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ORIGINAL ARTICLE

Gabapentin as Add-on Therapy to Trihexyphenidyl in Children with Dyskinetic Cerebral Palsy: A Randomized, Controlled Trial

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Abstract

Objective To compare the efficacy of gabapentin as add-on therapy to trihexyphenidyl in the treatment of children with dyskinetic cerebral palsy (CP).

Methods An open-labelled, randomized, controlled trial was conducted among children aged 3–9 y with dyskinetic CP [Gross Motor Functional Classification System (GMFCS) 4–5]. Participants were assigned into two groups: gabapentin with trihexyphenidyl ($n=30$) and trihexyphenidyl alone ($n=30$). Dyskinesia Impairment Scale (DIS), Dystonia Severity Assessment Plan (DSAP), and International Classification of Functioning, Disability, and Health–Children and Youth Version (ICF-CY) were measured at baseline, 4 and 12 wk.

Results There was significant reduction in baseline dystonia in both the groups (DIS: $p<0.001$; DSAP: $p=0.007$; ICF-CY: $p<0.001$) but when data were compared between the groups, there was no significant difference in the severity of dystonia at 4 wk and at 12 wk (DIS: $p=0.09$; DSAP: $p=0.49$; ICF-CY: $p=0.25$). Constipation was the commonest side effect observed in both the groups [3 (11.5%) vs. 4 (14.3%)].

Conclusion Trihexyphenidyl alone is as effective as combination of gabapentin with trihexyphenidyl in decreasing the severity of dystonia at 12 wk. Hence, there is no added benefit of gabapentin as add-on therapy for dystonia among children with dyskinetic CP.

Trial Registration CTRI/2019/04/018603.

Keywords Dystonia · Dystonic cerebral palsy · Tone · Quality of life

Introduction

Cerebral palsy (CP) is defined as a disorder of movement and posture resulting from nonprogressive damage to the developing brain. It is the leading cause of chronic disability in children, making them physically and mentally handicapped [1]. The disorder is broadly classified into spastic CP, dyskinetic CP, and ataxic CP based on the predominant motor involvement and site of involvement. Pyramidal tract involvement results in spastic CP, whereas extrapyramidal tract involvement, including basal ganglia, results in dyskinetic CP. The dyskinetic cerebral palsy is further divided into choreoathetoid CP and dystonic CP based on dominant movement pattern [2]. Common causes of CP include birth asphyxia, prematurity, kernicterus, maternal congenital cytomegalovirus and toxoplasma infection, and maternal chorioamnionitis [3–6]. The treatment of children with dyskinetic CP includes oral medication like trihexyphenidyl and baclofen [7]. In a systematic review on the management of dystonia in CP, it was observed that intrathecal baclofen and deep brain stimulation (DBS) were also effective [8]. However, the selection of medication has been mainly based on clinician experience rather than current evidence.

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Trihexyphenidyl is a centrally acting anticholinergic drug which is a competitive inhibitor of acetylcholine and has been used traditionally for management of children with dystonic cerebral palsy. It is effective in only 50% of the patients [9]. In a study by Carranza-del Rio et al., trihexyphenidyl showed a marked reduction in dystonia in upper (59.4%) and lower (37.6%) extremities [10].

Gabapentin is an analogue of gamma-aminobutyric acid, it interacts with an alpha subunit of voltage-gated calcium channels, inhibiting its entry into the presynaptic membrane, and hence, blocking the release of acetylcholine. There are reports of gabapentin showing its efficacy in reduction of dystonia in patients with paroxysmal dystonic choreoathetosis, hemifacial spasm, and dystonic cerebral palsy [11–13]. To the best of literature review, there are no randomized trials comparing gabapentin with trihexphenidyl. Hence, the present study was planned with a hypothesis that there was no significant reduction in the severity of dystonia between the gabapentin and trihexyphenidyl from baseline to 12 wk in children with dyskinetic CP.

Material and Methods

This open labelled, randomized, controlled trial was conducted in the Department of Pediatrics, Pharmacology and Neurology of a tertiary care teaching hospital of India from April 2019 to February 2020. Ethical clearance was obtained from the institutional ethics committee. The trial was registered in the Clinical Trial Registry of India (CTRI/2019/04/018603).

Children aged 3–9 y who had dyskinetic cerebral palsy with the Gross Motor Functional Classification System (GMFCS) 4–5 were enrolled in the study. Written informed consent was obtained from the parents or legal guardians. Children who had undergone any surgical procedure such as

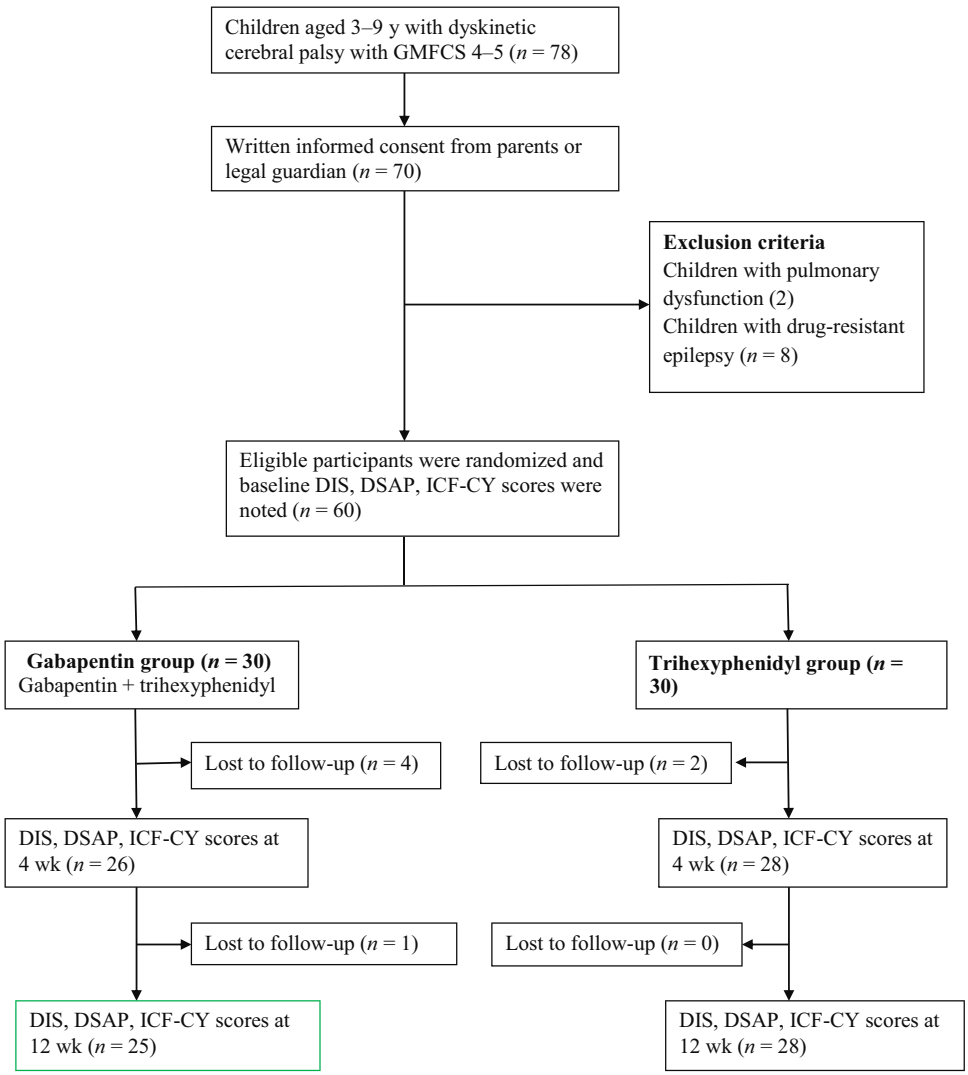

Fig. 1 Study flow diagram. *DIS* Dyskinesia Impairment Scale, *DSAP* Dystonia Severity Assessment Plan, *GMFCS* Gross Motor Functional Classification System, *ICF-CY* International Classification of Functioning, Disability, and Health–Children and Youth Version

orthopedic surgery or received botulinum toxin injection in the preceding 6 mo and children with known renal, pulmonary, cardiac, or hepatic dysfunction were excluded from the study. A convenient sample size of 30 in each group was chosen.

The eligible participants were enrolled consecutively. A predesigned case record form was filled. Demographic details (age, gender, socioeconomic status, etc.), perinatal history, development history, family history, magnetic resonance imaging findings, and detailed examination were recorded. Baseline Dystonia Severity Assessment Plan (DSAP) [14], Dyskinesia Impairment Scale (DIS) [15], and International Classification of Functioning, Disability, and Health–Children and Youth Version (ICF-CY) [16] score was assessed for all cases.

Eligible subjects were randomized into two groups: gabapentin group and trihexyphenidyl group using variable size, block randomization (2, 4, or 6) technique with computer-generated random number tables. Allocation of the group was concealed by having the name of the interventional drug stored in identical sealed envelope, which were opened after a patient had been enrolled in the study and assigned a study number.

Gabapentin group: participants were given Gabapentin (15–20 mg/kg/d in once a day dosage) along with trihexyphenidyl [0.2–2 mg/kg/d in three divided dosages (with upward dose escalation as 0.2 mg/kg/d in the first week followed by 0.5 mg/kg/d in the second week followed by 1 mg/kg/d in the third week followed by 2 mg/kg/d in the fourth week and same 2 mg/kg/d was continued for the next 8 wk)].

Trihexyphenidyl group: participants were given trihexyphenidyl alone (dose given in similar manner as described above). Participants were then advised to continue the treatment. At the end of 4 wk and 12 wk, patients were assessed and observed for the severity of dystonia as measured by outcome parameters DIS, DSAP, and ICF-CY scores. The tolerability of the drugs and side effects observed were also noted and compared between the two groups.

An SPSS version 15.0 was used for statistical analysis. The primary outcome variables including DIS score, DSAP score, and ICF-CY score were compared at different time periods (baseline, 4 wk and 12 wk) using repeated measure ANOVA test. These scores were compared between the gabapentin group and trihexyphenidyl group using two factors (time and group) repeated measure ANOVA test. Mean (SD) change in DIS, DSAP, and ICF-CY scores were compared between the two groups. The statistical analysis was performed with intention-to-treat protocol. A p value of <0.05 was considered significant.

Results

A total of 78 eligible children were screened; of whom, 60 children were recruited as study subjects. A total of 30 children received gabapentin along with trihexyphenidyl and 30 children received trihexyphenidyl alone with follow-up loss (Fig. 1). The baseline characteristics of the study subjects were comparable (Table 1). Among the enrolled subjects, 93.3% children in the gabapentin group and 90% children in the trihexyphenidyl group had generalized form of dystonia.

When the analysis of primary outcome measures was compared, there was a significant improvement in the severity of dystonia in terms of DIS ($p<0.001$), DSAP ($p=0.007$), and ICF-FY ($p<0.001$) from baseline to 4 wk and 12 wk in both the groups. However, the severity of dystonia was comparable between the gabapentin group and trihexyphenidyl group [DIS ($p=0.09$); DSAP ($p=0.49$); ICF-CY ($p=0.25$)] (Table 2). Further, when the data were analyzed with intention-to-treat protocol, there was also no significant difference observed in the severity of dystonia [DIS ($p=0.07$); DSAP ($p=0.55$); ICF-CY ($p=0.15$)] between the two groups. The mean change of DIS score (Fig. 2a), DSAP score (Fig. 2b), and ICF-CY score (Fig. 2c) between the two groups at baseline to 4 wk, 4 wk to 12 wk, and baseline to 12 wk was comparable. The

Table 1 Baseline characteristics of the study subjects ($n=60$)

Baseline characteristics	Gabapentin group ($n=30$)	Trihexyphenidyl group ($n=30$)	p value
Age in months			
Mean (SD)	52.3 (21.75)	49.9 (18.27)	0.65
Gender n (%)			
Male	21 (70%)	21 (70%)	0.84
Female	9 (30%)	9 (30%)	
Weight for height			
Below −3 SD	5 (20%)	7 (28%)	0.23
Above −3 SD	20 (80%)	18 (72%)	
BMI			
Below 3rd percentile	1 (20%)	1 (20%)	0.85
Between 3rd–50th percentile	2 (40%)	1 (20%)	
Above 50th percentile	2 (40%)	3 (60%)	
Comorbidities			
Epilepsy	11 (36.7%)	15 (50%)	0.30
Hearing defect	4 (13.3%)	2 (6.7%)	0.39
Vision defect	3 (10%)	0 (0%)	0.08
Etiology			
Perinatal asphyxia	14 (46.7%)	16 (53.3%)	0.30
Neonatal meningitis	2 (6.7%)	2 (6.7%)	1.00
Hemorrhage	2 (6.7%)	2 (6.7%)	1.00
Prematurity	4 (13.3%)	0 (0%)	0.04
Hyperbilirubinemia	2 (6.7%)	2 (6.7%)	1.00
Hypoglycemia	1 (3.3%)	1 (3.3%)	1.00
SGA	1 (3.3%)	1 (3.3%)	1.00
Duration of dystonia			
>90%	19 (63.3%)	16 (53.3%)	0.84
50%–90%	6 (20%)	9 (30%)	
10%–50%	4 (13.3%)	4 (13.3%)	
<10%	1 (3.3%)	1 (3.3%)	

BMI Body mass index, *SD* Standard deviation, *SGA* Small for gestational age

Table 2 Outcome variables of the study subjects at 4 wk and 12 wk ($n=60$)

Outcome measure [mean (SD)]	Gabapentin group ($n=25$)	Trihexyphenidyl group ($n=28$)	p value
Primary outcome			
DIS score			
Baseline	217.1 (59.5)	246.8 (36.2)	$p=0.09$
4 wk	196.0 (44.6)	220.4 (44.3)	(between group)
12 wk	174.8 (32.3)	188.7 (29.6)	
	p value <0.001 (within group)		
DSAP score			
Baseline	1.8 (2.2)	1.5 (0.6)	$p=0.49$
4 wk	1.1 (0.3)	1.1 (0.4)	(between group)
12 wk	1.0 (0.2)	1.0 (0.0)	
	p value $=0.007$ (within group)		
ICF-CY score			
Baseline	16.1 (5.5)	18.4 (5.3)	$p=0.25$
4 wk	14.4 (4.1)	15.6 (3.6)	(between group)
12 wk	12.5 (2.9)	13.6 (3.4)	
	p value <0.001 (within group)		
Outcome measure [n (%)]	Gabapentin group ($n=26$)	Trihexyphenidyl group ($n=28$)	p value
Secondary outcome			
Side effects			
Constipation	3 (11.5%)	4 (14.3%)	0.20
Sleep disruption	1 (3.8%)	0 (0%)	0.30
Agitation	1 (3.8%)	0 (0%)	0.30
Behavioral issues	2 (7.7%)	2 (7.7%)	1.0
Vomiting	1 (3.8%)	1 (3.8%)	1.0

DIS Dyskinesia Impairment Scale, *DSAP* Dystonia Severity Assessment Plan, *ICF-CY* International Classification of Functioning, Disability and Health–Children and Youth Version, *SD* Standard deviation

most common side effect observed was constipation in both the groups [3 (11.5%) in the gabapentin group and 4 (14.3%) in the trihexyphenidyl group]. Other side effects observed were sleep disturbance, behavioral issues, and vomiting (Table 2).

Discussion

The present study demonstrated that trihexyphenidyl with or without gabapentin is effective in decreasing the severity of dystonia in children with dyskinetic cerebral palsy at 4 wk and at 12 wk, and the efficacy was comparable between the two groups although there was a trend towards higher efficacy with no significant increase in adverse effect profile in those who received combination of trihexphenidyl and gabapentin. The adverse effect profile was also comparable with constipation being the most common side effect.

Gabapentin has demonstrated its efficacy in managing dystonia in children with dyskinetic cerebral palsy [9]. In the study by Liow et al. [9], 25 out of 69 children enrolled with dystonic cerebral palsy had shown significant decrease in severity of dystonia with significant improvement in sleep quality, pain, and in activities of daily living consistent with the present study results of combination of gabapentin and trihexyphenidyl. In a systematic review published in Cochrane database, the authors concluded that there was insufficient evidence regarding the efficacy of trihexyphenidyl in children with dyskinetic cerebral palsy in terms of change of dystonia, improvement in upper limb function and improvement in activities of daily living [17]. However, the present study demonstrated efficacy of trihexyphenidyl in decreasing the severity of dystonia whether administered alone or with gabapentin. The study findings of efficacy were consistent with previous studies [10, 18, 19].

The present study was performed among nonambulatory children with dyskinetic cerebral palsy, aged 3–9 y, with majority of children in the age group of 3–5 y. This is in contrast to other studies who had included both children, as well as, adults with dystonia of varying etiology [12, 20]. Hence, the study population in the present study is homogenous and the results of the present study could be extrapolated or generalized to children with dyskinetic cerebral palsy.

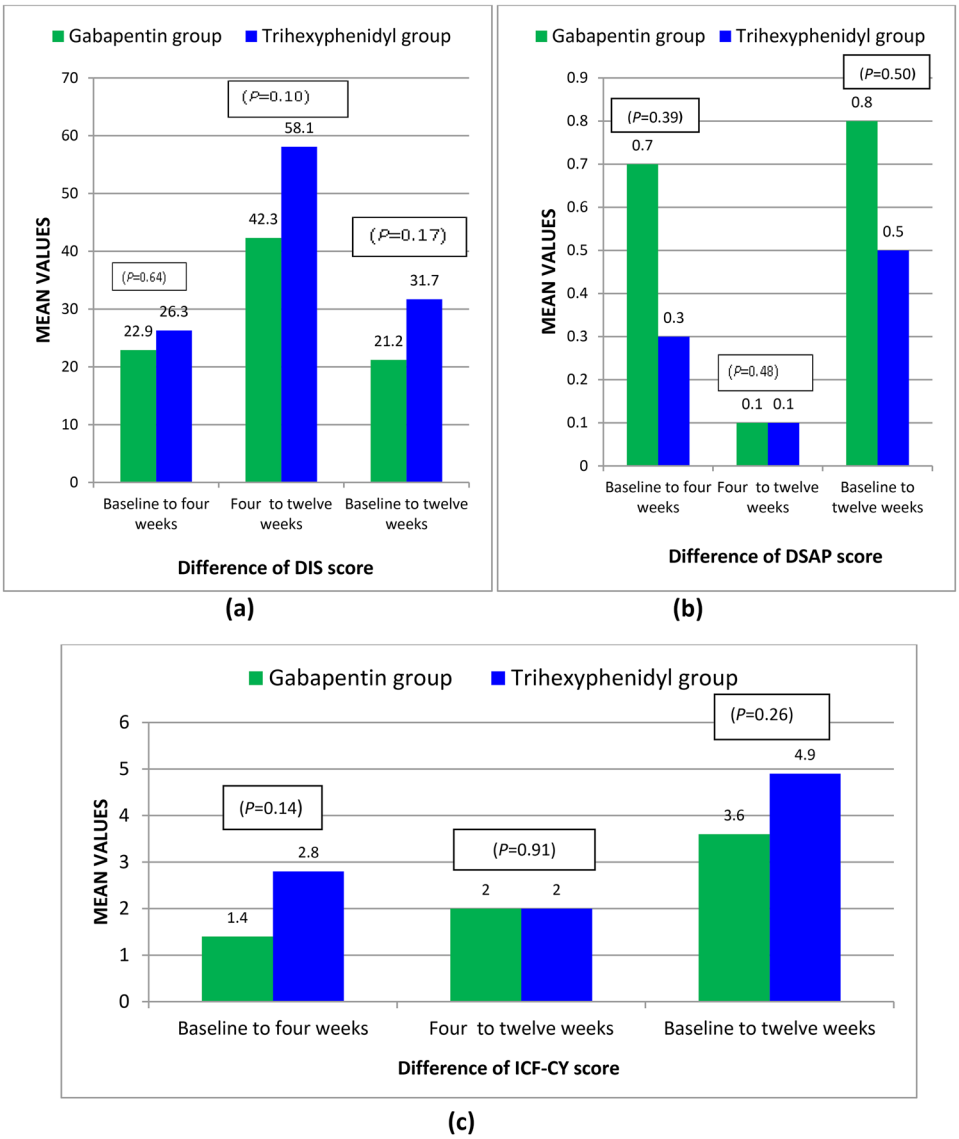

Fig. 2 Comparison of mean difference in (**a**) DIS score, (**b**) DSAP score, and (**c**) ICF-CY score among baseline to 4 wk, 4 wk to 12 wk, and baseline to 12 wk. *DIS* Dyskinesia Impairment Scale, *DSAP* Dystonia Severity Assessment Plan, *ICF-CY* International Classification of Functioning, Disability, and Health–Children and Youth Version

Various tools and scales had been used across the studies to assess the severity of dystonia [21]. Rice and Waugh [22], in their study, had used Barry–Albright Dystonia Scale, Quality of Upper Extremity Skills Test scale, Canadian Occupational Performance Measure, and Goal Attainment Scale. Other studies had also used Dystonia Movement Scale [20], Fahn–Marsden Scale [20], and Melbourne Assessment of Unilateral Upper Limb Function [23]. In the study by Liow et al. [9], the dystonia was measured in terms of DSAP score and the activities of daily living were measured in terms of ICF-CY score. The DSAP score alone lacks objectivity and does not measure both the components (dystonia and choreoathetosis), which often coexist in children with dyskinetic cerebral palsy. This depicts a wide variation in the scales used for assessment in severity of dystonia, thus restricting the comparability of the results of present study with the available literature. In a systematic review of the scales to measure dystonia and choreoathetosis in children with cerebral palsy, it was shown that the DIS scale was the only tool that evaluated both dystonia and choreoathetosis in children with cerebral palsy [21]. The present study also measured the activities of daily living by ICF-CY scale similar to Liow et al. [9] study. Hence, the present study which used DIS, DSAP, and ICF-CY scale to measure the severity of dystonia and functional ability had reliable and valid study tools.

In the present study, parent- or caregiver-reported side effects were recorded. Common side effects of gabapentin

are ataxia, dizziness, drowsiness, and nystagmus [9]. Considering them to be subjective symptoms, it might be difficult for children with dyskinetic CP to report such side effect. Common side effects with trihexyphenidyl include drowsiness, dizziness, constipation, and blurring of vision [22]. The present cohort also showed constipation as the most common side effect. However, children with CP have constipation in nearly 20%–30% cases, often it becomes difficult to attribute this adverse effect to the drug alone. Majority of side effects in the present study were mild and transient, and resolved when the dose was adjusted.

The strength of the present study was its robust study design and use of reliable and valid assessment tools for measuring the severity of dystonia. The previous studies on efficacy of gabapentin and trihexyphenidyl in children with dyskinetic cerebral palsy have limitation of small sample size ($n=31$ in Ben-Pazi [19], $n=16$ in Rice and Waugh [22], $n=23$ in Sanger et al. [23], and $n=31$ in Burke et al. [20]). The present study had certain limitations: the intervention was not masked; the study sample size was relatively small; convenient sample size was chosen; short follow-up period of 12 wk; parents/caregivers reported side effects because most of the present study subjects had developmental delay. In addition, there was a moderate follow-up loss, though, the follow-up losses were fairly acceptable considering the nature of illness, severity of dystonia, and enrollment of non-ambulatory children.

Conclusion

Trihexyphenidyl was an effective medication for reduction in severity of dystonia whether taken alone or in combination with gabapentin with no serious adverse effect. It is cheaper, and is an effective medication that can be used in children with dyskinetic CP. Addition of gabapentin might not be useful and may increase the cost of treatment. The comparable results of gabapentin and trihexyphenidyl in decreasing the severity of dystonia in the present study needs to interpreted in context of the limitation of small sample size and short follow-up of 12 wk. Hence, further studies with longer duration of study follow-up, larger sample size, and blinding are suggested.

Authors' Contributions JSK, SV, SD: Concept and design of the study; SK: Data collection under the supervision of JSK, SV, and SD; SK, JSK, SV, SD: Drafting the manuscript and review of literature; JSK, SV: Critical review of the manuscript for intellectual content and final approval of the version to be published; JSK: Clinician-in-charge, critical review of the manuscript for intellectual content, and final approval of the version to be published. All authors approve of the final version. JSK will act as the guarantor for this paper.

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Declarations

Conflict of Interest None.

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