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ORIGINAL ARTICLE

Long-Term Neurodevelopmental Outcomes of the SAFE Early Intervention in Infants at Risk: A Randomised Controlled Trial

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Received: 12 June 2025 | **Revised:** 5 August 2025 | **Accepted:** 28 August 2025

Funding: The authors received no specific funding for this work.

Keywords: early intervention | enriched environment | infants at risk | physiotherapy

ABSTRACT

Background: Early intervention for infants at risk of cerebral palsy (CP) plays a critical role in improving neurodevelopmental outcomes. Recently, approaches emphasising infant active participation and family collaboration have shown greater effectiveness compared to traditional methods.

Aims: This study aimed to evaluate the effects of the SAFE early intervention approach on cognitive, language, and motor development in infants at risk for CP, in comparison to conventional neurodevelopmental treatment (NDT) practices.

Methods: In this randomised controlled trial, 46 infants were assigned to either the SAFE intervention group ($n = 23$) or the control group receiving NDT-based care ($n = 23$). The intervention lasted for 3 months, with developmental assessments conducted at 6 and 12 months using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III).

Results: Significant improvements were observed in motor and language composite scores in the SAFE group between baseline (T1) and the 3-month follow-up (T2), while cognitive scores showed a non-significant increase. Compared to the control group, the SAFE group demonstrated significantly higher scores across all Bayley-III domains at T2. However, the time × group interaction was significant in favour of the SAFE group for motor scores, while cognitive scores favoured the control group. No significant interaction was observed for language scores. Over time, both groups showed developmental progress in various domains, with the SAFE group exhibiting significant motor gains from T1 to T3. The control group showed significant cognitive improvements from T1 and T2 to T3.

Conclusions: The SAFE early intervention model appears to be a feasible and effective approach for infants at risk for CP, especially before a formal diagnosis is made. Its focus on active infant participation, family engagement, and enriched environments supports improved motor development outcomes.

Trial Registration: NCT06930482

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1 | Introduction

Early intervention (EI) refers to services provided during the first 3 years of life to minimise developmental challenges in infants at biological or environmental risk [1]. The early years represent a critical window for brain plasticity, during which timely interventions can mitigate long-term adverse outcomes [2]. While EI has demonstrated positive effects on cognitive and motor development in preterm infants [3], term infants with perinatal distress or neurological dysfunction also benefit from such programmes. A systematic review confirmed that early developmental stimulation improves motor and cognitive outcomes in high-risk term infants [4].

The Neonatal Intensive Care Unit (NICU) environment, although life-saving, poses sensory challenges that may hinder neurodevelopment [5]. Sensory-based interventions during this sensitive period can enhance brain development and care quality [6]. Additionally, NICU graduates face increased health risks, leading to elevated maternal psychological stress and disrupted parent-infant interactions [7–9]. Consequently, effective EI must also empower families to support their child's needs.

In Turkey, Neurodevelopmental Treatment (NDT), or the Bobath approach, is the conventional standard. NDT emphasises therapist-guided facilitation to improve motor control [10], but recent research suggests that therapist-led methods may hinder active motor learning in infants without severe brain injuries [11]. Current guidelines promote child-initiated, task-specific and family-centred approaches within enriched environments [12].

Programs like GAME, COPCA, SPEEDI and Small Step reflect this paradigm shift, prioritising active infant participation and family involvement. However, these models were developed nationally and often focus primarily on motor development, overlooking sensory aspects. Recognising this gap, the SAFE approach incorporating Sensory strategies, Activity-based motor training, Family collaboration, and Environmental enrichment was developed to holistically support both motor and sensory development from early infancy [13].

This study aimed to evaluate the effectiveness of the SAFE early intervention program, applied between 3 and 6 months of corrected age, on the cognitive, motor, and language outcomes of infants at risk. The SAFE program was compared to standard NDT practices. We hypothesised that SAFE would result in superior developmental outcomes by 12 months of age.

2 | Methods

2.1 | Participants

Infants at risk for cerebral palsy (CP), aged 3 months (corrected), with a history of NICU stay ≥ 15 days and clinical signs suggestive of CP (e.g., perinatal stroke, HIE, PVL), were recruited from the Paediatric Rehabilitation Unit at Gazi University. Infants with congenital anomalies, genetic syndromes or non-Turkish-speaking parents were excluded. Written informed consent was obtained from all participating families.

2.2 | Power Calculation

This study used the G*Power (G*Power version 3.1.9.2, Axel Buchner, Universität Kiel) program for sample size calculation. The effect size for the effectiveness of the treatment programme (for a 10-point change according to the Bayley-III motor composite score) was determined as Cohen's d: 1.0427529 by examining the data of a similar study conducted by Apaydın et al. [14] According to this result, when $\alpha = 0.05$ and 1-β (power) = 0.90 and Cohen *d*: 1.0427529 (Allocation ratio: 1), it was determined that at least 21 cases should be included in both groups. The study was completed with 46 infants. The Consolidated Standards of Reporting Trials (CONSORT) flow chart in Figure 1 presents the research design.

2.3 | Study Design

Infants were randomised into two groups—SAFE (intervention) and NDT (control)—using a stratified method (by sex and gestational age). Assessments occurred at baseline (3 months, T1), post-intervention (6 months, T2), and follow-up (12 months, T3) by a blinded, experienced paediatric physiotherapist.

2.4 | Randomization

The study used a stratified randomisation method for gender (male/female) and gestational age (preterm/term) variables. Participants were randomly assigned to the SAFE (early intervention group) and the NDT (control group) within each subgroup. The randomisation process was done using a computer programme (random number generator), and equal distribution was ensured between both groups. Randomisation was completed, and groups were identified before the intervention process started.

2.5 | Outcome Measure

The Bayley-III scale evaluated all participants' cognitive, language and motor development. Bayley-III is an individually administered scale that assesses five basic developmental domains in children aged 1–42 months. These five areas of development are: cognitive development, language (receptive and expressive communication) development, motor (gross and fine) development, social–emotional development and adaptive behaviour [15]. The Bayley-III does not provide an overall total score but separately raw and scaled scores for each domain, composite scores and percentile ranks for each scale. All items on the scale are scored as 0 (unable to perform the desired skill) or 1 (able to perform the desired skill) to obtain a raw score. These raw scores are converted into a scale score and then into a composite score (mean: 100, standard deviation: 15). If the combined score is below 85, it is determined that there is a developmental delay in the relevant area [15]. The assessment was performed by a certified physiotherapist, trained in applying the test, in a unit where appropriate environmental conditions were provided and when the infant felt peaceful and happy. The assessor was blinded to group allocation to reduce potential bias in outcome evaluation.

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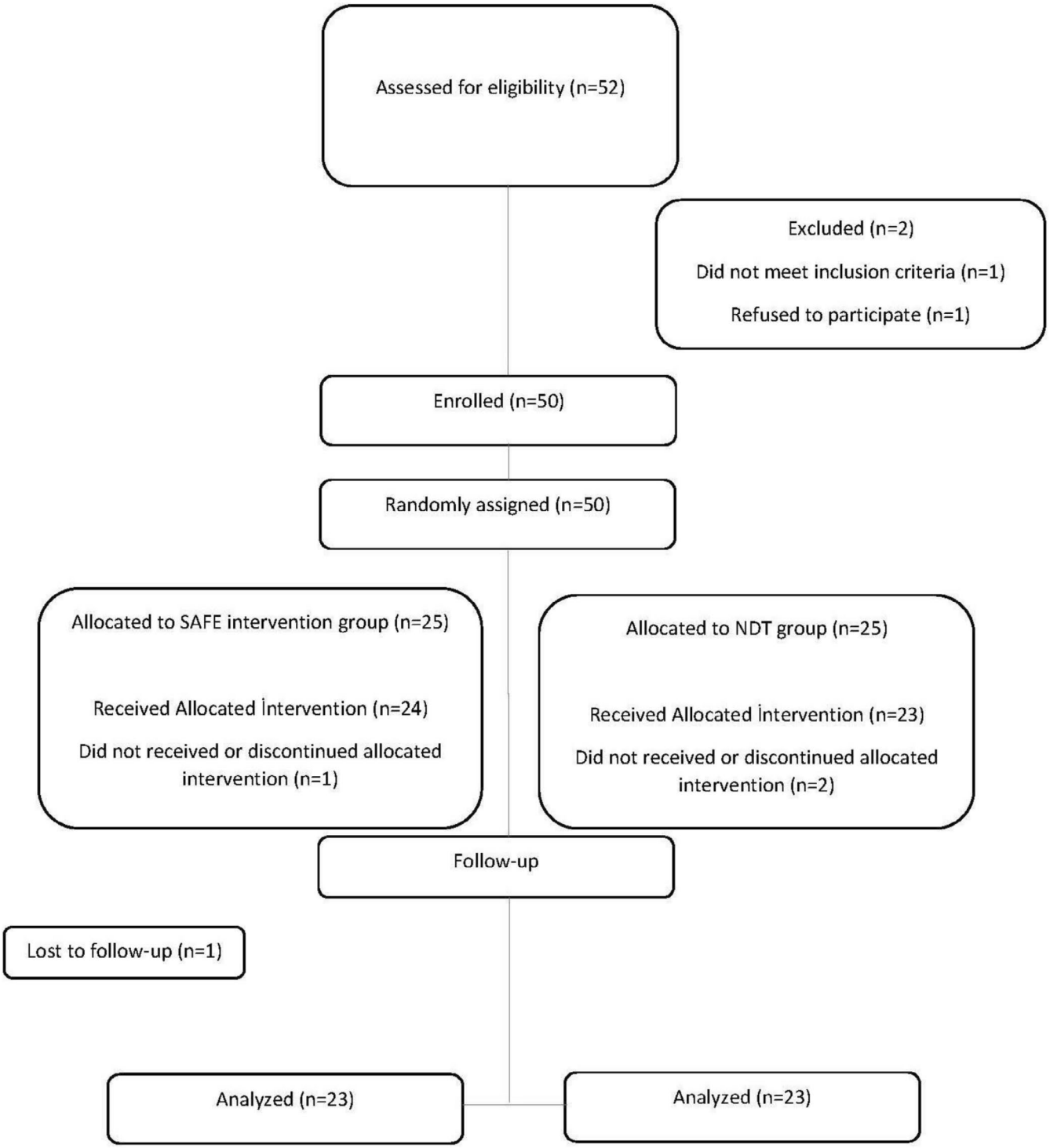


FIGURE 1 | CONSORT flowchart.

2.6 | Interventions

SAFE Early Intervention: The SAFE approach is a structured, family-centered early intervention programme designed to support both motor and sensory development in high-risk infants. The intervention emphasised voluntary, purposeful movement and active infant participation through enriched, developmentally appropriate environments. Sensory inputs, particularly tactile and vestibular stimuli, were integrated into daily routines to promote reaching, fine motor control and postural stability. Families were guided to structure the home environment with appropriate materials to stimulate sensory-motor integration.

Monthly home visits were conducted by trained physiotherapists to provide parent coaching, reinforce strategies, and address caregiver concerns. During these visits, the infant's developmental level was assessed, and interventions were adjusted accordingly. Parents were encouraged to embed targeted activities into daily routines to enhance imitation, communication and

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social engagement. The intervention aimed to foster caregiver sensitivity and confidence, supporting consistent parent-infant interaction beyond structured sessions [14].

NDT-based home program: Infants in the control group received a home-based intervention based on NDT principles. Parents were instructed on therapist-guided techniques to facilitate postural control and functional motor patterns appropriate to the infant's developmental stage. Training included how to handle the infant, provide manual facilitation, and promote transitions such as turning and sitting. Intervention plans were reviewed monthly in clinic visits, and weekly follow-up calls ensured adherence and allowed for problem-solving or modifications as needed [16].

2.7 | Dosage of Interventions

In both groups, parents received illustrated booklets outlining activity suggestions. Families maintained an activity diary and were contacted weekly by phone to monitor adherence. The intervention phase lasted 12 weeks. Monthly follow-up continued through the infant's first year, during which developmental status and neurologic outcomes were regularly monitored by a paediatric neurologist.

2.8 | Statistical Analysis

The SPSS program 26 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Data normality was evaluated using visual and analytical methods, such as histograms and the Shapiro–Wilk test. A paired sample *t*-test was used for pairwise comparisons within groups, and an independent sample *t*-test was used to compare groups. Cohen's norms were used to calculate the effect sizes for within-group T1 to T2 variations. Small effect (0.2), moderate impact (0.5), or substantial effect (0.8) were the reported Cohen's d findings. A 2 × 3 repeated-measures ANOVA was used to investigate the time × group interaction. T1 refers to the evaluation results in the third month, T2 refers to the evaluation results in the 6th month and T3 refers to the results in the 12th month. For the ANOVA tests, the Greenhouse–Geisser adjusted statistical values were provided if a violation of sphericity was discovered using Mauchly's test of sphericity ($p < 0.05$). The differences between group time points were measured using the Bonferroni correction (post hoc analysis). Partial eta-square (ηp2) was interpreted as an effect size as small (ηp2 = 0.01), medium (ηp2 = 0.06) and large (ηp2 = 0.14) [17].

3 | Results

3.1 | Between-Group Comparisons

There were no significant differences between the SAFE and control groups in demographic or clinical characteristics at baseline ($p > 0.05$), indicating that the groups were comparable. At 12 months, 7 infants (30.43%) in the SAFE group and 6 infants (26.09%) in the control group were diagnosed with CP (Table 1). At the 3-month follow-up (T2), the SAFE group outperformed the control group across all Bayley-III composite domains (motor, language, and cognitive) with statistically significant differences ($p < 0.05$, Table 2).

Analysis of the interaction effect of time × group demonstrated a significant improvement in favour of the SAFE group for the motor composite score ($p < 0.05$, Table 3; Figure 2), while a significant interaction was found in favour of the control group for the cognitive composite score ($p < 0.05$). No significant interaction effect was observed for the language composite score ($p > 0.05$).

3.2 | Within-Group Comparisons

In the SAFE group, motor and language composite scores showed significant improvements from baseline (T1) to 3 months (T2) ($p < 0.05$). While cognitive scores increased, the change did not reach statistical significance ($p > 0.05$). In contrast, the control group showed no significant improvements in language or cognitive scores between T1 and T2. Moreover, there was a significant decline in motor scores in this group ($p < 0.05$, Table 2).

Across timepoints, the main effect of time was significant for all Bayley-III domains ($p < 0.05$), indicating general developmental changes regardless of group. Similarly, the main effect of group was significant for all outcomes ($p < 0.05$). Bonferroni post hoc analysis revealed that in the control group, the cognitive composite score increased significantly from T1 to T3 ($p = 0.009$) and from T2 to T3 ($p = 0.002$). For the motor composite score, significant improvements were detected in the SAFE group between T1 and T3 ($p = 0.014$), and in the control group between T2 and T3 ($p = 0.012$) (Figure 2).

4 | Discussion

This study revealed that the SAFE early intervention approach applied to infants at risk of CP in the first year of life had more positive and sustainable effects on motor development than traditional NDT-based practices. Significant improvements were observed in motor development in the SAFE group, especially in the 6th month evaluations; however, gains in language development were not sustained at the 12th month. Cognitive outcomes showed limited improvement in the SAFE group and were more pronounced in the control group by 12 months.

Motor development is critical for acquiring basic movement skills in early childhood and for performing independent living activities in later ages. Supporting motor skills in early childhood increases physical functions and positively affects cognitive and social development processes. Therefore, targeting motor development in early intervention contributes to the child's overall neurodevelopmental progress [18]. In the literature, it has been emphasised that activity-based and goal-oriented interventions are effective in improving motor skills in children with CP [19, 20]. It has also published international guidelines stating that early interventions encouraging child-initiated movements and prioritising family participation in the early years when brain development is most rapid are effective [13]. In this context, the SAFE approach was developed by considering these modern principles based on sensory strategies,

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TABLE 1 | Demographic characteristics of infants.

		SAFE group ($n = 23$)		NDT group ($n = 23$)		
		n	**%**	***n***	**%**	***p***
Sex	Female	10	56.5	13	56.5	0.38
	Male	13	43.5	10	43.5	
Birth term	Preterm	17	73.9	14	60.9	0.27
	Term	6	26.1	9	39.1	
Pregnancy type	Normal	14	60.9	17	73.9	0.27
	IVF	9	39.1	6	26.1	
Delivery method	Normal	3	12.5	6	26.1	0.46*
	Caesarean	20	87.5	17	73.9	
Mother's education status	<12 years	4	17.4	3	13	0.44*
	12 years	5	21.7	9	39.1	
	>12 years	14	60.9	11	47.8	
Father's education status	<12 years	3	13	1	4.3	0.22*
	12 years	6	26.1	12	52.2	
	>12 years	14	60.9	10	43.5	

	SAFE group Mean ± SD	**NDT group Mean ± SD**	***p***
Gestational age (weeks)	32.88 ± 5.14	34 ± 4.97	0.441
Birth length (cm)	45.53 ± 5.87	44.3 ± 6.79	0.749
Birth weight (g)	1962.92 ± 855.53	2350.68 ± 1086.42	0.140
Head circumference (cm)	31.13 ± 4.53	31.78 ± 4.46	0.726
Duration of stay in NICU (days)	41.79 ± 39.71	33.04 ± 32.69	0.394

Note: Mann–Whitney *U* test, chi squared test or Fisher's exact test, $p < 0.05$.
Abbreviations: MRI: magnetic resonance imaging; NDT: neurodevelopmental treatment; NICU: neonatal intensive care unit; SAFE: SAFE early intervention approach; SD: standard deviation; USG: ultrasound imaging.

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TABLE 2 | Bayley-III scores of infants at 3 and 6 months.

Outcome	Group	T1 mean ± SD	T2 mean ± SD	Change T2-T1 mean ± SD	Cohen *d*	*p* value paired sample	*p* value independent sample
Bayley-III cognitive composite score	SAFE	106.73 ± 19.10	115 ± 10.22	8.26 ± 20.92	0.40	0.072	**T1: 0.035** **T2: < 0.001**
	NDT	96.30 ± 12.89	94.56 ± 10.54	−1.73 ± 15.71	0.11	0.601	
Bayley-III language composite score	SAFE	113.04 ± 16.31	124.39 ± 16.35	11.34 ± 21.42	0.52	**0.019**	**T1: 0.005** **T2: < 0.001**
	NDT	100.86 ± 11.18	103.86 ± 9.18	3 ± 10.99	0.27	0.204	
Bayley-III motor composite score	SAFE	101 ± 17.56	107.82 ± 11.78	6.82 ± 14.67	0.46	**0.036**	T1: 0.373 **T2: < 0.001**
	NDT	97.21 ± 9.86	89.52 ± 14.05	−7.69 ± 15.83	0.48	**0.029**	

Note: T1: 3rd month assessment, T2: 6th month assessment.
Abbreviations: NDT: neurodevelopmental treatment; SAFE: SAFE early intervention approach; SD: standard deviation.

TABLE 3 | Bayley-III scores of infants at 3, 6 and 12 months.

					Main effect for group	Main effect for time	Time × group
					p value	*p* value	*p* value
					F statistics	F statistics	F statistics
Outcome	Group	T1 mean ± SD	T2 mean ± SD	T3 mean ± SD	η2p	η2p	η2p
Bayley-III cognitive composite score	SAFE	106.73 ± 19.10	115 ± 10.22	114.13 ± 17.42	**< 0.001** **20.536** **0.318**	**0.002** **6.692** **0.132**	**0.026** **3.825** **0.080**
	NDT	96.30 ± 12.89	94.56 ± 10.54	107.34 ± 8.89			
Bayley-III language composite score	SAFE	113.04 ± 16.31	124.39 ± 16.35	114.43 ± 21.65	**< 0.001** **24.411** **0.357**	**0.020** **4.129** **0.086**	0.221 1.539 0.034
	NDT	100.86 ± 11.18	103.86 ± 9.18	101.82 ± 9.60			
Bayley-III motor composite score	SAFE	101 ± 17.56	107.82 ± 11.78	110.56 ± 21.55	**0.003** **9.651** **0.180**	**0.016** **4.452** **0.092**	**0.017** **4.358** **0.090**
	NDT	97.21 ± 9.86	89.52 ± 14.05	99.91 ± 14.20			

Note: T1: 3rd month assessment, T2: 6th month assessment, T3: 12th month assessment.
Abbreviations: NDT: neurodevelopmental treatment; SAFE: SAFE early intervention approach.

activity-based motor training, family cooperation and environmental enrichment principles. This structure is similar to programmes such as COPCA, GAME, SPEEDI and Small Step in the literature. Evaluating the COPCA programme, Hielkema et al. reported that challenging motor activities and caregiver coaching were associated with better motor outcomes in children with CP [21]. Another study by the same research group reported that COPCA provided higher cognitive scores than passive, therapist-controlled techniques, while NDT was associated with lower functional mobility [22]. Another approach that supports motor development, GAME, is based on environmental enrichment, parent coaching and active motor learning. In a randomised controlled study by Morgan et al. significant progress was seen in the GAME group regarding motor and cognitive development at the end of 12 months [23]. Similarly, Holmström et al. who evaluated the Small Step programme, stated that this programme had a protective effect on motor development, especially in the most affected children, and lasted until age 2 [24]. The effectiveness of the SAFE approach in motor development can be explained by its structure, which supports the active participation of the baby, integrates sensory inputs, and is based on environmental enrichment.

Language development is a cornerstone of early childhood cognitive and social development. Appropriate stimuli and parental support during this period strengthen the child's

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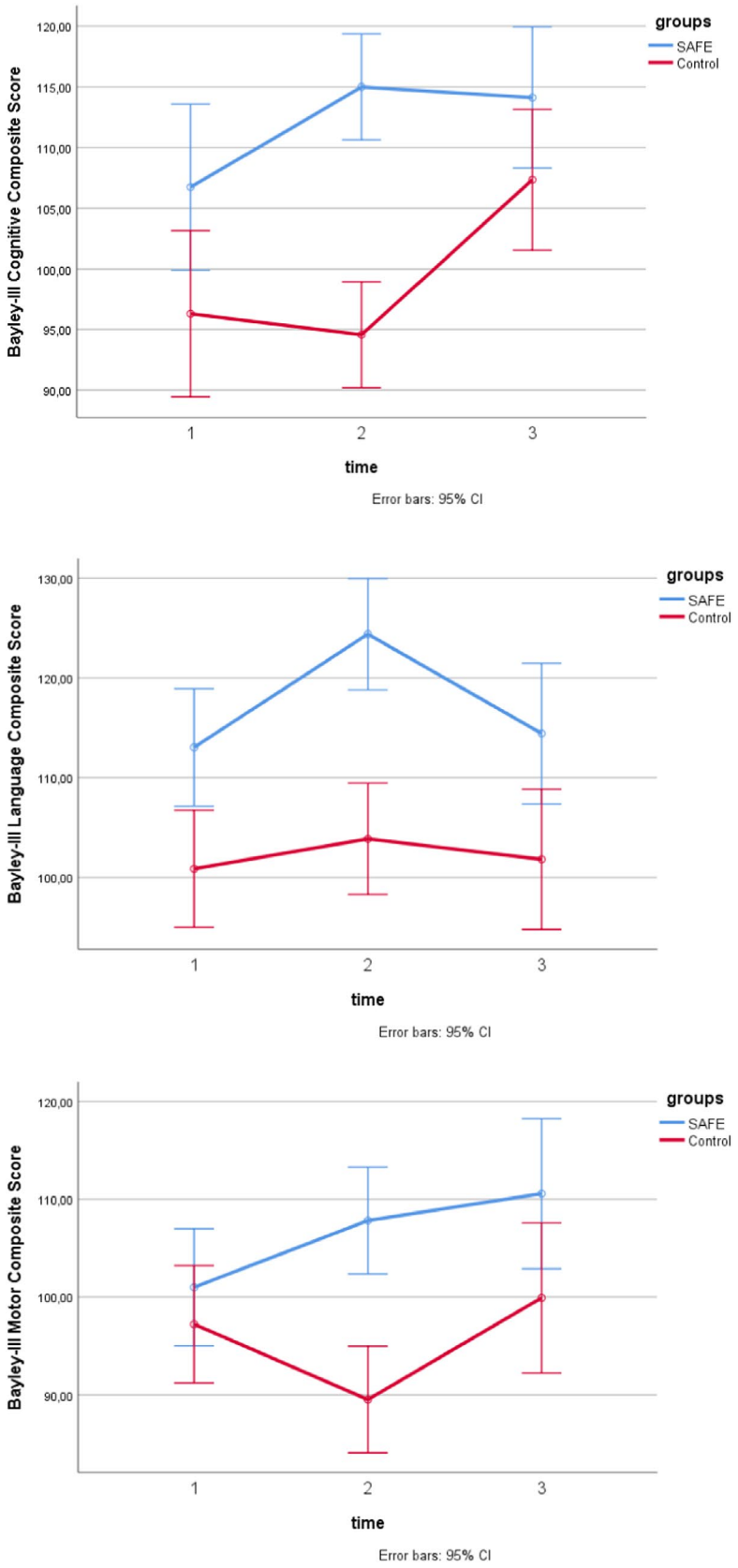


FIGURE 2 | Comparisons of treatment and control groups.

communication skills, thus providing significant advantages in terms of academic success and social adaptation in later ages [25]. Supporting language development in early intervention is critical in maximising the child's neurodevelopmental potential [26]. In fact, among early intervention approaches, the SPEEDI intervention has been reported to significantly support receptive

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and expressive language development, and structured parent-led games at home have been shown to contribute to cognitive and social development [27, 28]. Similarly, in the current study, progress was seen in the SAFE group regarding language development. This situation can be explained by daily routines that increase parent-infant interaction in the early period and structured activities that support imitation and communication skills. In the SAFE group, limited gains in cognitive development were observed in the early period but were maintained in the following months. This development was more pronounced in the NDT group at 12 months. This situation may be related to the recovery of initially low scores over time. Such 'developmental recovery' situations have been described in the literature, especially in groups exposed to standard care. Blauw-Hospers et al. who examined the COPCA approach, stated that differences in early motor and cognitive development can be balanced over time [4].

One of the unique contributions of this study is that the intervention was initiated only in infants with neurodevelopmental risk, before the diagnosis of CP was made. Novak et al. and McIntyre et al. emphasised that early diagnosis of CP and interventions initiated without waiting for diagnosis are more beneficial for long-term development [29, 30]. Due to the lack of widespread early intervention services in our country in the pre-diagnosis period, the importance of structured, applicable, and family-centred approaches such as SAFE increases.

The 10-point change in the Bayley-III motor composite score used as the reference in our power analysis corresponds to approximately 0.67 SD, given that the SD for composite scores is 15 as specified in the Bayley-III test manual [15]. [Bayley, 2006]. In the literature, a change of half a standard deviation (approximately 0.5 SD) is generally accepted as the threshold for the minimal clinically meaningful difference (MCID) [31]. Therefore, the 10-point difference used in our study is above this widely accepted threshold and is considered a clinically meaningful difference. Furthermore, one commonly used method for defining MCID is to calculate effect sizes based on baseline SD, which is consistent with our approach. Therefore, the use of a 10-point difference is meaningful and justified from both methodological and clinical perspectives.

The study's strengths include its randomised controlled design, 12-month long-term follow-up, structured intervention content based on literature, and the evaluation of a model centred on family participation. However, the fact that the SAFE approach was based on home visits created some logistical limitations regarding transportation and time management in rural areas. In addition, it was not always possible to standardise the assessment processes in the home environment. However, 30.43% of the children who followed the SAFE intervention were diagnosed with CP at 12 months, indicating that the study accurately covered the target group.

This study's findings indicate that the SAFE early intervention approach may effectively support motor and language development in infants at risk for neurodevelopmental disorders. Due to its organised yet home-based framework, SAFE can be incorporated into early intervention programmes at both clinical and community levels, especially in resource-constrained environments. The ability for trained caregivers to implement the intervention is a notable advantage that enhances its accessibility. To enhance comprehension of the effects of SAFE, studies incorporating neuroimaging and neurophysiological evaluations would be advantageous. Moreover, multicentre randomised controlled trials are essential to evaluate the efficacy of SAFE across diverse cultural and healthcare systems. Evaluations of scalability and analyses of cost-effectiveness are essential for prospective applications. Although sustained developmental improvements were noted in this study until 12 months corrected age, it is important to recognise that this timeframe does not entirely represent conventional 'long-term' developmental outcomes. Evaluations during the preschool phase are crucial for comprehending the longevity and developmental impacts of early intervention, particularly for high-risk infants in neurodevelopment. Consequently, it is essential that forthcoming research incorporates long-term follow-up to ascertain whether advancements in motor and language domains endure into preschool. Longitudinal studies would yield comprehensive insights into the sustainability and developmental impacts of the SAFE intervention.

5 | Conclusion

This study demonstrated that the SAFE early intervention approach resulted in significant improvements in motor and language development in infants at risk of CP, both within the SAFE group over time (from 6 to 12 months corrected age) and in comparison to the control group receiving conventional NDT-based practices. By emphasising infant activity, family collaboration, and enriched environments, SAFE offers a practical, family-centred model for early intervention. Importantly, initiating intervention prior to formal diagnosis appears to contribute to developmental gains observed during the first year of life. Given its adaptability to national conditions, the SAFE approach presents a promising option for early neurodevelopmental support.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Gazi University Ethics Committee (91610558–302.08.01–122723). Parents were asked to sign a consent form to allow their infants to participate in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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