System, **MAS:** Modified Ashworth Scale, **ML-LOS:** Medio-Lateral Limits of Stability, **MRI:** Magnetic Resonance Imaging, **O-LOS:** Overall Limits of Stability, **OGS:** Observational Gait Scale, **PGA:** Physician Global Assessment, **PROM:** Passive Range of Motion, **PSFS:** Patient-Specific Functional Scale, **RES:** Reciprocal Electrical Stimulation, **ROM:** Range of Motion, **SCALE:** Selective Control Assessment of the Lower Extremity.

Table 2 PEDro Scale.

Study	Total Score
Elnaggar et al., 2019 [11]	8
Dursun et al., 2017 [4]	8
Williams et al., 2013 [12]	7
Yigitoglu et al., 2019 [13]	6
Bottos et al., 2003 [10]	6

The studies included in this review provide compelling evidence of the effectiveness of combining botulinum toxin type A (BONT-A) with various rehabilitative interventions in children with spastic diplegia. The study by Elnaggar et al. [11] demonstrated that integrating reciprocal electrical stimulation (RES) with BONT-A significantly improved the dynamic limits of postural stability and ankle kinematics compared to either treatment alone. Specifically, the group receiving both RES and BONT-A showed substantial enhancements in anterior-posterior (AP-LOS), mediolateral (ML-LOS), and overall limits of stability (O-LOS), as well as in ankle dorsiflexion during the stance phase and swing phase. These improvements suggest that a multimodal approach can better address the neuromuscular limitations contributing to gait abnormalities in children with spastic diplegia.

Dursun et al. [4] investigated the effects of intermittent serial casting combined with standard BONT-A treatment on spastic equinus foot in children with cerebral palsy. The study found that the casting group experienced significant reductions in spasticity as measured by the Modified Ashworth Scale (MAS) and the Tardieu Scale, as well as notable improvements in passive range of motion (PROM). Additionally, the casting group showed significant enhancements in gait function, as evidenced by higher scores on the Observational Gait Scale (OGS) and the Physician Global Assessment (PGA), both at weeks 4 and 12 post-treatment. These findings underscore the added value of serial casting in prolonging and enhancing the therapeutic effects of BONT-A.

Williams et al. [12] explored the impact of combining muscle-strengthening exercises with BONT-A injections on muscle morphology and strength in children with cerebral palsy. Both the PRE and POST BONT-A groups exhibited significant gains in muscle strength, particularly in knee flexors and extensors, and improvements in muscle volume as assessed by MRI. However, the timing of the muscle strengthening relative to the BONT-A injections appeared to influence the outcomes. The PRE BONT-A group showed more pronounced long-term improvements, suggesting that reducing spasticity before initiating a strength training program might optimize muscle performance and functional gains. The Goal Attainment Scaling (GAS) scores indicated significant functional improvements for both groups, highlighting the practical benefits of this combined approach.

In the study by Yigitoglu et al. [13], adding electrical stimulation to BONT-A treatment did not yield statistically significant differences in spasticity reduction, gait function, or muscle spasms compared to BONT-A treatment alone. Both groups showed similar improvements in these areas, indicating that while electrical stimulation may support BONT-A therapy, it might not provide substantial additional benefits in this context. The study did, however, report significant gains in standing and walking abilities as measured by the Gross Motor Function Measure (GMFM-88), reflecting the overall effectiveness of BONT-A in improving functional outcomes.

Lastly, Bottos et al. [10] conducted a study comparing the effects of BONT-A with and without inhibitory casting in children with spastic diplegia and dynamic equinus foot. The casting group demonstrated significant reductions in spasticity and improvements in gait parameters, including walking speed and step length, at the four-month follow-up. These children also performed better standing and walking on the Gross Motor Function Measure (GMFM) compared to those who only received BONT-A. Despite the lack of significant changes in the kinetic and kinematic parameters of the ankle, the study confirmed the added benefits of combining inhibitory casting with BONT-A to enhance functional mobility and reduce muscle spasticity.

Overall, these studies collectively highlight the importance of a comprehensive, multimodal approach in managing spastic diplegia in children. Combining BONT-A with additional rehabilitative strategies such as serial casting, muscle strengthening, and electrical stimulation can significantly improve spasticity, muscle strength, range of motion, and gait function. These findings support integrating rehabilitation plans tailored to the individual needs of pediatric patients with cerebral palsy, aiming to maximize therapeutic outcomes and enhance their quality of life.

4. Discussion

The present review aimed to identify and synthesize the most effective rehabilitative strategies following botulinum toxin type A (BONT-A) injections in children with spastic diplegia, focusing on outcomes such as spasticity reduction and gait improvement. The collective findings from the included studies underscore the significant benefits of integrating BONT-A with various rehabilitative interventions, providing valuable insights for clinical practice [10, 13]. The reviewed studies demonstrated that BONT-A injections, when combined with tailored rehabilitative strategies, consistently significantly reduce spasticity and improve gait function across different age groups and therapeutic settings [11, 12]. Intensive physical therapy [23, 24], serial casting [25], electrical stimulation [26], combined physiotherapy and occupational therapy, and robotic-assisted gait training [27] all showed marked benefits when used in conjunction with BONT-A. An essential aspect of successful rehabilitation protocols in cerebral palsy treatment is promoting motor learning. Utilizing interventions such as electrical stimulation or orthoses without ensuring that motor learning is integrated may limit the effectiveness of these treatments. Motor learning facilitates the long-term retention of motor skills, ensuring that improvements in spasticity and mobility persist. Future rehabilitation protocols should incorporate motor learning principles, emphasizing task-specific, repetitive, and engaging activities that promote neuromuscular adaptation alongside traditional interventions like BONT-A injections and physical therapy [13, 28, 29]. These interventions significantly enhanced spasticity reduction and gait improvements compared to traditional or placebo-controlled therapies. The consistent improvements observed in spasticity and gait function highlight the importance of an integrated treatment approach [20, 30]. Clinicians should consider combining BONT-A with comprehensive rehabilitative strategies tailored to each child's specific needs. Personalized rehabilitation plans that account for individual capabilities and therapeutic goals are crucial for achieving the most significant functional improvements. The findings suggest that early intervention with BONT-A and rehabilitative therapies can be particularly effective. Additional studies have emerged that further support the integration of rehabilitative strategies following Botulinum Toxin A treatment. For example, Lannin et al. [31] demonstrated the importance of early intensive therapy combined with BONT-A in improving motor function in children with cerebral palsy. Similarly, Güç et al. [32] highlighted the benefits of combining electrical stimulation with BONT-A, showing improved outcomes in spasticity reduction and functional mobility. These studies underscore the evolving understanding of how to maximize outcomes post-BONT-A treatment. Early treatment may prevent the progression of spasticity and the development of secondary complications, leading to better long-term outcomes. This emphasizes the need for timely and proactive management of spastic diplegia in children. Interdisciplinary collaboration among physiotherapists, occupational therapists, pediatric neurologists, and other healthcare professionals is essential for effective management. A coordinated approach ensures that all aspects of the child's care are addressed comprehensively, optimizing therapeutic outcomes and enhancing the quality of life for pediatric patients with cerebral palsy. Despite the robust findings, several limitations must be acknowledged [10-12, 33]. The studies included in this review varied significantly in their rehabilitative approaches, making direct comparisons challenging. This heterogeneity limits the ability to draw definitive conclusions about the superiority of specific interventions. Additionally, some studies had relatively small sample sizes and limited age ranges, which may affect the generalizability of the findings to broader populations. The duration of follow-up varied among studies, with some not extending beyond six months. Longer follow-up periods are necessary to assess the sustained impact of these interventions on spasticity and gait function. Furthermore, the studies employed different outcome measures to evaluate spasticity and gait, complicating cross-study comparisons. Standardized outcome measures would enhance the comparability and reliability of results. The findings of this review have significant implications for clinical practice. The integration of BONT-A with various rehabilitative strategies should be considered a standard approach in managing children with spastic diplegia [10, 13]. The consistent evidence supporting improved outcomes through such integrative methods emphasizes the necessity of personalized and early interventions. Tailored rehabilitation plans that address the unique needs of each child can maximize therapeutic benefits, ultimately leading to better functional outcomes and quality of life. Future research should focus on addressing the limitations identified in this review. Larger, multicenter randomized controlled trials (RCTs) with standardized outcome measures and longer follow-up periods are needed to validate the findings and assess the long-term sustainability of treatment benefits. Additionally, studies exploring the cost-effectiveness of different rehabilitative strategies will provide valuable insights into healthcare policy and resource allocation. The potential for improved clinical outcomes through integrating BONT-A with rehabilitative therapies is significant [34-36]. As such, healthcare providers should be encouraged to adopt these combined approaches and collaborate across disciplines to ensure comprehensive care. By doing so, the full spectrum of therapeutic benefits can be realized, significantly enhancing the quality of life for children with spastic diplegia. The integration of BONT-A with various rehabilitative strategies significantly enhances spasticity reduction and gait function in children with spastic diplegia. Recent evidence suggests that Omega-3 fatty acids may be important in modulating inflammation and neuropathic pain associated with spasticity. Omega-3 supplementation could help reduce pro-inflammatory cytokine levels, potentially improving functional outcomes in children with spastic diplegia [37]. Another emerging treatment is rhizotomy, a neurosurgical procedure that selectively disrupts nerve roots responsible for spasticity, providing long-term improvements in muscle tone in severe cases. Additionally, pharmacological treatments such as baclofen, diazepam, and tizanidine, used to reduce muscle tone, can be combined with botulinum toxin and rehabilitation to optimize spasticity management [38, 39]. However, further research is needed to confirm the long-term benefits of these therapeutic options in combination with post-BONT-A rehabilitative therapy [40, 41].

These findings support implementing comprehensive, personalized rehabilitation plans in clinical practice to optimize therapeutic outcomes and improve the quality of life for pediatric patients with cerebral palsy. The evidence underscores the need for interdisciplinary collaboration and early intervention to maximize the benefits of these combined therapeutic approaches. The consistent results across studies highlight the critical role of tailored rehabilitation in achieving substantial improvements in both spasticity and gait functionality, making it an essential component of effective cerebral palsy management.

5. Conclusions

This review demonstrates that integrating botulinum toxin type A (BONT-A) with tailored rehabilitative strategies significantly reduces spasticity and improves gait in children with spastic diplegia. Personalized rehabilitation plans, including intensive physical therapy, serial casting, electrical stimulation, and robotic-assisted gait training, are essential for optimizing outcomes. Early intervention and interdisciplinary collaboration are crucial for maximizing therapeutic benefits. Future research should focus on more extensive trials with standardized measures to validate these approaches further. The findings support comprehensive care strategies to enhance the quality of life for pediatric patients with cerebral palsy.

Author Contributions

Danilo Donati, Roberto Tedeschi: Conceptualization, Methodology, Software, Data curation, Writing-Original draft preparation. **Federica Giorgi, Riccardo Marvulli, Laura Dell'Anna:** Supervision. **Vincenza Amoruso, Valentina Boetto, Andrea Bernetti, Giacomo Farì:** Visualization, Investigation, Writing-Reviewing and Editing.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: The definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007; 109: 8-14.
2. Yeargin-Allsopp M, Van Naarden Braun K, Doernberg NS, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: A multisite collaboration. Pediatrics. 2008; 121: 547-554.
3. Bjornson K, Hays R, Graubert C, Price R, Won F, McLaughlin JF, et al. Botulinum toxin for spasticity in children with cerebral palsy: A comprehensive evaluation. Pediatrics. 2007; 120: 49-58.
4. Dursun N, Gokbel T, Akarsu M, Dursun E. Randomized controlled trial on effectiveness of intermittent serial casting on spastic equinus foot in children with cerebral palsy after botulinum toxin-A treatment. Am J Phys Med Rehabil. 2017; 96: 221-225.

5. Novak I, Mcintyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: State of the evidence. Dev Med Child Neurol. 2013; 55: 885-910.
6. Casadei I, Betti F, Tedeschi R. Assessment of muscle tone in patients with acquired brain injury: A systematic review. Mot Cereb. 2024; 45: 5-14. doi: 10.1016/j.motcer.2023.09.005.
7. Fortuna R, Vaz MA, Youssef AR, Longino D, Herzog W. Changes in contractile properties of muscles receiving repeat injections of botulinum toxin (Botox). J Biomech. 2011; 44: 39-44.
8. Kang BS, Bang MS, Jung SH. Effects of botulinum toxin A therapy with electrical stimulation on spastic calf muscles in children with cerebral palsy. Am J Phys Med Rehabil. 2007; 86: 901-906.
9. Strobl W, Theologis T, Brunner R, Kocer S, Viehweger E, Pascual-Pascual I, et al. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. Toxins. 2015; 7: 1629-1648.
10. Bottos M, Benedetti MG, Salucci P, Gasparroni V, Giannini S. Botulinum toxin with and without casting in ambulant children with spastic diplegia: A clinical and functional assessment. Dev Med Child Neurol. 2003; 45: 758-762.
11. Elnaggar RK, Elbanna MF. Evaluation of independent versus integrated effects of reciprocal electrical stimulation and botulinum toxin-A on dynamic limits of postural stability and ankle kinematics in spastic diplegia: A single-blinded randomized trial. Eur J Phys Rehabil Med. 2018; 55: 241-249.
12. Williams SA, Elliott C, Valentine J, Gubbay A, Shipman P, Reid S. Combining strength training and botulinum neurotoxin intervention in children with cerebral palsy: The impact on muscle morphology and strength. Disabil Rehabil. 2013; 35: 596-605.
13. Yiğitoğlu P, Kozanoğlu E. Effectiveness of electrical stimulation after administration of botulinum toxin in children with spastic diplegic cerebral palsy: A prospective, randomized clinical study. Turk J Phys Med Rehabil. 2019; 65: 16-23.
14. Turolla A, Guccione AA, Tedeschi R, Pillastrini P. Is clinical research as helpful to clinicians as it could be? Phys Ther. 2023; 103: pzad060.
15. Tedeschi R, Platano D, Donati D, Giorgi F. Integrating the Drucebo effect into PM&R: Enhancing outcomes through expectation management. Am J Phys Med Rehabil. 2024. doi: 10.1097/PHM.0000000000002544.
16. Tedeschi R. Briser le cycle nocebo: Stratégies pour améliorer les résultats en podiatrie. Douleurs. 2023; 24: 241-247.
17. Tedeschi R. Unveiling the potential of trigger point therapy exploring its efficacy in managing muscular spasticity-a scoping review. Muscles Ligaments Tendons J. 2023; 13: 564-573.
18. Tedeschi R. Unlocking the power of motor imagery: A comprehensive review on its application in alleviating foot pain. Acta Neurol Belg. 2024. doi: 10.1007/s13760-024-02492-2.
19. Tedeschi R. An overview and critical analysis of the Graston technique for foot-related conditions: A scoping review. Man Med. 2024; 62: 22-28.
20. Sassi S, Faccioli S, Farella GM, Tedeschi R, Garavelli L, Benedetti MG. Gait alterations in two young siblings with progressive Pseudorheumatoid dysplasia. Children. 2022; 9: 1982.
21. University of Bologna. Peters: Joanna Briggs Institute Reviewer's Manual, JBI - Google Scholar [Internet]. Bologna, Italy: University of Bologna; 2024. Available from: https://scholar-google-com.ezproxy.unibo.it/scholar_lookup?hl=en&publication_year=2020&author=MDJ+Peters&a

uthor=C+Godfrey&author=P+McInerney&author=Z+Munn&author=AC+Tricco&author=H+Khalil&title=Joanna+Briggs+Institute+Reviewer%27s+Manual%2C+JBI.

22. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med. 2018; 169: 467-473.
23. Tedeschi R. Case report: Integrating aerobic activity in post-surgical management of plurifragmentary distal clavicle fractures-a holistic approach to pain modulation and recovery. Int J Surg Case Rep. 2023; 113: 109024.
24. Tedeschi R. Assessment of postural control and proprioception using the delos postural proprioceptive system. Reabil Moksl Slauga Kineziter Ergoter. 2023; 2: 93-109. doi: 10.33607/rmske.v2i29.1428.
25. Shirel T, Sylvanus T, Cho K, Authement A, Krach LE. Efficacy of serial casting protocols in idiopathic toe-walking. J Pediatr Rehabil Med. 2024; 17: 179-184.
26. Abd Elmonem YM, Salem EE, Elshafey MA, Mostafa AH. Efficacy of neuromuscular electrical stimulation and interrupted serial casting in children with spastic diplegia. J Taibah Univ Med Sci. 2024; 19: 628-636.
27. Fabbri I, Betti F, Tedeschi R. Gait quality after robot therapy compared with physiotherapy in the patient with incomplete spinal cord injured: A systematic review. Eneurologicalsci. 2023; 31: 100467.
28. Picelli A, DI Censo R, Angeli C, Spina S, Santamato A, Baricich A, et al. Is the Silfverskiöld test a valid tool for evaluating calf muscles spastic overactivity in patients with stroke? A retrospective observational study. Eur J Phys Rehabil Med. 2024. doi: 10.23736/S1973-9087.24.08153-X.
29. Blumetti FC, Belloti JC, Tamaoki MJ, Pinto JA. Botulinum toxin type A in the treatment of lower limb spasticity in children with cerebral palsy. Cochrane Database Syst Rev. 2019. doi: 10.1002/14651858.CD001408.pub2.
30. Tedeschi R. Mapping the current research on mindfulness interventions for individuals with cerebral palsy: A scoping review. Neuropediatrics. 2024; 55: 77-82.
31. Lannin NA, Ada L, English C, Ratcliffe J, Faux S, Palit M, et al. Long-term effect of additional rehabilitation following botulinum toxin-A on upper limb activity in chronic stroke: The InTENSE randomised trial. BMC Neurol. 2022; 22: 154.
32. Güç A, Çebiçci MA, Sütbeyaz ST, Çalış HT, Abakay H. Comparison of the effectiveness of conventional physiotherapy methods and robot-assisted gait training after botulinum toxin injection of lower extremities in children with cerebral palsy: Prospective randomized controlled study. J Pediatr Neurol. 2024; 22: 194-201.
33. Tedeschi R. The effectiveness of postural insoles in posture management in people with cerebral palsy: A scoping review. Mot Cereb. 2024; 45: 15-22.
34. Molenaers G, Fagard K, Van Campenhout A, Desloovere K. Botulinum toxin A treatment of the lower extremities in children with cerebral palsy. J Child Orthop. 2013; 7: 383-387.
35. Fonseca Jr PR, Galli M. Effect of physiotherapeutic intervention on the gait after the application of botulinum toxin in children with cerebral palsy: Systematic review. Eur J Phys Rehabil Med. 2017; 54: 757-765.
36. Molenaers G, Van Campenhout A, Fagard K, De Cat J, Desloovere K. The use of botulinum toxin A in children with cerebral palsy, with a focus on the lower limb. J Child Orthop. 2010; 4: 183-195.
37. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients. 2010; 2: 355-374.

38. DuDley RW, PaRolin M, GaGnon B, Saluja R, Yap R, Montpetit K, et al. Long-term functional benefits of selective dorsal rhizotomy for spastic cerebral palsy. J Neurosurg Pediatr. 2013; 12: 142-150.
39. Park TS, Dobbs MB, Cho J. Evidence supporting selective dorsal rhizotomy for treatment of spastic cerebral palsy. Cureus. 2018; 10: e3466.
40. Peacock WJ, Arens LJ. Selective posterior rhizotomy for the relief of spasticity in cerebral palsy. S Afr Med J. 1982; 62: 119-124.
41. Chang EY, Ghosh N, Yanni D, Lee S, Alexandru D, Mozaffar T. A review of spasticity treatments: Pharmacological and interventional approaches. Crit Rev Phys Rehabil Med. 2013; 25: 11-22.