



EFFECT OF INTENSIVE REHABILITATION PROGRAMS ON MOTOR AND COGNITIVE FUNCTIONS IN CHILDREN WITH CEREBRAL PALSY

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Abstract

Objective: This study aimed to investigate the impact of intensive rehabilitation programs (IRPs) on the motor and cognitive functions of children diagnosed with cerebral palsy (CP) who have undergone multi-level Botulinum toxin-A (BoNT-A) injections, aligning with their individualized treatment goals and clinical characteristics.

Methods: In this prospective controlled clinical study, a cohort of 50 children aged 4-18 years diagnosed with CP and classified as level I-IV on the Gross Motor Function Classification System (GMFCS) participated. After multi-level BoNT-A injections, participants in the study group underwent a comprehensive IRP lasting for 3 weeks, with sessions conducted 5 days a week, either half or full day, tailored to the unique needs of each child. The evaluation of outcomes encompassed the Gross Motor Function Measure-66 (GMFM-66), Observational Gait Scale (OGS), and Goal Attainment Scale (GAS) for assessing motor functions, whereas cognitive functions were measured using the Stroop Test and Auditory Verbal Learning Test (AVLT).

Results: The analysis revealed statistically significant enhancements in various parameters for both groups, including OGS, GMFM-66 total score, total goal achievement, and scores in the C, D, and E dimensions. Notably, the study group exhibited significantly greater improvements in OGS, GAS, and GMFM-66 total score, total goal achievement, and D, E dimensions' scores compared to the control group by the fourth week of intervention. Furthermore, significant improvements were observed in Stroop test S5T and S5C scores, and AVLT scores across all parameters in the study group.

Conclusion: The results of this study showed that intensive rehabilitation practices had positive effects on motor and cognitive functions in children with CP who underwent multi-level BoNT-A-application to spastic muscles.

Keywords: Cerebral palsy, intensive rehabilitation, cognitive function, botulinum toxin.

Introduction

Cerebral palsy (CP) encompasses a cluster of neurological disorders resulting from non-progressive damage to the developing fetal and/or infant brain. It manifests as impaired body movement, balance, and posture, ranking among the leading causes of childhood disability. The global prevalence of CP stands at 2-3 per 1000 live births, and its impact extends beyond motor function, encompassing sensory, perceptual, communication, behavioral, and cognitive impairments, as well as epilepsy and secondary musculoskeletal issues.¹ These challenges contribute significantly to the overall burden of care and healthcare utilization for both children with CP and their families,^{2,3} necessitating timely recognition and targeted management.⁴ Effective rehabilitation strategies play a pivotal role in improving independence, mobility, and cognitive functions in children with CP. The International Classification of Functioning, Disability and Health (ICF) model guides the assessment and treatment plan, emphasizing the importance of evaluating how motor and cognitive impairments impact daily activities.^{5,6} Multidisciplinary collaboration remains paramount in addressing the diverse medical and psychosocial needs of children with CP throughout their lifespan.^{7,8,9}

Designing rehabilitation programs requires a nuanced approach that considers factors such as functional level, age, cognitive-social aspects, environmental influences, musculoskeletal issues, comorbidities, and participation levels.¹⁰ Rather than conventional or packaged programs, current recommendations advocate intensive active training protocols, lifestyle modifications, mobility-enhancing devices, and activity-based approaches in CP rehabilitation.¹¹ In our clinic, we implement goal-oriented and intensive rehabilitation programs (IRPs) post botulinum toxin-A (BoNT-A) injections for children with CP. Our philosophy revolves around purposeful treatments tailored to each child's clinical features, treatment goals, and requirements, emphasizing intensity and duration to influence neuroplasticity.

Contrary to the conventional understanding that gross motor potentials plateau at 3.5-5 years in children with CP, a retrospective evaluation of 503 cases in our clinic revealed

that a remarkable 42% achieved at least one level of improvement in their Gross Motor Function Classification System (GMFCS) levels following integrated IRPs with two or more BoNT-A injections between 2007 and 2017.¹² Building on the premise that IRPs, individually crafted for each child's specific goals and combined with BoNT-A injections, surpass the efficacy of BoNT-A and standard care, this research aims to prospectively and rigorously elucidate the effects of IRPs on motor and cognitive functions in children with CP undergoing multi-level BoNT-A applications targeting spastic muscle groups.

Methods

This prospective controlled study was conducted at the Department of Physical Medicine and Rehabilitation Clinic, Kocaeli University Faculty of Medicine. Approval for the study was obtained from the Kocaeli University Clinical Research Ethics Committee (KU GOKAEK-2021/20.05), and written informed consent was obtained from all participating children and their families. Inclusion criteria included children aged 4-18 years, diagnosed with cerebral palsy (CP) according to the Rosenbaum criteria, and possessing Gross Motor Function Classification System (GMFCS) levels I - IV. These children were scheduled for Botulinum toxin-A (BoNT-A) injections targeting spastic muscle groups. The exclusion criteria comprised clinically severe dystonia, severe contractures in the upper and lower extremities, hearing or visual impairments, and communication or behavioral disorders significantly impeding participation.

Families meeting the inclusion criteria were invited to participate in randomization, and those declining were given the option to select their preferred group. Randomization was embraced by 41% of the families, while 59% opted out. Among those declining randomization, 44% chose the treatment group and, 56% chose the control group for social reasons. Using a computerized randomization system, 55% of the 22 families who accepted randomization were assigned to the treatment group and, 45% to the control group (Figure 1). All families in the control group were subsequently invited to our clinic to participate in an intensive rehabilitation program (IRP) following the research.

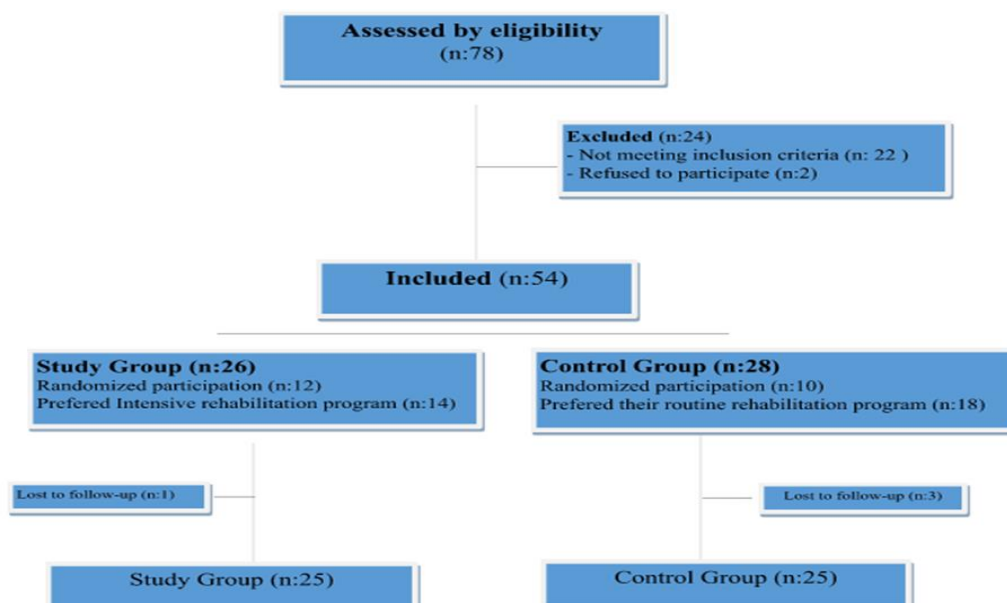


Figure 1: Flow-chart of patient selection

Data collection included age, gender, type of involvement, personal and family medical history, as well as systemic and neuromuscular examination details for all participating children. Hypertonia and spasticity levels in specific muscle groups were measured using the Modified Ashworth Scale (MAS) and the Tardieu Scale. Gross motor function levels were assessed using GMFCS, while motor functions were evaluated with the Gross Motor Function Measure-66 (GMFM-66). Gait function was examined using the Observational Gait Scale (OGS). Specific treatment goals were determined and assessed using the Goal Attainment Scale (GAS). Cognitive functions were evaluated with the Stroop test and the Auditory Verbal Learning Test (AVLT), which measures various aspects of verbal learning and memory.

Botulinum toxin-A injections were administered in the operating room of Kocaeli University Faculty of Medicine Hospital under moderate to deep sedation. Muscle selection, doses, and dilution were individualized based on the severity and pattern of spasticity, body weight, muscle size, clinical examination, and predetermined treatment goals. Guided by electrical stimulation, BoNT-A was injected into the target muscles. Subsequently, the children enrolled in the study underwent a personalized, goal-oriented, multimodal IRP for 3 weeks, 5 days a week, either half or full day, commencing between 1 week to 10 days post-procedure. The multimodal treatment program encompassed various therapeutic approaches, such as physiotherapy, occupational therapy, orthotics, serial casting, cognitive rehabilitation, special education programs, transcranial direct current stimulation, neurofeedback, biofeedback, electrical stimulation, constraint-induced therapy, bimanual training, robotic rehabilitation, hydrotherapy, music therapy, functional ambulation training, and virtual reality. Children in the control group adhered to their routine rehabilitation program,

consisting of 45-60 minute sessions 3-5 days per week post-BoNT-A injection. After the research, families of the control group were also invited to participate in an IRP at our clinic. Both groups underwent assessments, including GMFM-66, OGS, GAS, Stroop test, and AVLT, at baseline and during week 4.

Statistical Analysis

The statistical analysis employed IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) software. The normal distribution of data was assessed using the Shapiro-Wilk test. Numerical variables were expressed as median (25th-75th percentile) and frequency (percentages). The Mann-Whitney U test was utilized to compare differences between groups for numeric variables lacking normal distribution. For categorical variables, Fisher's exact chi-square test, Yates' chi-square test, and Monte Carlo chi-square test were employed to assess differences between groups. A significance level of <0.05 was deemed statistically significant for two-tailed tests.

Results

During this clinical research, 78 children were initially screened for potential enrollment. Subsequently, 54 patients underwent evaluation, 50 of whom were included in the statistical analysis (see Figure 1). The research, which started in December 2021, was successfully concluded in April 2022. The study group comprised 12 (48%) girls and 13 (52%) boys, while the control group consisted of 11 (44%) girls and 14 (56%) boys. Notably, there were no statistically significant differences in terms of age, gender, type of involvement, or Gross Motor Function Classification System (GMFCS) level between the study and control groups ($p>0.05$) (refer to Table 1).

Table 1. Demographic and clinical characteristics of the study and control groups

		Study Group (n=25)	Control Group (n=25)	<i>p</i> *
Age (month) (Mean±SD)		111.04±50.24	113.16±41.86	0.75
Gender	Female	12 (%48)	11 (%44)	1
	Male	13 (%52)	14 (%56)	
Type of Involvement	Hemiplegic	6 (%24)	8 (%32)	0.69
	Diplegic	17 (%68)	14 (%56)	
	Quadriplegic	2 (%8)	3 (%12)	
GMFCS Level n(%)	Level 1	6 (%24)	8 (%32)	0.83
	Level 2	8 (%32)	5 (%20)	
	Level 3	5 (%20)	5 (%20)	
	Level 4	6 (%24)	7 (%28)	

GMFCS: Gross Motor Function Classification System; *Mann-Whitney U test

Upon baseline assessment, there were no statistically significant differences in the Modified Ashworth Scale (MAS) and Tardieu scale results for the hip adductor, gracilis, hamstring, gastrocnemius, and soleus muscle groups between the study and control groups ($p>0.05$) (see Table 2). Among the children included in the study group, a comprehensive array of interventions was implemented, with 88% receiving orthotics, 72% undergoing robotic rehabilitation, 48% undergoing serial casting, 68% engaging in neurofeedback, 20% participating in virtual reality programs, 68% benefiting from hydrotherapy, 76% undergoing functional ambulation applications, and 44% enrolled in special education programs.

Upon evaluating the results of the Observational Gait Scale (OGS) at week 4, a statistically significant improvement was

noted in both the study and control groups. However, a noteworthy observation emerged when comparing the OGS results of both groups at week 4, revealing significantly superior outcomes and greater changes in favor of the study group (refer to Table 3).

Despite no statistically significant difference in the Gross Motor Function Measure-66 (GMFM-66) results between the two groups at baseline and week 4, both groups exhibited substantial improvement in the GMFM-66 total score, total goal score, and scores for dimensions C, D, and E at week 4. A closer examination of the changes recorded in week 4 highlighted significantly higher results for the study group, particularly in the GMFM-66 total score, total goal score, and scores for dimensions D and E (see Table 3).

Table 2. Results of MAS and TS of lower extremity muscle groups in the study and control groups

	Study Group (n=25) (Mean±SD)	Control Group (n=25) (Mean±SD)	p*
Hip Adductor			
MAS	1.00±0.81	1.08±0.86	0.65
TS			
XV1	44.20±9.96	41.60±8.25	0.41
XV3	39.00±12.91	36.20±11.92	0.48
X	5.20±3.94	5.40±4.31	0.84
Y	1.68±0.55	1.68±0.47	0.83
Gracilis			
MAS	1.40±0.70	1.60±0.81	0.27
TS			
XV1	33.20±8.52	31.20±7.81	0.41
XV3	26.40±10.75	24.00±10.20	0.34
X	6.80±3.18	7.20±3.25	0.46
Y	1.92±0.40	1.92±0.27	0.58
Hamstring			
MAS	1.76±0.72	2.08±0.57	0.07
TS			
XV1	136.20±11.39	130.00±11.72	0.16
XV3	109.80±18.17	100.60±12.61	0.05
X	26.40±12.70	29.40±9.82	0.21
Y	2.00±0	2.00±0	1.00
Gastrocnemius			
MAS	2.36±0.81	2.44±0.58	0.77
TS			
XV1	77.20±16.58	79.60±12.24	0.49
XV3	62.60±17.14	64.60±10.98	0.53
X	14.80±5.09	15.40±5.57	0.60
Y	2.40±0.50	2.24±0.436	0.23
Soleus			
MAS	2.08±0.95	1.96±0.73	0.68
TS			
XV1	88.20±14.05	91.20±11.01	0.26
XV3	72.60±17.50	76.80±12.57	0.30
X	15.60±6.97	14.40±6.17	0.56
Y	2.36±0.49	2.16±0.37	0.11

MAS: Modified Ashworth Scale, TS: Tardieu Scale; MAS scores were converted into "0 = 0, 1 = 1, +1 = 2, 2 = 3, 3 = 4, and 4 = 5" for statistical analysis; *Mann-Whitney U test

Outcome Assessment

Upon evaluating the goals established for both body structure and function, as well as activity domains in both the study and control groups, notable achievements were observed. In the study group, it was evident that treatment goals were successfully met in all children concerning body structure and function, as per the Goal Attainment Scale (GAS). Moreover, an impressive 96% of children in the study group demonstrated the attainment of treatment goals in the realm of activity. In the individual and collective evaluation of the predetermined goals within the study group, the average T-score results reflected outcomes that were "better than expected," falling within the range of 50-59. Conversely, in the control group, treatment goals were achieved in 92% of children with regard to body structure and function, and in 64% of children concerning activity, according to the GAS (see Figure 2). These findings underscore the efficacy of the comprehensive treatment approach, particularly in the study group, where a higher percentage of children achieved their predetermined goals across both assessed domains.

Outcome Evaluation: Comparative Analysis

In scrutinizing the average T-score results for the established goals within the body structure and function domain, the control group exhibited outcomes that were "better than expected," falling within the range of 50-59. However, a distinct pattern emerged in the activity area, where the average T-score results were "lower than expected," ranging between 40-49. Contrastingly, the study group consistently demonstrated "better than expected" results in both the body structure and function and activity domains, as well as in the combined evaluation. Upon conducting a thorough comparison between the two groups concerning the determined goals and average T-score results for body structure and function, activity areas, and the combined evaluation, statistically significant superiority was consistently observed in favor of the study group (refer to Table 4). These findings emphasize the pronounced efficacy of the individualized and intensive rehabilitation programs in achieving optimal outcomes, particularly in body structure and function and activity domains, thereby contributing to the overall enhanced well-being of the children in the study group.

Table 3. Pre- and post-treatment assessment results of OGS and GMFM-66 for the study and control groups.

	Baseline Median (25-75%)	Week 4 Median (25-75%)	Change from Baseline, at week 4 Median (25-75%)	<i>p</i> *
OGS				
Study Group	5.0 (3,0-9,0)	14.0 (11,0-15,5)	8.0 (6,0-9,0)	0.00
Control Group	7.0 (2,5-10,5)	9.0 (6,5-13,5)	3.0 (2,0-3,5)	0.00
<i>p</i> **	0.44	0.00	0.00	
GMFM-66				
Dimension B				
Study Group	100 (100-100)	100 (100-100)	0,0 (0,0-0,0)	0.10
Control Group	100 (100-100)	100 (100-100)	0,0 (0,0-0,0)	0.15
<i>p</i> **	0.65	0.55	0.56	
Dimension C				
Study Group	100 (68.5-100)	100 (93.0-100)	0.0 (0.0-18.5)	0.00
Control Group	100 (70.0-100)	100 (73.5-100)	0.0 (0.0-5.0)	0.01
<i>p</i> **	0.90	0.30	0.056	
Dimension D				
Study Group	51.0 (27.0-73.0)	69.0 (45.0-88.5)	15.0 (8.5-18.0)	0.00
Control Group	54.0 (23.5-75.5)	61.0 (25.0-83.0)	5.0 (2.0-9.0)	0.00
<i>p</i> **	0.94	0.25	0.00	
Dimension E				
Study Group	47.0 (13.5-69.5)	64.0 (17.0-86.0)	9.0 (4.5-16.0)	0.00
Control Group	42.0 (15.5-77.0)	44.0 (16.0-80.0)	3.0 (0.0-4.0)	0.00
<i>p</i> **	0.37	0.74	0.00	
Total Goal Score				
Study Group	58.0 (47.5-70.5)	77.0 (66.5-89.5)	14.0 (11.5-19.0)	0.00
Control Group	68.0 (51.0-78.0)	75.0 (57.0-82.0)	5.0 (3.5-7.0)	0.00
<i>p</i> **	0.26	0.409	0.00	
Total Score				
Study Group	80.0 (61.5-88.0)	88.0 (70.5-95.0)	6.0 (5.0-9.0)	0.00
Control Group	77.0 (60.5-90.0)	80.0 (60.5-92.5)	2.0 (1.0-3.0)	0.00
<i>p</i> **	0.93	0.32	0.00	

*Wilcoxon test, **Mann-Whitney U test

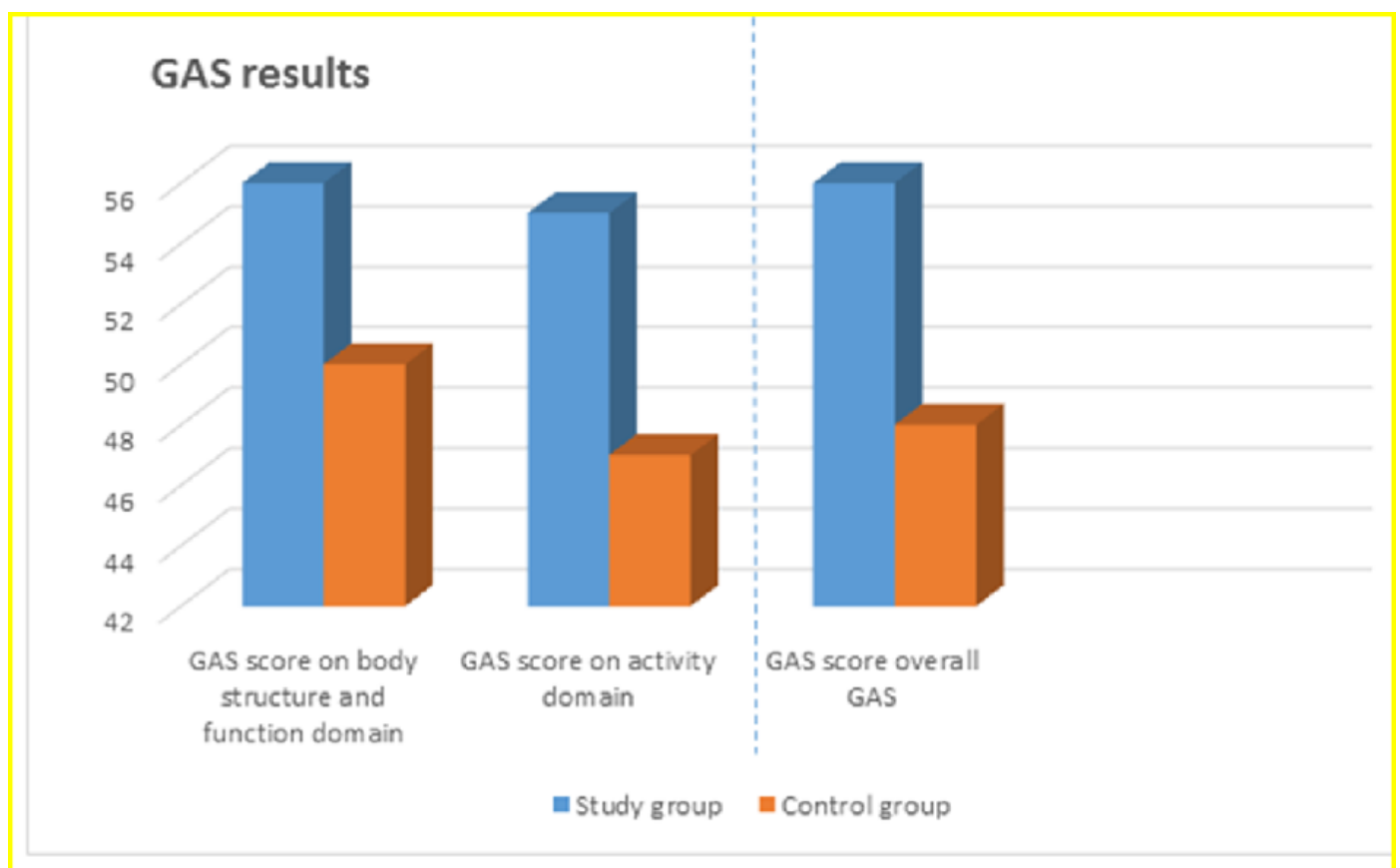
**Figure 2:** The GAS scores of study and control group. T>50=goal achieved, T<50=goal not achieved.

Table 4. GAS T-score results

	Body structure and function domains	Activity domain
Study group GAS scores	n (%)	n (%)
+2	-	-
+1	14 (%56)	14 (%56)
0	11 (%44)	10 (%40)
-1	-	1 (%4)
-2	-	-
Control group GAS scores	n (%)	n (%)
+2	-	-
+1	4 (%16)	1 (%4)
0	19 (%76)	15 (%60)
-1	2 (%8)	9 (%36)
-2	-	-

Cognitive Function Assessment

In the evaluation of the Stroop test results, specifically the 5th section time (S5T), error (S5E), and correction (S5C) scores, significant advancements were noted in the study group. At week 4, statistically significant improvements in S5T and S5C values were observed although no statistically significant change was observed in S5E values. Conversely, the control group displayed no statistically significant differences in the S5T, S5E, and S5C parameters. While both groups did not show significant alterations when comparing baseline and week 4 values in S5T, S5E, and S5C, a notable finding emerged when assessing the amount of change at week 4. Specifically, a statistically significant improvement was observed solely in S5T, favoring the study group (see Table 5). In the analysis of the Auditory Verbal Learning Test (AVLT) scores, significant improvements were witnessed in all parameters

for the study group at week 4. Conversely, the control group displayed significant improvement only in the AVLT A1-A5 average score. When comparing the results between the study and control groups, it became clear that the study group outperformed in various parameters. Specifically, the results of A6, A7, and A1-A5 average scores of the AVLT at week 4, along with the amount of improvement obtained in all parameters, were significantly higher in favor of the study group (refer to Table 5). These findings underscore the positive impact of intensive rehabilitation programs on cognitive functions in children with CP.

Discussion

The findings of this research underscore the positive impact of IRPs tailored to the individual needs and clinical characteristics of children with cerebral palsy (CP) who have undergone multi-level Botulinum toxin-A (BoNT-A) injections. Notably, these programs exhibit favorable effects on both motor and cognitive functions, encompassing gross motor functions, gait skills, attention, memory, and learning. The existing literature on IRPs for children with CP lacks consensus on the optimal treatment dosage, with variations in session frequency and duration reported across different studies. While some studies suggest positive outcomes with frequencies exceeding three sessions per week, the lack of a standardized approach poses challenges in determining the most effective treatment dosage.^{13,14} The present study aligns with previous research emphasizing the importance of a multidisciplinary team approach in developing customized, intensive, and goal-oriented rehabilitation programs for children with CP.

Table 5. Results of Stroop Test 5th section and AVLT for the study and control group

	Baseline Median (25-75%)	Week 4 Median (25-75%)	Change from Baseline, at week 4 Median (25-75%)	p*
Stroop Test				
S5 Time (sec)				
Study group	35.50 (24.50-57.50)	25.50 (18.75-36.5)	7.50 (5.75-19.75)	0.005
Control group	25.00 (20.00-48.00)	26.00 (18.00-46.00)	2.00 (1.00-4.00)	0.344
p **	0.230	1.000	0.001	
S5 Error				
Study group	0.00 (0.00-0.25)	0.00 (0.00-0.00)	0.00 (0.00-0.25)	0.180
Control group	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	1.000
p **	0.536	1.000	0.223	
S5 Correction				
Study group	2.00 (0.75-3.00)	1.00 (0.00-1.25)	1.00 (0.00-1.25)	0.024
Control group	1.00 (0.00-2.00)	1.00 (0.00-1.00)	1.00 (-1.00-1.00)	0.414
p **	0.270	0.887	0.347	
AVLT				
A1				
Study group	6.00 (4.75-7.75)	9.50 (8.00-11.00)	4.00 (2.00-5.00)	0.004
Control group	7.00 (5.00-9.00)	7.00 (6.00-7.00)	1.00 (1.00-2.00)	0.053
p **	0.417	0.109	0.005	
A6				
Study group	9.50 (7.00-10.25)	12.50 (11.00-14.25)	3.00 (1.75-5.25)	0.008
Control group	7.00 (7.00-14.00)	9.00 (7.00-13.00)	0.00 (0.00-2.00)	0.131
p **	0.813	0.043	0.014	
A7				
Study group	9.00 (7.50-11.25)	11.00 (11.00-12.75)	2.00 (1.00-3.50)	0.007
Control group	9.00 (7.00-12.00)	10.00 (9.00-11.00)	1.00 (-1.00-1.00)	0.589
p **	0.887	0.043	0.043	
A1-A5				
Study group	45.00 (41.75-50.25)	58.00 (54.50-64.50)	12.50(10.25-18.25)	0.005
Control group	46.00 (39.00-53.00)	50.00 (42.00-52.00)	4.00 (3.00-4.00)	0.040
p **	0.887	0.010	0.007	

S5T: 5th section time score of Stroop Test, S5E: 5th section error scores of Stroop Test, S5C: 5th section correction scores of Stroop Test, AVLT: Auditory Verbal Learning Test *Wilcoxon test, **Mann-Whitney U test



The pharmacological treatment of spasticity through BoNT-A injections, targeting selective muscles, is a common practice in managing CP. This study supports the notion that BoNT-A treatment, when combined with IRPs, can enhance motor control and the efficacy of other therapeutic modalities. The success of BoNT-A treatment depends on careful patient selection, individualized treatment planning, and timely IRP implementation. This aligns with research suggesting that various therapies, including occupational therapy, bimanual training, constraint-induced therapy, and others, can be effective in treating motor disorders in children with CP after BoNT-A administration.^{15,16}

The study's approach of combining BoNT-A injections with a personalized IRP led to significant improvements in gross motor functions, gait skills, and cognitive functions in the study group. The emphasis on real-world tasks and activities designed collaboratively with families underscores the importance of active involvement and high-intensity interventions in achieving positive outcomes. These results are consistent with previous studies highlighting the benefits of IRPs, particularly for gross motor functions, in children with spastic CP.^{17,18,19}

The utilization of the Observational Gait Scale (OGS) as a cost-effective and efficient alternative to computerized gait analysis systems adds practical value to the study. The observed enhancements in gait skills in children following a high-IRP further validate the effectiveness of this approach. Similarly, the study recognizes the intricate relationship between motor and cognitive development, supporting the integration of cognitive rehabilitation into the treatment of children with CP.

Limitations

Despite the strengths of this research, including its focus on both motor and cognitive functions and the inclusion of a control group, limitations such as the quasi-randomized design, a relatively small sample size, and short-term follow-up underscore the need for larger, randomized controlled studies with longer-term assessments. The heterogeneous nature of CP poses challenges in standardizing treatment programs, emphasizing the importance of individualized approaches in clinical settings.

Conclusion

This study provides valuable insights into the positive outcomes of IRPs tailored to the unique needs of children with CP who have undergone multi-level BoNT-A injections. The results highlight the potential for additional benefits in cognitive functions, emphasizing the necessity of a multidisciplinary team approach for the development and implementation of individualized, goal-oriented, multimodal rehabilitation programs. Multidisciplinary approaches encourage collaboration between physiotherapists and other healthcare professionals, allowing for the creation of more comprehensive and effective treatment plans. Therefore, it is of great importance for professionals working in the field of physiotherapy to adapt rehabilitation programs to individual needs and work with multidisciplinary teams.

Further research with larger cohorts and extended follow-up periods is warranted to strengthen the evidence supporting the effectiveness of these programs.

Conflict of Interest

There are no disclosed conflicts of interest for the author.

Compliance with Ethical Statement

Approval for the study was obtained from the Kocaeli University Clinical Research Ethics Committee (KU GOKAEK-2021/20.05), and written informed consent was obtained from all participating children and their families.

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Author Contributions

G.G., T.G., N.D.: Study idea/Hypothesis; G.G., T.G.: Design; G.G., T.G., B.Ç.T., M.A.: Data Collection; G.G.: Analysis; G.G., T.G., B.Ç.T.: Literature review; G.G., T.G., B.Ç.T.: Writing; T.G., B.Ç.T., N.D.: Critical review

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