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Efficacy of Ketogenic Diet, Modified Atkins Diet, and Low Glycemic Index Therapy Diet Among Children With Drug-Resistant Epilepsy
A Randomized Clinical Trial

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IMPORTANCE The ketogenic diet (KD) has been used successfully to treat children with drug-resistant epilepsy. Data assessing the efficacy of the modified Atkins diet (MAD) and low glycemic index therapy (LGIT) diet compared with the KD are scarce.

OBJECTIVE To determine whether the MAD and LGIT diet are noninferior to the KD among children with drug-resistant epilepsy.

DESIGN, SETTING, AND PARTICIPANTS One hundred seventy children aged between 1 and 15 years who had 4 or more seizures per month, had not responded to 2 or more antiseizure drugs, and had not been treated previously with the KD, MAD, or LGIT diet were enrolled between April 1, 2016, and August 20, 2017, at a tertiary care referral center in India.

EXPOSURES Children were randomly assigned to receive the KD, MAD, or LGIT diet as additions to ongoing therapy with antiseizure drugs.

MAIN OUTCOMES AND MEASURES Primary outcome was percentage change in seizure frequency after 24 weeks of dietary therapy in the MAD cohort compared with the KD cohort and in the LGIT diet cohort compared with the KD cohort. The trial was powered to assess noninferiority of the MAD and LGIT diet compared with the KD with a predefined, noninferiority margin of −15 percentage points. Intention-to-treat analysis was used.

RESULTS One hundred fifty-eight children completed the trial: KD (n = 52), MAD (n = 52), and LGIT diet (n = 54). Intention-to-treat analysis showed that, after 24 weeks of intervention, the median (interquartile range [IQR]) change in seizure frequency (KD: −66%; IQR, −85% to −38%; MAD: −45%; IQR, −91% to −7%; and LGIT diet: −54%; IQR, −92% to −19%) was similar among the 3 arms (P = .39). The median difference, per intention-to-treat analysis, in seizure reduction between the KD and MAD arms was −21 percentage points (95% CI, −29 to −3 percentage points) and between the KD and LGIT arms was −12 percentage points (95% CI, −21 to 7 percentage points), with both breaching the noninferiority margin of −15 percentage points. Treatment-related adverse events were similar between the KD (31 of 55 [56.4%]) and MAD (33 of 58 [56.9%]) arms but were significantly less in the LGIT diet arm (19 of 57 [33.3%]).

CONCLUSIONS AND RELEVANCE Neither the MAD nor the LGIT diet met the noninferiority criteria. However, the results of this study for the LGIT diet showed a balance between seizure reduction and relatively fewer adverse events compared with the KD and MAD. These potential benefits suggest that the risk-benefit decision with regard to the 3 diet interventions needs to be individualized.

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Supplemental content

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The International League Against Epilepsy defines drug-resistant epilepsy as "failure of adequate trials of 2 tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[1(p28)] Drug-resistant epilepsy responds poorly to pharmacologic management and frequently requires intervention via other modalities, including surgery, vagus nerve stimulation, and dietary therapy. However, standards of care for drug-resistant epilepsy management have not been well defined. In addition, the coexistent motor, language, and memory deficits may render some patients unsuitable for curative epilepsy surgery.

Dietary therapies have been reported to be effective and safe, and can be administered synergistically with other treatment options.[2] The classic ketogenic diet (KD) is a high-fat, adequate protein, low-carbohydrate diet. The KD has been shown to be effective in randomized clinical trials, and benefits have been reported across various retrospective and prospective observational studies.[3,4] However, some families and patients find adherence to the KD difficult, and it has an established adverse effect profile.[5] Therefore, other diets, such as the modified Atkins diet (MAD) and low glycemic index therapy (LGIT) diet, have been investigated.[6,7] Results from various studies have indicated that the MAD is as effective as the KD for drug-resistant epilepsy management, but the evidence is limited.[6,8]

In 2018, the International Ketogenic Consensus Guideline stated that the diet should be "individualized based on the family and child situation, rather than perceived efficacy,"[2(p181)] and that there was reasonable class III evidence to support its use. However, a Cochrane review, which included 7 randomized clinical trials assessing the efficacy of the KD in drug-resistant epilepsy, concluded that other more palatable diets "may have a similar effect on seizure control as classical KD but this assumption requires more investigation."[9(p2)] This randomized trial was undertaken to assess whether addition of either the MAD or LGIT diet to ongoing antiseizure drug therapy was noninferior to the KD with regard to seizure reduction at 24 weeks among children aged 1 to 15 years with drug-resistant epilepsy.

Key Points

Question Are the modified Atkins diet and low glycemic index therapy diet noninferior to the ketogenic diet with regard to seizure reduction at 24 weeks among children aged 1 to 15 years with drug-resistant epilepsy?

Findings In this randomized clinical trial of 158 children with drug-resistant epilepsy, the median reduction in seizure burden was similar between the ketogenic diet, modified Atkins diet, and low glycemic index therapy diet, although the noninferiority of the modified Atkins diet and low glycemic index therapy diet was not proven. The adverse events were least with the low glycemic index therapy diet, and 1 adverse event may be avoided for every 4.3 children treated with the low glycemic index therapy diet compared with a ketogenic diet.

Meaning The findings of this trial indicate that guidelines should support the use of the ketogenic, modified Atkins, and low glycemic index therapy diets for management of drug-resistant epilepsy; each dietary therapy should be discussed with caregivers in terms of the benefit in reducing seizure burden and the risk of adverse events.

Methods

Study Design

This noninferiority randomized clinical trial was conducted at All India Institute of Medical Sciences, New Delhi, India, between April 1, 2016, and August 20, 2017. The trial protocol was approved by the All India Institute of Medical Sciences Institutional Ethics Committee. Written informed consent was obtained from caregivers of participating children. Children between age 1 and 15 years with drug-resistant epilepsy presenting to the pediatric neurology outpatient clinic were considered for inclusion. Drug-resistant epilepsy was defined as seizure frequency of 4 or more seizures per month and treatment failure of 2 or more prescribed antiseizure drugs in maximum tolerated doses.[8] For West syndrome, drug-resistant epilepsy was defined as more than 4 spasm clusters per month despite treatment with 2 or more antiseizure drugs and either adrenocorticotropic hormone or vigabatrin. Exclusion criteria included surgically remediable cause of drug-resistant epilepsy, inborn errors of metabolism, and known chronic systemic disorder. Children treated with the KD, MAD, or LGIT diet in the past were also excluded. A detailed study protocol is presented in Supplement 1. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for equivalence and noninferiority trials.

Enrolled children underwent a 4-week run-in period. During the run-in period, baseline investigations were undertaken, and syrups were reformulated to tablets that were then ground and either sprinkled over food or mixed with water to facilitate ingestion by young children. Parents were advised to maintain a daily seizure log. Demographic data and medical history were chronicled. Changes to the child's diet were not advised during the run-in period. No changes in antiseizure drug dosages were made during the run-in period or during the 24-week intervention phase. Following the run-in period, children were randomly assigned to 1 of 3 interventions: KD, MAD, or LGIT diet. Computer-generated, random, permuted blocks stratified by age (1-5, >5-10, and >10-15 years) were used to generate a randomization list. Sealed and serially numbered opaque envelopes were used for allocation concealment. The dietitian and one of us (V.S.) directly involved with diet prescription could not be blinded to treatment. Participants, other study personnel, and those who analyzed the data were blinded.

Tailored diet prescriptions were developed for each patient based on food preferences and staple diet of the family. A gradual-initiation, nonfasting protocol was used for introducing the KD, which involved administering 75% of total daily caloric requirement on the day of the KD initiation and gradually increasing it to full calorie level over 2 to 4 weeks, as tolerated by the child.[10] Classic KD was started at a 1:1 ratio (lipids: nonlipids). Lipid content was gradually increased to 2:1, 2.5:1,

3:1, and 4:1 every 48 hours while urinary ketosis and tolerance were monitored. The MAD group patients followed the Johns Hopkins protocol.[11] Initiation of the LGIT diet involved restricting high glycemic index (>55) food items and limiting carbohydrates to approximately 10% of daily calories. All families were educated about the diet and provided with a detailed menu plan. The MAD and LGIT diets were started in the outpatient setting, while children were admitted for initiating the KD. For the MAD and LGIT diets, a list of food replacement options was also provided. Diets were supplemented with vitamins and minerals. Each patient's caregiver maintained a daily log of meals, seizure frequency, urinary ketones, and dietary intolerance symptoms. Patients were followed up as outpatients at 4, 12, and 24 weeks after intervention initiation. Twice-weekly telephone calls were made to ensure dietary adherence, monitor for adverse events, and address any caregivers' concerns.

Seizure frequency was assessed from the daily log (eAppendix 1 in Supplement 1). Mean and median number of seizures at a time point were calculated from seizure counts in the preceding 28 days and expressed as percentage change from baseline. Diet tolerance and adverse events were evaluated in interviews with caregivers. Evaluation details performed at each hospital visit are reported in eAppendix 2 and eAppendix 3 in Supplement 1. Serum was isolated within 2 hours of blood sample collection at baseline and at 24 weeks and stored at −80 °C. Levels of copper, selenium, and zinc in all serum samples were measured in a single batch.

The primary outcome was percentage change in seizure frequency from baseline at 24 weeks of therapy. The primary outcome measure was assessed in a blinded manner; daily logs were coded with unique identification numbers and assessed by an individual (R.M.P.) blinded to intervention. Secondary outcomes, which were analyzed 24 weeks after intervention initiation, included proportion of patients with greater than 50% seizure reduction from baseline, proportion of patients showing improvement in social quotient on the Vineland Social Maturity Scale (scores of 85-110 considered normal; higher scores, higher levels of function),[12] changes in T score on the Child Behavior Checklist (normal score, <60; borderline, 60-63; and clinically impaired, >63),[13] and changes in serum levels of copper, selenium, and zinc. Urinary ketone levels, recorded by parents as numeric values of 0 to 4 on urinary dipstick, were used to assess the level of ketosis. The median urinary ketone level over the past 4 weeks was associated with mean and median percentage decline in seizure frequency. The rate of seizure decline was calculated for each week using the formula $100 \times (y - x)/x$, where y indicates the mean or median number of daily seizures in the preceding week and x indicates the mean or median baseline number of daily seizures during run-in. Adherence to the prescribed diet was assessed from daily logs, which included the number of meals given and portions left uneaten. The proportion of prescribed diet that was consumed was computed every 4 weeks. A minimum 80% value was required for inclusion in the final analysis.

Sample size calculations were based on the study by Kim et al,[8] who reported that, after 6 months of the KD and MAD, the KD group had 33.8% and the MAD group had 44.6% of baseline seizure frequency. Guided by this 10.8-percentage point difference, the predetermined noninferiority margin was set at a 15-percentage point difference between the treatment arms. Testing for this margin with 80% power at an α level of .05, assuming an SD of 30% for outcomes after 24 weeks of treatment, requires 50 patients per group. Assuming a 10% dropout rate, the required sample size was 165.

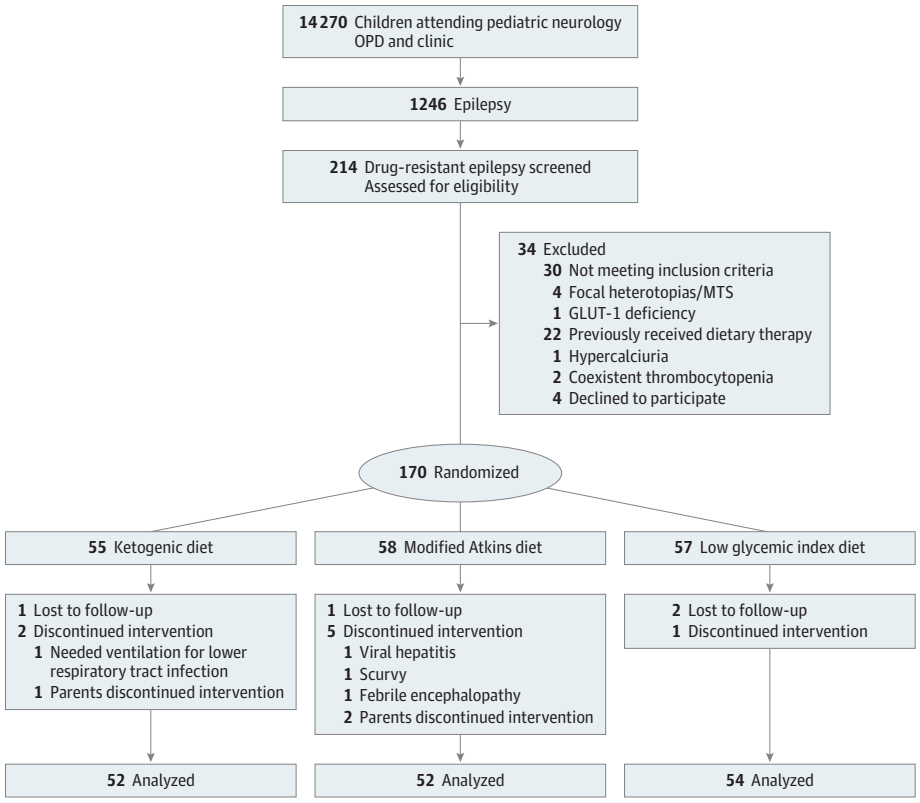
Statistical Analysis

The primary outcome of percentage seizure reduction at 24 weeks was analyzed by computing the effect size (mean or median difference) and determining its 95% CI. The MAD and LGIT diet were considered noninferior to the KD when the lower limit of the 95% CI of effect size was greater than −15 percentage points. Results were checked for distribution normality, and mean or median values were used as appropriate. The intention-to-treat (ITT) population included all patients who fulfilled eligibility criteria and were assigned an intervention. With ITT analysis, for patients who could not be contacted at 24 weeks of intervention, the number of mean or median daily seizures over the last 4 weeks of last contact with the patient was used for primary end-point calculation. The per-protocol population was defined to exclude randomly assigned patients who did not receive the full allocated treatment up to 24 weeks. For secondary outcomes, the intervention groups were compared using the χ^2 test or Fisher exact test for categorical variables and standard unpaired, 2-tailed t test or Wilcoxon-Mann-Whitney test for continuous variables. P values <.05 were considered statistically significant. Adverse events were summarized per treatment group and compared as proportions with a χ^2 test. Statistical analysis was conducted using R, version 3.5.1 (R Foundation).

Results

Of 214 children with drug-resistant epilepsy who were screened, 170 were randomly assigned to receive the KD (n = 55), MAD (n = 58), or LGIT diet (n = 57) and were included in ITT analysis (**Figure 1**). Twelve patients were withdrawn, and the remaining 158 patients (KD, 52; MAD, 52; and LGIT diet, 54) were included in per-protocol analyses. Their baseline characteristics are shown in **Table 1**. The 3 groups were similar for median baseline daily seizures (KD, 9; MAD, 8.5; and LGIT diet, 9; P = .99), proportion of patients with structural epilepsy (KD, 33; MAD, 41; and LGIT diet, 41; P = .33), and proportion of patients requiring 4 or more antiseizure drugs (KD, 20; MAD, 31; and LGIT diet, 31; P = .16). Baseline clinical examination was normal in 9 patients (16.4%) receiving a KD compared with 2 children (3.4%) receiving an MAD and 2 children (3.5%) receiving an LGIT diet (P = .01). Details of drug-resistant epilepsy causes and antiseizure drug use are given in eAppendix 4 and eAppendix 5 in Supplement 1, respectively. Mean (SD) dietary adherence was significantly better with the LGIT diet (94.3% [2.6%]) compared with the KD (91.4% [2%]) or MAD (90.6% [2.4%]). All patients had greater than 80% adherence throughout the study (eAppendix 6 in Supplement 1).

Figure 1. Flow of Patients



GLUT-1 indicates glucose transporter type 1; MTS, mesial temporal sclerosis; and OPD, outpatient department.

Outcomes

Twenty-four weeks after intervention, the median daily seizure frequency was 3.3 (interquartile range [IQR], 1.2-14) with the KD, 4 (IQR, 0.5-10) with the MAD, and 4 (IQR, 0.4-11) with the LGIT diet (**Table 2**). After 24 weeks of intervention, the median change in seizure frequency was similar among the 3 arms in both the ITT (KD: −66%; IQR, −85% to −38%; MAD: −45%; IQR, −91% to −7%; and LGIT diet: −54%; IQR, −92% to −19%; $P = .39$) and per-protocol populations ($P = .57$) (Table 2). The median difference in change in seizure frequency between the KD and MAD was −21 percentage points (95% CI, −29 to −3 percentage points) in ITT and −10 percentage points (95% CI, −26 to 5 percentage points) in per-protocol analysis. The median difference in change in seizure burden between the KD and LGIT diet was −12 percentage points (95% CI, −21 to 7 percentage points) in ITT analysis and −7 percentage points (95% CI, −17 to 10 percentage points) in per-protocol analysis (**Table 3**).

Proportions of patients with greater than 50% seizure reduction at 24 weeks were comparable across the 3 arms: KD, 35 of 52 (67.3%); MAD, 27 of 52 (51.9%); and LGIT diet, 32 of 54 (59.3%). The odds ratio (OR) between KD and MAD was 0.16 (95% CI, 0.86-4.22); between KD and LGIT diet, 1.42 (95% CI, 0.64-3.13); and between MAD and LGIT diet, 0.74 (95% CI, 0.34-1.60) (**Figure 2**). The change in seizure frequency was not associated with urinary ketone levels (eAppendix 7 in Supplement 1). There was rapid seizure reduction over the initial 4 weeks of the study with the KD and MAD, while the decrease was gradual over 10 to 12 weeks with the LGIT diet (eAppendix 8 in Supplement 1). Post hoc subgroup analysis by age (1-5, >5-10, and >10-15 years) was performed for percentage reduction in seizures and proportion of children with greater than 50% seizure reduction. All subgroups were comparable for reduction in seizure burden between the 3 interventions (eAppendix 9 in Supplement 1). At 24 weeks after the intervention, the mean social quotient improved in 83 children (54.2%) (eAppendix 10A in Supplement 1). The improvement was most notable with the KD (34 of 52 [65.4%]) followed by the LGIT diet (29 of 54 [53.7%]) and MAD (20 of 52 [38.5%]) ($P = .02$). After 24 weeks, the change in mean total T score was nonsignificant and similar for the 3 interventions (eAppendix 10B in Supplement 1).

Adverse Events

Adverse events noted among 83 of 170 patients (48.8%) were comparable between the KD (31 of 55 [56.4%]) and MAD (33 of 58 [56.9%]) but were significantly less with the LGIT diet (19 of 57 [33.3%]) (eAppendix 11 in Supplement 1). The commonest clinical adverse event was vomiting, which was noted in 28 patients (50.9%) receiving the KD, 26 patients (44.8%) receiving the MAD, and 18 patients (31.6%) receiving the LGIT diet (eAppendix 12 in Supplement 1). Investigation-based adverse events were reported in 59 patients (34.7%) (KD, 21 [38.2%]; MAD, 24 [41.4%]; and LGIT diet, 14 [24.6%]; $P = .14$). Two patients receiving the LGIT diet and 1 patient receiving the KD were noted to have thrombocytopenia during evaluation at 24 weeks. Both patients were also receiving sodium val-

Table 1. Demographic and Clinical Characteristics at Baseline

Variable	No. (%)		
	KD (n = 55)	MAD (n = 58)	LGIT diet (n = 57)
Age, mo			
Mean (SD)	62.2 (38.1)	62.3 (40.2)	63.8 (37.0)
Median (IQR)	52 (31-89)	51 (31-79)	54 (32.5-82)
Male sex	37 (67.3)	49 (84.5)	42 (73.7)
Diagnosis			
Structural epilepsy	33 (60.0)	41 (70.7)	41 (71.9)
Genetic epilepsy	16 (29.1)	12 (20.7)	14 (24.6)
Genetic epilepsy with structural abnormality	6 (10.9)	5 (8.6)	2 (3.5)
Age at first seizure, mo			
Mean (SD)	6.74 (11.46)	9.5 (21.03)	9.19 (18.92)
Median (IQR)	2 (0-8)	2 (0-8)	0 (0-8.5)
Type of seizure at enrollment			
Spasms	33 (60.0)	41 (70.7)	38 (66.7)
Myoclonic (other than spasms)	26 (47.2)	23 (39.7)	21 (36.8)
Tonic	31 (56.4)	33 (56.9)	39 (68.4)
GTCS	3 (5.5)	3 (5.2)	1 (1.8)
Focal	10 (18.2)	11 (18.9)	17 (29.8)
Absence	13 (23.6)	14 (24.1)	13 (22.8)
Multifocal	31 (56.3)	35 (60.3)	41 (71.9)
Antiepileptic drugs			
2-3	35 (63.6)	27 (46.6)	26 (45.6)
≥4	20 (36.4)	31 (53.4)	31 (54.4)
Median (IQR)	3 (3-4)	4 (3-4)	4 (3-4)
Developmental delay			
GM	41 (74.5)	46 (79.3)	43 (75.4)
FM	44 (80.0)	49 (89.1)	49 (85.9)
Language	50 (90.9)	50 (86.2)	52 (91.2)
Sociocognitive	51 (92.7)	52 (89.7)	54 (94.7)
Clinical examination			
Normal	9 (16.4)	2 (3.4)	2 (3.5)
Pyramidal signs	36 (65.5)	43 (74.1)	45 (78.9)
Extrapyramidal signs	10 (18.2)	13 (22.4)	10 (17.5)
Cranial nerve palsy	13 (23.6)	17 (29.3)	12 (21.1)
Baseline daily seizures			
Mean (SD)	20.2 (25.1)	20 (29.3)	20.1 (38.7)
Median (IQR)	9 (6-19)	8.5 (5-20)	9 (4.5-19.5)

Abbreviations: FM, fine motor; GM, gross motor; GTCS, generalized tonic clonic seizures; IQR, interquartile range; KD, ketogenic diet; LGIT, low glycemic index therapy; MAD, modified Atkins diet.

proate. Ten patients, all receiving concomitant zonisamide therapy, were found to have hypercalciuria at 24 weeks. In addition, 2 patients receiving the MAD developed scurvy, detected at 24 weeks in one child and at 12 weeks in the other, who was withdrawn from the study. Both of these children presented with extreme irritability and incessant crying. Owing to unavailability of resources for serum vitamin C assay, the diagnosis of scurvy was based on characteristic radiologic findings and clinical response to vitamin C therapy.

Three patients developed a prolonged QTc interval. For 2 of these children, the prolonged interval was detected at 24 weeks' assessment, while for the third patient, the observation was made following hospital admission for respiratory tract infection, which necessitated diet discontinuation. The baseline QTc intervals for these 3 patients were 0.30, 0.31, and 0.36 seconds; following intervention, the intervals were 0.51, 0.54, and 0.52 seconds. Serum samples were additionally tested for zinc, selenium, and copper levels; preintervention and postintervention comparisons are provided in eAppendix 13 in Supplement 1. Children receiving the KD and MAD had significant decreases in their serum selenium levels, although the levels remained within the reference range. Preintervention/postintervention and intergroup anthropometric comparisons did not show any statistically significant differences (eAppendix 14 in Supplement 1).

Discussion

In this randomized clinical trial involving children with drug-resistant epilepsy, the MAD and LGIT diets were not noninferior to the KD with respect to seizure reduction at 24 weeks

Table 2. Seizure Frequency

Variable	No. (%)		
	KD (n = 52)	MAD (n = 52)	LGIT diet (n = 54)
Seizure frequency at 24 wk			
Median (IQR)	3.3 (1.2 to 14)	4 (0.5-10)	4 (0.4-11)
Mean (SD)	9.4 (14)	11 (19)	8.7 (12)
Achieved specific cutoff points after 24 wk of intervention			
Complete resolution	6 (11.5)	8 (15.4)	9 (16.7)
>90% Reduction	6 (11.5)	6 (11.5)	8 (14.8)
>50% Reduction	23 (44.2)	13 (25.0)	15 (27.8)
≤50% Reduction	13 (25.0)	14 (26.9)	15 (27.8)
Increase in seizure frequency at 24 wk	4 (7.7)	11 (21.2)	7 (12.9)
% Change in seizure frequency			
Per-protocol analysis			
Median (IQR)	−67 (−87 to −37)	−57 (−92 to −5.5)	−60 (−92 to −24)
Mean (SD)	−60 (33)	−48 (46)	−55 (40)
Intention-to-treat analysis			
Median (IQR)	−66 (−85 to −38)	−45 (−91 to −7)	−54 (−92 to −19)
Mean (SD)	−60 (32)	−46 (45)	−52 (41)

Abbreviations: IQR, interquartile range; KD, ketogenic diet; LGIT, low glycemic index therapy; MAD, modified Atkins diet.

Table 3. Difference in Seizure Reduction With the 3 Treatment Strategies[a,b]

Comparison between interventions	Per-protocol analysis		Intention-to-treat analysis	
	Median (95% CI)	Mean (95% CI)	Median (95% CI)	Mean (95% CI)
KD-MAD	−10 (−26 to 5)	−12 (−28 to 3.2)	−21 (−29 to 3)	−14 (−28 to 0.61)
KD-LGIT	−7 (−17 to 10)	−5.7 (−20 to 8.4)	−12 (−21 to 7)	−8.1 (−22 to 5.5)

Abbreviations: KD, ketogenic diet; LGIT, low glycemic index therapy; MAD, modified Atkins diet.

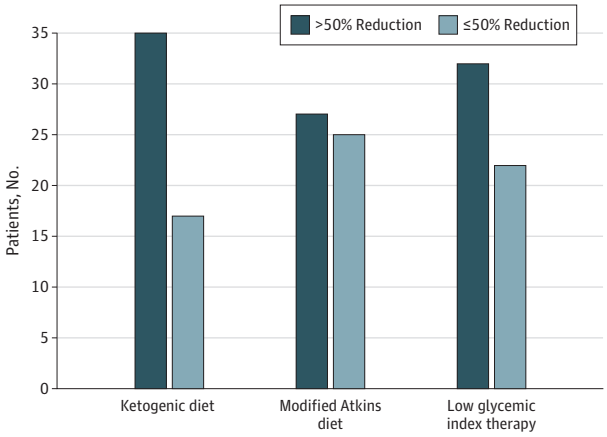
[a] In both the per-protocol and intention-to-treat analyses, the lower limit of the 95% CI of the median difference and mean difference in seizure reduction between MAD and KD, as well as between LGIT diet and KD, breached the noninferiority margin of −15 percentage points.

[b] Data are given as percentage points.

after diet initiation. In ITT analysis, median seizure reductions were 66% for the KD, 45% for the MAD, and 54% for the LGIT diet. The median difference in seizure frequency between the MAD and KD (−21 percentage points; 95% CI, −29 to 3 percentage points) and between the LGIT diet and KD (−12 percentage points; 95% CI, −21 to 7 percentage points) both breached the noninferiority limit of −15 percentage points. Hence, the trial failed to demonstrate that the LGIT diet or MAD is noninferior to the KD in children with drug-resistant epilepsy. However, the proportions of patients with greater than 50% seizure reduction at 24 weeks were similar across the 3 diets.

Our results should be interpreted in 5 main aspects that go beyond the noninferiority domain. First, this trial addressed the treatment strategies in terms of seizure reduction at a given time, expressed as percentage change with respect to baseline seizures. Most previous literature expresses the outcomes as proportions of patients with greater than 50% seizure reduction.[3,7,14] Our approach gives a more absolute seizure reduction with each strategy. The proportion of children with greater than 50% seizure reduction after 24 weeks of the interventions was 67.3% with the KD, 51.9% with the MAD, and 59.3% with the LGIT diet. To put things into perspective, the median number of daily seizures at the beginning of the trial was nearly 9 per day per group. After 24 weeks of intervention, the per-day seizure burden had decreased to 3 with the KD and 4 with both the MAD and LGIT diet. For the subsequent analysis, a noninferiority margin of −15 percentage points implied a difference of nearly 1 to 2 seizures per day for a child having nearly 9 seizures per day at the start of the study. Both the MAD and LGIT diet were not noninferior to the KD as the lower limit of the 95% CI of effect size crossed the margin of −15 percentage points. The seizure reduction noted with the KD and LGIT diet is comparable with published reports; however, the present study demonstrated lesser reduction of seizures with the MAD.[3,7,8,14] This difference can be partially accounted for by the fact that a diet was started late in the clinical course in our study, probably rendering the patients more drug resistant. The differences in seizure reduction with 3 interventions can be partly accounted for by the type of patients in each arm. Nine patients in the KD group had a normal neurologic examination compared with 2 each in the MAD and LGIT diet groups (P = .01). In addition, 20 patients in the KD group required 4 or more antiseizure drugs compared with 31 patients in both of the other groups. This difference may suggest that the patients in the MAD and LGIT diet groups had more refractory causes of seizures than those in the KD group.

Figure 2. Numbers of Patients With Greater Than 50% Reduction vs 5% or Less Reduction in Daily Seizure Frequency 24 Weeks After Intervention



Proportions of patients with greater than 50% reduction in seizure frequency with ketogenic diet, modified Atkins diet, and low glycemic index therapy diet were comparable between ketogenic diet and modified Atkins diet (odds ratio [OR], 1.42; 95% CI, 0.64-3.13), between KD and MAD (OR, 0.16; 95% CI, 0.86-4.22), and between MAD and LGIT diet (OR, 0.74; 95% CI, 0.34-1.60).

Second, the daily seizure log allowed for assessment of the rate of decline in seizures with each intervention. Administration of the KD was associated with an approximate 50% decline in seizure frequency in the first 4 weeks, and a further 10% reduction in seizure frequency was noted over the subsequent 20 weeks. Seizure reduction with the MAD was also rapid, with an approximate 40% decrease in the number of seizures by 4 weeks; seizure frequency plateaued between 40% and 50% over the next 20 weeks. With the LGIT diet, however, the seizure decline was gradual, with 50% reduction attained between 10 and 12 weeks. This understanding is necessary before a patient is considered to be a nonresponder and also to give a realistic perspective to caregivers. The rate of decline was considerably more rapid with the lipid-rich KD and MAD compared with the LGIT diet, which is primarily associated with restriction of carbohydrates to low glycemic index foods. While the KD and MAD are associated with ketosis, the exact role of ketone bodies in seizure control is unclear. Some animal studies have suggested that acetoacetate might reduce glutamate release at hippocampal synapses, while other studies have failed to show any association between ketone bodies and synaptic transmission.[15-17] Studies have suggested an association between seizure control and serum levels of β-hydroxybutyrate.[18] We measured urinary ketone levels and failed to show any association with change in seizure frequency, although serum ketone level estimation might have been more appropriate.

Third, this study assessed the effect of dietary strategies on drug-resistant epilepsy as a complete group and not etiologic or syndromic subcategories, which increases the generalizability of results and captures the complexity of clinical practice. Most enrolled children had spasms or generalized or multifocal seizures. The children with focal epilepsy were underrepresented because most children with lesional focal epilepsy were candidates for epilepsy surgery and, hence, were excluded from the study.

Fourth, this study demonstrated an improvement in social quotient with all 3 interventions; this improvement was statistically significantly better with the KD compared with the MAD, while the response was comparable between the KD and LGIT diet, as well as between the MAD and LGIT diet. In a randomized clinical trial assessing the cognitive and behavioral effect of the KD in children and adolescents with drug-resistant epilepsy, participants receiving the KD had lower levels of anxious and mood-disturbed behavior.[19] To our knowledge, there are no comparable studies for MAD and LGIT diet interventions. Although the delineation of mechanisms explaining the improvement in social quotient is beyond the scope of this study, the improvement in social quotient can be partly attributed to the reduced seizure burden with each of the interventions. The change in the T score was not significant in our trial, and it is possible that the 24-week interval of observation was too brief to observe a change in this measure.

Fifth, all interventions were associated with adverse events. The KD and MAD were associated with poor dietary tolerance with vomiting, difficulties with palatability, diarrhea, and constipation.[3,6,14] In addition, lipid profiles in these patients were altered owing to prolonged ingestion of high-lipid diets. Nephrocalcinosis and increased urinary calcium excretion in patients receiving the KD and MAD can be related to fat malabsorption and chronic acidosis, partly attributable to concurrent zonisamide therapy. In contrast, the LGIT diet was associated with minimal adverse events, none of which was life threatening. These reduced adverse events associated with the LGIT diet suggest a trade-off between the efficacy and harmful effects of the intervention. Although the risk-benefit trade-off was not considered at the beginning of the intervention, our results suggest that the LGIT diet led to lesser seizure reduction than the KD (average difference of approximately 1 seizure per day). However, absolute risk reduction of adverse events was approximately 23% among study participants treated with the LGIT diet compared with children receiving the KD. Hence, 1 adverse event can be avoided for every 4.3 children treated with the LGIT diet compared with the KD.

Strengths and Limitations

The strengths of our study are its embedment within the clinical practice setting with the inclusion of all children with drug-resistant epilepsy, irrespective of the underlying cause, allowing for generalizability of its results. To our knowledge, this is the first trial to analyze the 3 primary dietary options for drug-resistant epilepsy—KD, MAD, and LGIT diet—for seizure reduction, adverse events, and cognitive effects. The dropout rate of less than 10% in each of the 3 arms and dietary adherence greater than 80% further strengthen the results.

The trial also has limitations. The scientific weight of the study would have been better if the SD in each cohort was smaller. However, this was a close representation of a clinical setting with different drug-resistant forms of epilepsy responding to different degrees and at different rates. The study would also have been improved by blinding all involved individuals. However, it was impossible to blind dietitians, as the diet pre-

scriptions required close parental interaction. The use of daily logs maintained by caregivers would have missed some seizures, including nocturnal seizures, and runs the risk of introducing subjective errors. In addition, a selection bias cannot be ruled out because this was a single-center study.

Conclusions

The data from this study show that all 3 dietary regimens—KD, MAD, and LGIT diet—significantly reduce the seizure burden in children with drug-resistant epilepsy. This information supports the use of all 3 dietary therapies. Still, the results are inconclusive with regard to noninferiority of the MAD and LGIT diet. The risk profiling illustrates that the LGIT diet is associated with the least number of and least severe adverse events, while the other 2 diets are more likely to be associated with serious and life-threatening events. It appears that each dietary intervention should be assessed in terms of the benefit in reducing seizure burden and the risk of adding adverse events before starting the KD, MAD, or LGIT diet in children.

ARTICLE INFORMATION

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Brain Stimulation and Constraint Induced Movement Therapy in Children With Unilateral Cerebral Palsy: A Randomized Controlled Trial

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Abstract

Background. There is a crucial need to devise optimum rehabilitation programs for children with cerebral palsy (CP). *Objective.* This study aimed to assess the feasibility, safety, and efficacy of combining 6-Hz primed, low-frequency, repetitive transcranial magnetic stimulation (rTMS) with modified constraint-induced movement therapy (mCIMT) in improving upper limb function in children with unilateral CP. *Methods.* Children aged 5 to 18 years with unilateral CP were randomized (23 in each arm) to receive 10 sessions of mCIMT with real rTMS (intervention arm) or mCIMT with sham rTMS (control arm), on alternate weekdays over 4 weeks. The primary outcome was the difference in mean change in Quality of Upper Extremity Skills Test (QUEST) scores. Secondary outcomes were changes in QUEST domain scores, speed and strength measures, CP quality of life (CP-QOL) scale scores, and safety of rTMS. *Results.* All 46 children completed the trial except one. At 4 weeks, the mean change in total QUEST scores was significantly higher in the intervention arm as compared to the control arm (11.66 $\pm$ 6.97 vs 6.56 $\pm$ 4.3, $d = 5.1$, 95% CI 1.7-8.5, $P = .004$). Change in "weight bearing" and "protective extension" domain score was significantly higher for children in the intervention arm. These improvements were sustained at 12 weeks ($P = .028$). CP-QOL scores improved at 12 weeks. No serious adverse events were seen. *Conclusion.* A 6-Hz primed rTMS combined with mCIMT is safe, feasible, and superior to mCIMT alone in improving the upper limb function of children with unilateral CP.
Trial Registration: ClinicalTrials.gov Identifier: NCT03792789.

Keywords

transcranial magnetic stimulation, unilateral cerebral palsy, constraint, children, efficacy, safety

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Abbreviations

CP, cerebral palsy; rTMS, repetitive transcranial magnetic stimulation; mCIMT, modified constraint-induced movement therapy; QUEST, Quality of Upper Extremity Skills Test; CP-QOL scale, cerebral palsy quality of life scale.

Introduction

Cerebral palsy (CP) is the most common motor disability in childhood and unilateral CP accounts for about one-third of the cases.[1] Constraint-induced movement therapy (CIMT) has been shown to result in an improvement in bimanual performance and unimanual capacity in children with unilateral CP, however, the quality of evidence is low.[2,3] Moreover, the effect sizes are modest, with a mean difference (MD) of 5.44 Assisting Hand Assessment (AHA) units and MD ranging from 5.95 to 12.54 across various domains of the Quality of Upper Extremity Skills Test (QUEST).[2] Given these modest effect sizes, there is a need to explore additional neurorehabilitation measures like neuromodulation, in this population. Various modifications of CIMT have been used, with a lesser duration of daily training, lasting for 30 minutes to 3 hours, and using a sling/glove for restraining.[4-7] Choudhary et al[4] demonstrated a significant improvement in upper limb function, with modified CIMT (mCIMT; 2 hours/day for 10 days, over 4 weeks), which was sustained at 12 weeks follow-up. In addition, an increase in blood oxygen level-dependent cluster activation was recorded on functional magnetic resonance imaging (fMRI) post mCIMT.[8] A subsequent clinical trial at our center demonstrated an additive effect of virtual reality therapy (VRT) when given along with mCIMT.

Transcranial magnetic stimulation (TMS) which is based on the principle of electromagnetic induction is an upcoming non-invasive modality with a variety of diagnostic and therapeutic applications.[9] For intervention, TMS is used in a repetitive manner, which can modulate the excitability of the brain, thereby influencing motor function. Repetitive TMS (rTMS) has been shown to be beneficial in adults with hemiparesis resulting from stroke, however, the corresponding data in the pediatric population is limited.

In adults with chronic stroke, the non-lesioned primary motor cortex has been demonstrated to exert an inhibitory influence, over the lesioned hemisphere.[10] This inter-hemispheric inhibition (IHI) is exerted possibly through transcallosal pathways and could adversely influence motor recovery. Broadly, 2 types of neuro-modulation strategies could result in a better motor function in such cases: (1) excitatory rTMS to promote the success of ipsilesional or (2) inhibitory rTMS to the contra-lesional upper motor neuron systems.[11] Hence, a pathologically overactive contra-lesional hemisphere is a potential target for therapeutic neuro-modulation.[12,13] However, it is prudent to note that these interhemispheric motor interactions are altered in children with perinatal stroke. Effects can be seen in both directions and may include interhemispheric facilitation rather than the normal inhibitory relationship.[14] Therefore, further work is required to develop IHI models specific to perinatal stroke, wherein adult stroke models may not be applicable.

The depression of the motor cortex by 1 Hz rTMS can be enhanced by priming with 6 Hz rTMS, as demonstrated by Iyer et al.[15] The rationale for priming is based on "metaplasticity," which refers to the phenomenon, wherein previous cellular activity leads to a change in the ability to induce subsequent synaptic plasticity.[16] Although the safety of 6-Hz primed low frequency rTMS has been demonstrated in adults previously,[17] it was first explored in children by Gillick et al.[18] It was a phase 1 clinical trial exploring the safety and feasibility of combining 6-Hz primed 1-Hz rTMS to the contralesional hemisphere with CIMT, in 19 children. A significant improvement in AHA scores was noted in the real rTMS + CIMT group. Although, TMS has been shown to have additive effects when combined with CIMT, there is a paucity of data from clinical trials in children, none from a resource-limited setting so far. The only other trial (PLASTIC CHAMPS) in children, employed a factorial design, using inhibitory (1 Hz) rTMS to the contra-lateral primary motor cortex.[19] AHA gains at 6 months were additive and largest with the rTMS + CIMT group. The present trial was planned to explore the safety, and efficacy 6-Hz primed rTMS with mCIMT in improving the upper limb function of children with unilateral CP in the setting of a motor training program.

Methods

Study Design

This randomized, double-blind, placebo-controlled clinical trial was conducted at the Department of Pediatrics, All India Institute of Medical Sciences (AIIMS), New Delhi, which is a tertiary care referral center in India, from February 2019 to March 2020. A data safety monitoring board was constituted for adverse event monitoring. The institute resources were utilized and no external funding was obtained.

Within 1 week of baseline functional and neuro-physiological assessment, children with unilateral CP were enrolled in a motor training program for 4 weeks. They were randomized (in a 1:1 ratio) to mCIMT + real rTMS (intervention arm) or mCIMT + sham rTMS (control arm). It comprised 10 sessions of 20 minutes of rTMS (sham or real) followed by 2 hours of mCIMT on alternate weekdays.

Standard Protocol Approvals, Registrations, and Patient Consents

The trial was prospectively registered in the database of the US National Library of Medicine (clinicaltrials.gov;

NCT03792789) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The protocol, informed consent (IC) forms and other documents of the study were reviewed and approved by an independent institutional ethics Committee (IECPG-574/14. 11.2018.RT-32/19.12.2018). Written informed consent was taken from the parents or legally authorized representatives of the children, following regional laws/regulations. A written assent was taken by children more than 7 years of age. All participants were informed thoroughly about the study, in language and terms they were able to comprehend.

Participants

Children with unilateral CP (secondary to asymmetrical periventricular leukomalacia or stroke) were eligible for participation if they were in the age range of 5 to 18 years, had an intelligence quotient (IQ) >70 with preserved vision (able to at least see 1 in.^{2} object from 1 m distance) and hearing and had a functional status as follows: gross motor function classification system (GMFCS) stage 1 to 4 and manual ability classification stage (MACS) stage 1 to 3. Unilateral CP was defined as those children with motor impairment involving 1 half of the body, with a MAS score of ≥1, with an opposite limb MAS score of 0. Children were excluded from the trial for the following reasons: a MAS score of more than 3 at shoulder/elbow/wrist or presence of contractures in the affected limb, uncontrolled epilepsy (defined by seizure frequency >1/month for preceding 3 months); severe concurrent illness or disease not associated with CP or unstable medical conditions like pneumonia; genetic or syndromic associations and diagnosis of autism spectrum disorder and any contraindications for TMS like implanted electronic device and non-removable metallic objects near the coil, for example, Pacemaker, cochlear implant. They were also excluded if they underwent a recent surgery/cast/splint or botulinum toxin/phenol block in the past 6 months or were planned to receive in the study period. Children with a severe movement disorder like dystonia, choreo-athetosis, or ballismus interfering with purposeful limb movement, those with any congenital brain malformation detected on conventional MRI brain, those receiving tone modifying agents within 2 weeks before enrolment (tizanidine, baclofen, benzodiazepines, and dantrolene), or the ones who had received mCIMT in last 6 months, were also excluded.

Study Interventions

CIMT Sessions (All Participants). Structured mCIMT sessions were provided in groups of 3 or 4 by the principal investigator and a trained occupational therapist along with the participation of the primary caregiver at the department of physical medicine and rehabilitation (PMR). An arm sling was used for the restraint of the non-affected limb and was worn only during the intervention (an arm sling was provided free of cost to the children in both groups). The mCIMT sessions were structured and individualized for each child and conducted in a child-friendly atmosphere. During the 2-hour intervention period, they were constantly given instructions involving the specific practice of the designated task movement by the affected, unrestrained extremity. They were made to perform various repetitive and shaping activities of practicing a target movement in isolation from other movements in the given time frame. The activities were graded and selected according to the relative function. Successively the difficulty of the tasks was increased on completion of a particular task and children were given constant reinforcement throughout the session. At the end of each visit, a specific and individualized exercise plan was provided to be practiced at home for 2 hours a day on non-supervised days. The total duration of CIMT was 56 hours. Primary caregivers were asked to maintain an activity log (preferably with video records whenever feasible) to ensure compliance with the therapy on non-supervised days, which was checked by the principal investigator on each visit.

Real rTMS or Sham rTMS (1:1 Randomization). For rTMS Sessions, the Child was seated comfortably in a reclining chair with their unaffected forearm supinated and hand supported. The elbow was positioned in 90° flexion. EMG electrodes (Ag-AgCl electrodes, solid gel) were secured on the tendon and belly of abductor pollicis brevis. EMG signals were recorded using MATRIX LIGHT amplifier (Micromed) data acquisition and amplifier system with a bandpass filter of 10 to 5000 Hz at a display sensitivity of 1 mV/division (amplifier measuring range 51.2 mV), using a recording time from stimulus onset to 500 ms after stimulus onset. The EMG data were collected using System Plus Evolution software. For hotspot identification (location of the hand area of motor cortex), a figure of 8 TMS coils (MCF B65) connected to the stimulator (Magventure Denmark, X100 with magoption) was held by hand over the approximate M1 hotspot area for the un-affected hand, tangential to the scalp with the handle pointing posterolaterally at a 450 angle to the sagittal line. It was moved systematically to find the hotspot. Single-pulse magnetic stimuli were delivered at approximately 0.1 Hz, starting at an intensity of 50% of the stimulator maximum. For the determination of resting motor threshold (RMT), stimulation intensity was adjusted systematically until a minimum intensity required to elicit Motor evoked potential (MEPs) greater than or equal to 50 μv peak-to-peak in at least 5 out of 10 trials was reached (defined as RMT).

After RMT determination, children received priming rTMS followed by 1 Hz rTMS to the contra-lesional primary motor cortex with the TMS stimulator. Evidence for inhibitory rTMS is based on studies in adults[20] as well as children.[18,19,21] Priming consisted of 10 minutes of 6 Hz rTMS at 90% of RMT, delivered in 2 trains per minute with

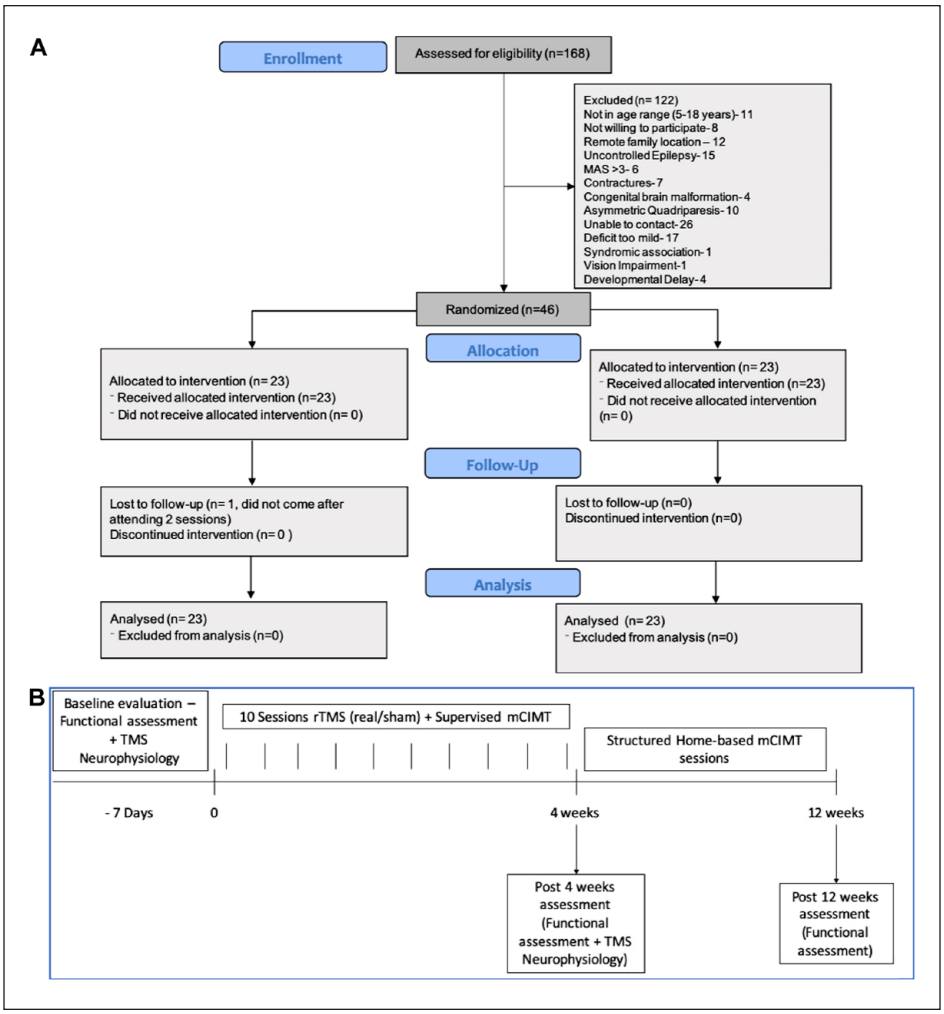

Figure 1. (A) CONSORT diagram depicting flow of the study and (B) flow of the trial.

5 seconds per train and 25-seconds intervals between trains (a total of 600 priming pulses). Priming was followed immediately by additional 10 minutes of 1 Hz rTMS at 90% of RMT without interruption (a total of 600 low-frequency pulses). At the end of each rTMS session, children were screened for any adverse event, by the rTMS administration adverse event monitoring log.

Outcomes

The primary outcome was the difference in mean change in the total QUEST score after completing 4 weeks of intervention, between the intervention and control group. There are only a few evaluation tools for assessment of upper limb function in children, to date. QUEST and AHA are the 2 most commonly used scales.[2,5] AHA assesses bimanual function, while QUEST scale examines each upper limb separately, across 4 domains. QUEST has been used in multiple studies involving children with unilateral CP, involving CIMT.[4,5,7,22] Additionally, the proportion of children with improvement ≥5 points in total QUEST score was compared between the 2 groups.

Secondary outcomes included change in domain-wise scores of QUEST score (dissociated movements, grasp, weight-bearing, and protective extension), speed of upper limb movements (measured by the time taken to complete 9-hole peg board), muscle strength (measured by hand-held dynamometers), improvement in quality of life scores (measured by CP-QOL child and CP-QOL teen as per the age of the child), and compliance to therapy. The subjects were assessed at 4 weeks and 12 weeks from baseline (Figure 1B). Neurophysiology parameters were assessed at baseline and 4 weeks. Two types of dynamometers were used—one for measuring hand-grip strength and the other one for push-pull strength. The un-affected upper limb function was assessed and compared, pre- and

post-intervention by using 9-hole peg board and dynamometers. Adverse events were recorded using rTMS administration adverse event monitoring log maintained from enrolment till the end of the follow-up period.

Evaluation Tools

Quality of Upper Extremity Skills Test. This is a validated and reliable tool devised for measuring the upper limb functions and the quality of movements in children with spastic CP in response to therapy and is valid for children from 18 months to 8 years.[23,24] Further studies have also validated the score in children aged 2 to 12 years.[25] It mainly examines each limb separately, in the 4 domains of function, namely, dissociated movements, grasp, protective extension, and weight bearing, and has 36 test items. Combined scores for 2 limbs are calculated and the maximum score in each domain is 100. A child with 1 fully functioning arm and another completely hemiplegic arm would be scored 50. All the scores from the individual domains are then averaged to obtain the final percentage score. This scoring system has been validated against the Peabody development scale and has high inter-observer reliability ranging from 0.51 to 0.96. The test-retest reliability of QUEST and its domains ranged from 0.75 to 0.95.[23] The QUEST has been used in several previous trials involving CIMT.[4,5,23,25]

Nine-Hole Peg Board Test. It is a tool for assessing the fine motor function and dexterity of the hand, and the ability to manipulate small objects (grasp and release). It has been validated against the Purdue pegboard test and normative data for children aged 4 to 19 years are available.[26,27] In this test, both hands are tested separately. The time taken to insert and remove the nine pegs into the holes in the peg board with first the dominant hand and then the non-dominant hand is calculated. The best of 2 trials for the time taken to insert all the pegs and then remove them from the board were taken. This test has a high inter-rater agreement of >0.99 and moderately high test-retest reliability (rs = .81 and .79).[26]

Hand Held Dynamometer. Hand-held dynamometers are used for the assessment of muscle strength in children as well as adults. Pull strength was assessed using Baseline push-pull dynamometer and pinch strength was assessed by a Baseline hydraulic pinch gauge in this study. Validity and reproducibility of hand-held dynamometry have high reproducibility and discriminative power in children which has been illustrated using the Jamar dynamometer in the past.[28] Reference values of isometric muscle force by hand-held dynamometry have also been established for children aged 4 to 16 years.[29] The test-retest reliability of the electronic push-pull dynamometer for measurement of extensor and flexor muscle strength has been found to be 0.85 to 0.99.[30]

CP Quality of Life Questionnaire for Children (CPQOL-Child)[31]. This is a questionnaire devised for the assessment of the quality of life for children with CP. It assesses the quality of life on the basis of 7 main domains—social well-being and acceptance, functioning, participation and physical health, emotional well-being, access to services, pain and impact of disability, and family health. It can be used for 4 to 12 years old children. There are 2 versions of CP-QOL child: the parent-proxy version (for parents of children aged 4-12 years) which comprises 65 items and the child self-report version (for children aged 9-12 years) which comprises 53 items. It has a high internal consistency (.74-.92) and 2-week test-retest reliability (.76-.89).[32]

Further details regarding assessment tools and evaluation scales are provided in Supplemental Appendix A.

Statistical Analysis

For sample size calculation, the anticipated increase in total QUEST scores at 4 weeks in the mCIMT group was taken as 10.7 ± 5.2 (mean $\pm$ SD) based on a previous trial by Choudhary et al.[4] The anticipated increase in total QUEST scores at 4 weeks in the mCIMT + rTMS group was taken as 15.0 ± 5.0 (mean $\pm$ SD) based on the gain in hand function reported in the PLASTIC CHAMPS trial.[19] Considering alpha error as 0.5 and power as 90% the calculated sample size was 30 in each group.

Participants were randomized in a 1:1 ratio to mCIMT + real rTMS (intervention arm) and mCIMT + sham rTMS (control arm), using the block randomization method. Randomization was performed with the use of computer-generated, non-stratified sequences, and assignments were prepared in sequentially numbered, sealed, opaque envelopes. Randomization was performed by persons not involved in the trial. For sham rTMS, a sham coil was used which simulated the tactile and auditory effect of the real coil but did not generate magnetic pulses. The subjects, caregivers, and outcome assessor were blinded to the subject's group allocation. Structured application of outcome parameters was performed by a separate physical therapist, blinded to subject characteristics and treatment allocation.

Statistical analysis was done using Stata 14.0 statistical software. For comparing baseline characteristics, chi-square and Fisher's exact tests were used for categorical variables and the Student t-test/Wilcoxon rank-sum test was used for continuous variables. A P value of less than .05 was considered to indicate statistical significance. Intention to treat analysis and a secondary per-protocol analysis was done for the primary and all the secondary outcomes. For patients

who were lost to follow-up, the last observation was carried forward. None of the following intention-to-treat analysis conclusions were altered by the secondary per-protocol analysis.

The primary outcome of the difference in mean change in QUEST score from baseline at 4 weeks was analyzed using a student *t*-test. For comparing the proportion of subjects with change ≥5 point change in QUEST score amongst the 2 study arms, the test of proportions was used. For analysis of secondary outcomes, the student *t*-test/ Wilcoxon rank sum test was used. We used repeated measures ANOVA along with post hoc comparison with the Bonferroni test for within-the-group analysis of various parameters across three-time points (baseline, 4, and 12 weeks).

The study protocol and statistical analysis plan is available for further reference in Supplemental Appendix A.

Results

Characteristics of the Study Population

During the enrolment period (February 2019-March 2020) 168 children were screened for eligibility; of these 122 children were excluded (reasons in Figure 1A) and 46 met the inclusion criteria and were randomized into the 2 study groups (23 in each arm). All children completed the study except 1 child in the intervention arm who did not return for further visits after 2 sessions. The CONSORT flow diagram for the study is illustrated in Figure 1A. Trial enrolment had to be discontinued due to the national lockdown enforced during the beginning of the COVID-19 pandemic. There were no significant differences in the baseline characteristics of the 2 groups (Table 1). All the participants either had GMFCS level I or II, with no difference in distribution amongst the study arms. The distribution for co-morbidities of movement disorder, behavioral problems, ophthalmological co-morbidities, hearing impairment, and epilepsy was also similar.

Primary outcome: Change in Upper Limb Function at 4 weeks

The mean change in total QUEST score after completing 4 weeks of therapy, was significantly higher in the intervention arm as compared to the control arm [absolute difference (*d*), 5.1; 95% Confidence Interval (CI), 1.7-8.5; $P = .004$; Table 2, Figure 2]. The proportion of subjects with an increase in QUEST total score ≥5 was significantly higher in the intervention arm [absolute difference (*d*), 30.4%; 95% CI, 4.8-56.0; $P = .027$].

Change in "weight bearing" and "protective extension" domain score was significantly higher for children in the real rTMS + mCIMT arm as compared to those in sham rTMS + mCIMT arm [14 (*Q*1, *Q*3—6, 18) vs. 4 (*Q*1, *Q*3—0, 8), $P = .004$] and [11.1 (*Q*1, *Q*3—2.8, 25) vs. 0 (*Q*1, *Q*3—0, 8.4), $P = .004$] respectively (Table 2). Change in the "dissociated movements" domain score was not found statistically significant amongst both arms ($P = .20$). Change in the "grasps" domain score was similar across both the study groups pre- and post-therapy ($P = .59$). Change in upper limb speed by 9-HPG ($P = .81$), pull strength ($P = .96$), and push strength ($P = .28$) by dynamometry was not found to be significantly different amongst both the study groups (Table 2).

Change in Upper Limb Function at 12 weeks

The mean change in total QUEST scores at 12 weeks (8 weeks after stopping supervised interventions) was significantly higher in the real rTMS + mCIMT arm as compared to the sham rTMS + mCIMT arm ($d = 3.8$, 95% CI 0.4-7.2, $P = .028$). The improvement in QUEST domain scores of weight bearing ($P = .002$) and protective extension ($P = .005$) was sustained as well (Figure 3).

Within the group comparison, both groups showed statistically significant improvement in QUEST total scores, domain-wise scores, time to complete 9-HPG scores and Pull strength and Push strength scores from baseline at 4 weeks ($P < .001$). This improvement was sustained at 12 weeks which is 8 weeks after stopping supervised therapy ($P < .001$).

CP-QOL Scores

Significantly better improvement in CP-QOL scores for "feelings about functioning" (Median [*Q*1, *Q*3], 12.5 [6.25, 12.5] vs 6.25 [6.25, 7.29], $P = .01$) and "participation and physical health" (Median [*Q*1, *Q*3], 9.37 [6.25, 12.5] vs 6.25 [6.25, 11.94], $P = .02$) domains was seen at 12 weeks in the intervention arm as compared to the control arm.

The Function of the Un-Affected Upper Limb

There was no decrease in the function of the unaffected upper limb as measured by speed and strength assessments using a 9-hole peg board and dynamometers (Figure 4).

Safety

No serious adverse events were seen. Minor adverse events seen were mild and brief headache and light-headedness reported by 1 subject each which was self-remitting within a few minutes. One child, who was a known case of epilepsy, had an episode of vacant stare lasting for a few seconds, a few hours after the intervention. This child was in the sham group and this episode of brief breakthrough seizure was reported to the ethics committee.

Table 1. Baseline Characteristics of the Study Population.[a]

Baseline characteristics	mCIMT + real rTMS n = 23	mCIMT + sham rTMS n = 23	*P* value
Age, y, Mean (SD)	8.65 (2.8)	8.63 (3.2)	.98
Range	5-15	5-15	
Gender, male, n (%)	13 (56.5)	17 (73.9)	.21
Side of hemiparesis Right, n (%)	16 (69.6)	11 (47.8)	.13
GMFCS I, n (%)	12 (52.2)	16 (69.6)	.23
GMFCS II, n (%)	11 (47.8)	7 (30.4)	
MACS I, n (%)	1 (4.4)	0	1.00
MACS II, n (%)	11 (47.8)	12 (52.2)	
MACS II, n (%)	11 (47.8)	11 (47.8)	
MAS 1, n (%)	3 (13)	1 (4.4)	.77
MAS 1+, n (%)	3 (13)	4 (17.4)	
MAS 2, n (%)	17 (73.9)	18 (78.3)	
IQ, Mean (SD)	75.7 (6.8)	74.3 (4.9)	.42
QUEST,[b] Mean (SD)	71.5 (8.7)	73.0 (10.9)	.60
Dissociated movements Mean (SD)	74.5 (13.0)	78.6 (11.9)	.26
Grasps, Mean (SD)	58.9 (14.5)	55.6 (17.3)	.32
Weight bearing, Mean (SD)	75.6 (10.2)	78.5 (12.3)	.38
Protective extension Mean (SD)	77.1 (10.4)	79.5 (12.5)	.47
9-HPG Median (*Q*1, *Q*3)	570.22 (142.9,1041)	827.65 (268.2,1481.7)	.29
Pull strength[c] Median (*Q*1, *Q*3)	7 (4, 10)	6 (4, 10)	.92
Push strength Median (*Q*1, *Q*3)	3 (2, 5)	3 (2, 4)	.69
Periventricular leukomalacia, n (%)	4 (17.4)	3 (13)	1.0
Stroke, n (%)	19 (82.6)	20 (86.95)	
RMT (%), Mean (SD)	64.7 (9.7)	62.8 (8.6)	.49

Abbreviations: CIMT, Constraint Induced Movement Therapy; GMFCS, Gross Motor Function Classification Scale; 9-HPG, 9-Hole Peg Board; IQ, Intelligence Quotient; MAS, Modified Ashworth Scale; MACS, Manual Ability Classification System; QUEST, Quality of Upper Extremity Skills Test; RMT, Resting Motor Threshold; rTMS, repetitive transcranial magnetic stimulation.

[a]There was no significant difference between the groups.

[b]Scores on Quality of Upper Extremity Strength Test range from 0 to 100, the higher scores indicate better upper limb function.

[c]Push and Pull strength were measured using dynamometers, the minimum score is 0, higher scores indicate greater muscle strength.

Discussion

In this single-center, randomized, controlled trial, combining rTMS with mCIMT was found significantly better in improving upper limb function in comparison to mCIMT alone, in children with unilateral CP in the setting of a motor training program. All children enrolled in the program had a significant improvement in upper limb function which was sustained at 12 weeks follow-up. To the best of our knowledge, this is the first such study from a low-to-middle-income country. Two previous trials have shown the additive effect of rTMS and CIMT in children with congenital hemiparesis.[18,19] In the PLASTIC CHAMPS trial, an improvement of 5.91 AHA logit units was seen at 6 months, in the rTMS + CIMT group as compared to the group receiving neither. Gillick et al, had reported a mean gain of 3.67 AHA logit units. A mean gain of 5.10 (1.7-8.5) in the QUEST total score was noted in the current trial, which is comparable to the previous studies.

This trial employed 6-Hz primed low frequency rTMS to the contra-lesional motor cortex. rTMS at frequency >1 Hz has been observed to enhance synaptic transmission (long-term potentiation), while low frequency rTMS (<1 Hz) has been demonstrated to decrease the efficacy of synaptic transmission (long-term depression).[33] However, there can be high inter-individual variability in response to various neuromodulation paradigms.[34] For the use of priming, we were guided by the trial by Gillick et al, in 19 children with hemiparesis. The rationale for the use of priming is based on the Bienenstock-Cooper-Munro theory.[35]

Table 2. Change in Functional Scales at 4 Weeks From Baseline.

	mCIMT + real rTMS	mCIMT + sham rTMS	
Outcome measures	n = 23	n = 23	*P* value
Change in QUEST Mean, (SD)	11.66 (6.97)	6.56 (4.3)	.004
Dissociated movements Median (Q1, Q3)	6.3 (2.6, 11)	3.1 (0, 9.4)	.20
Grasps Median (Q1, Q3)	11.1 (3.7, 22.2)	11.1 (3.7, 17.6)	.59
Weight bearing Median (Q1, Q3)	14 (6, 18)	4 (0, 8)	.004
Protective extension Median (Q1, Q3)	11.1 (2.8, 25)	0 (0, 8.4)	.004
9-HPG (seconds) Median (Q1, Q3)	120.2 (52.7, 682.2)	235.5 (30.96, 749.9)	.81
Pull strength Median (Q1, Q3)	2 (0, 4)	1 (0, 3)	.96
Push strength Median (Q1, Q3)	1 (0, 2)	1 (0, 2)	.28

Abbreviations: CIMT, Constraint Induced Movement Therapy; 9-HPG, 9-Hole Peg Board; QUEST, Quality of Upper Extremity Skills Test; rTMS, repetitive transcranial magnetic stimulation.

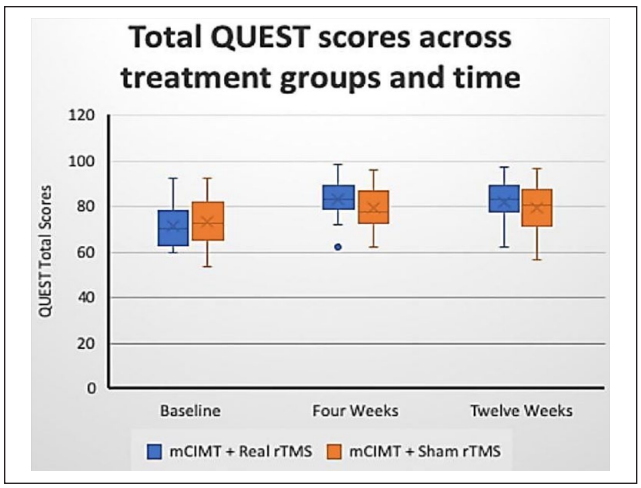

Figure 2. Primary outcome. Change in QUEST total score across time and treatment groups.

In the current study's total duration of CIMT was 56 hours, over 4 weeks. This was a relatively low dose, however, was comparable to previous studies.[4,18,19] It was 10 hours in the trial by Gillick et al (5 sessions of 2-hour each), and 80 hours (20 hours of individualized, 5.5 hours of group, and 5 hours of rTMS) in the PLASTIC CHAMPS trial. In a Cochrane review, the average length of CIMT programs was 4 weeks, with a frequency of twice weekly to 7 days per week, and the mean total number of hours was 137 hours (range 20-504).[2]

In addition to motor benefits, significant improvement in quality of life (CP-QOL) scores was seen. Children had to work in groups for mCIMT sessions. Most had never met another child with unilateral CP. It may be speculated that these sessions stimulated mutual interaction, and healthy competition and instilled confidence amongst children and caregivers. It would be interesting to capture this aspect of a group training program, on a subjective scale.

None of the children had any serious adverse event, which re-enforces the safety of rTMS in children as demonstrated in prior studies.[1] Only 1 child who was a known case of epilepsy and was in the mCIMT + Sham rTMS group had a brief breakthrough seizure which was self-aborted. Minor side-effects like mild headache and lightheadedness post rTMS sessions were seen in 1 child each. This is similar to past studies.[36,37] Gillick et al[37] reported headache in 50% and 89% of children receiving real and sham rTMS respectively. Mild TMS-related headache was reported in 40% of children with perinatal stroke as compared to 13% of healthy children in a study reporting data from 3.5 million stimulations.[36]

Most children with unilateral CP have average intelligence[38,39] and it is the motor disability that poses a major challenge in performing activities of daily living. An optimum motor rehabilitation regimen can result in a significant improvement in their quality of life. There are several trials and systematic reviews on the usefulness of CIMT in this population, however, the data on TMS and its combination with CIMT is scarce.[4,22,40-42] Moreover, the data on whom to give rTMS, the optimum dose and duration of therapy is further lacking.

Besides, the number of studies from developing countries is minuscule, owing to various reasons such as the cost

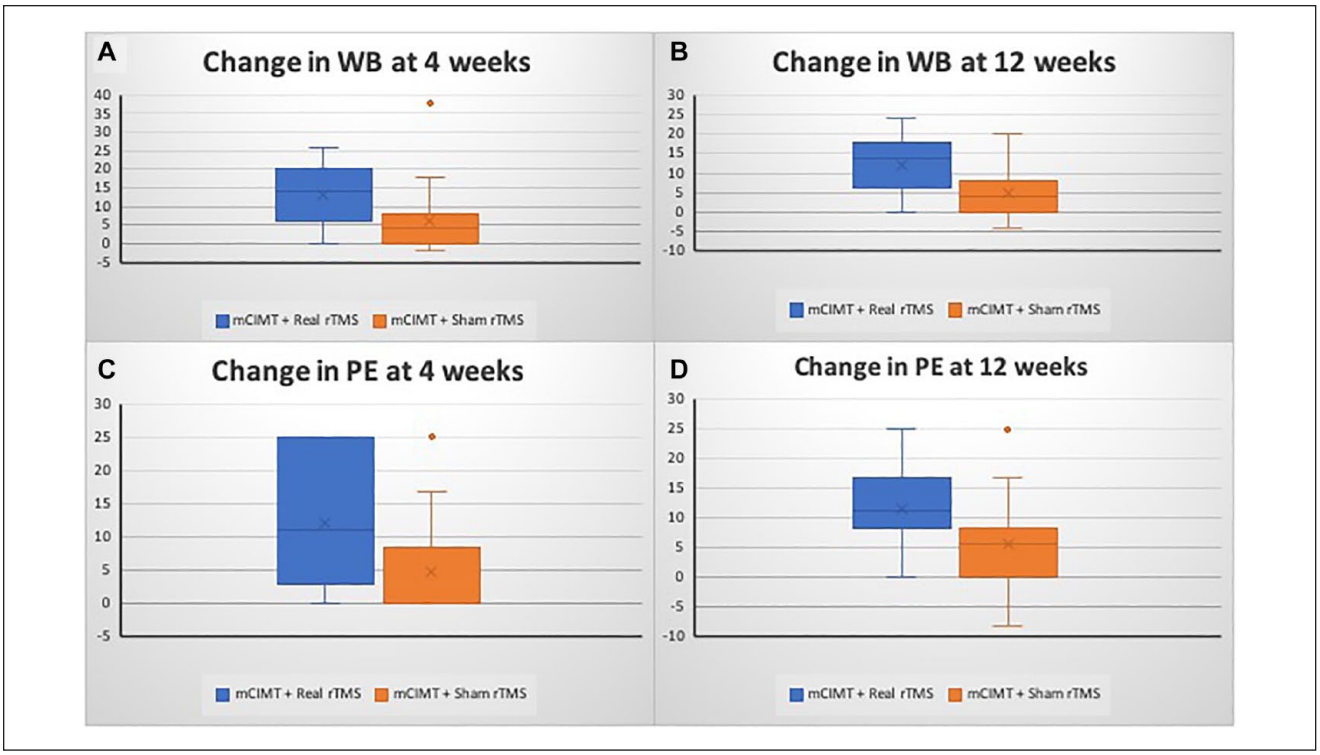

Figure 3. Secondary outcomes. (A) Change in Weight Bearing Domain (WB) scores at 4 weeks. (B) Change in WB Domain scores at 12 weeks. (C) Change in Protective Extension (PE) Domain at 4 weeks. (D) Change in PE Domain at 12 weeks.

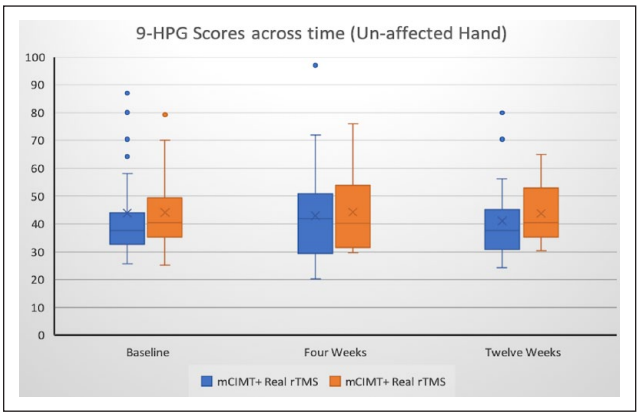

Figure 4. Unaffected hand function did not decrease with intervention- 9-Hole Peg Board Scores across time.

of the TMS machine, limited centers with TMS facilities, and a paucity of trained personnel to provide therapy, especially to children. Our institute is a tertiary care, teaching institute, which caters to multiple states in the northern part of the country. As many children would be visiting from neighboring states, it would pose a challenge to stay and travel to the hospital for therapy sessions. Hence, families were provided with free or low-cost accommodations near the institute, managed by social workers or non-government organizations.

This study has some limitations. First, the enrolment had to be closed due to a nation wide lockdown amidst the COVID-19 pandemic. Second, the follow-up could be done at 12 weeks, a longer follow-up would better estimate the long-term outcomes. Third, the last observation was carried forward for missing data, but the effect is minor as only 1 patient did not complete the trial intervention. Fourth, no individualized goal-setting (or measurement of subjective goal achievement) was done, apart from CP-QOL scores, and the subjects were not asked to guess their treatment allocation.

In conclusion, this study provides Class II evidence that combining rTMS with mCIMT was superior in improving upper limb function in children with unilateral CP as compared to mCIMT alone, which was sustained at 12 weeks.

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Author Contributions

Juhi Gupta: Conceptualization, Methodology, Investigation, Data curation, Project administration, Writing—original draft, review and editing, Formal analysis, Visualization. Sheffali Gulati: Conceptualization, Methodology, Investigation, Writing—review and editing, Visualization. U Singh: Supervision, Investigation. Atin Kumar: Methodology, Investigation. Prashant Jauhari: Methodology, Visualization, Supervision. Biswaroop Chakrabarty: Methodology, Visualization. R M Pandey: Methodology, Formal Analysis. Renu Bhatia: Investigation. Suman Jain: Investigation, writing-original draft. Achal Srivastava: Methodology, Supervision.

Declaration of Conflicting Interests

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Data Availability

The full trial protocol is available as an online appendix and is also freely available from the US National Library of Medicine (clinicaltrials.gov; NCT03792789). A deidentified dataset will be archived and upon request will be available from the corresponding author at the All India Institute of Medical Sciences, New Delhi, India.

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