ORIGINAL ARTICLE

Surgery for Drug-Resistant Epilepsy in Children

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ABSTRACT

BACKGROUND

Neurosurgical treatment may improve seizures in children and adolescents with drug-resistant epilepsy, but additional data are needed from randomized trials.

METHODS

In this single-center trial, we randomly assigned 116 patients who were 18 years of age or younger with drug-resistant epilepsy to undergo brain surgery appropriate to the underlying cause of epilepsy along with appropriate medical therapy (surgery group, 57 patients) or to receive medical therapy alone (medical-therapy group, 59 patients). The patients in the medical-therapy group were assigned to a waiting list for surgery. The primary outcome was freedom from seizures at 12 months. Secondary outcomes were the score on the Hague Seizure Severity scale, the Binet–Kamat intelligence quotient, the social quotient on the Vineland Social Maturity Scale, and scores on the Child Behavior Checklist and the Pediatric Quality of Life Inventory.

RESULTS

At 12 months, freedom from seizures occurred in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group (P<0.001). Between-group differences in the change from baseline to 12 months significantly favored surgery with respect to the score on the Hague Seizure Severity scale (difference, 19.4; 95% confidence interval [CI], 15.8 to 23.1; P<0.001), on the Child Behavior Checklist (difference, 13.1; 95% CI, 10.7 to 15.6; P<0.001), on the Pediatric Quality of Life Inventory (difference, 21.9; 95% CI, 16.4 to 27.6; P<0.001), and on the Vineland Social Maturity Scale (difference, 4.7; 95% CI, 0.4 to 9.1; P=0.03), but not on the Binet–Kamat intelligence quotient (difference, 2.5; 95% CI, −0.1 to 5.1; P=0.06). Serious adverse events occurred in 19 patients (33%) in the surgery group, including hemiparesis in 15 (26%).

CONCLUSIONS

In this single-center trial, children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone at 12 months. Surgery resulted in anticipated neurologic deficits related to the region of brain resection. (Funded by the Indian Council of Medical Research and others; Clinical Trial Registry–India number, CTRI/2010/091/000525.)

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Children and adolescents with drug-resistant epilepsy are at increased risk for poor long-term intellectual and psychosocial outcomes, along with a poor health-related quality of life.[1-3] In this form of recalcitrant epilepsy, appropriate surgical management is often undertaken with the goal of reducing or stopping seizures, but there is limited evidence from randomized trials showing the benefit in this age group.

The region of the cerebrum that is subjected to surgery depends on the localization of the origin of seizures in the cerebral cortex and the functional importance of the surrounding brain tissue. These factors are determined on presurgical evaluation, including simultaneously acquired video electroencephalographic (video EEG) recordings and structural and functional imaging of the brain. The type of surgery is dependent on the underlying cause of epilepsy and may include resection of the mesial temporal lobe or other regions of the cerebral cortex, excision of a focal lesion or developmental malformation, sectioning of the corpus callosum (corpus callosotomy), disconnection of a part of the cerebral cortex, or disconnection of an entire hemisphere (hemispherotomy). Some of these procedures necessarily result in neurologic deficits.

Two randomized trials of temporal lobectomy for drug-resistant epilepsy included only adults.[4,5] A Cochrane review of epilepsy surgery included only four trials that had more than 30 participants, and these trials involved patients in all age groups.[6] Three of these trials compared different surgical techniques or compared different extents of surgical resection, but only one[4] randomly assigned patients to surgical and medical groups. A meta-analysis of uncontrolled studies that compared seizure outcomes of surgeries in children showed that 74% of those with brain lesions and 45% of those without lesions had become seizure-free at the 1-year follow-up.[7] In a retrospective analysis involving 142 children who had undergone surgery for drug-resistant epilepsy at a mean age of 9.8 years between 2000 and 2011 at our center, 79.3% were free from disabling seizures after a mean follow-up of approximately 4 years.[8] To follow up on these results, we performed a trial involving children and adolescents with drug-resistant epilepsy to compare epilepsy surgery with continued medical therapy alone in patients on a waiting list for surgery.

Methods

Trial Design and Oversight

The trial was conducted from November 2010 through March 2015 at the All India Institute of Medical Sciences in New Delhi, which is the referral center for epilepsy surgery in northern India. The trial was approved by the institutional ethics committee; written informed consent was provided by parents or legally authorized representatives of the children. An independent data and safety monitoring board reviewed the records of the recruited patients for adverse events at annual meetings. The trial was funded by the Indian Council of Medical Research and the Department of Biotechnology, Government of India. The trial was initiated by the last author, and all the authors contributed to its design. The first and second authors wrote the first draft of the manuscript, and all the authors reviewed the manuscript and vouch for adherence of the trial to the protocol (available with the full text of this article at NEJM.org) and for the completeness and accuracy of the data.

Presurgical Evaluation and Surgical Intervention

Patients were evaluated with long-term video EEG monitoring with the use of scalp electrodes in the standard 10–20 system of electrode placement and with 3-Tesla magnetic resonance imaging (MRI) that included an epilepsy protocol. This protocol involved the use of T_1-weighted sagittal three-dimensional (3D) and 3D FLAIR (fluid-attenuated inversion recovery) sequences with a slice thickness of less than 1 mm without an intervening gap, coronal T_2-weighted and FLAIR sequences with a 2.5-mm slice thickness without a gap (perpendicular to the hippocampus), and axial susceptibility-weighted images.

Drug-resistant epilepsy was defined as the failure of adequate trials of two appropriately chosen antiepileptic drug schedules with acceptable side effects.[9] Patients who had no definite localization of seizures on video EEG, those who had no concordance of the EEG results and a lesion on MRI, and those who had no lesion, more than one lesion, or lesions with poorly defined margins on imaging underwent ictal and interictal single-photon-emission computed tomography (SPECT), positron-emission tomography (PET), or magnetoencephalography (MEG) as part of the presurgical evaluation.[10]

Each patient was discussed at the weekly multidisciplinary epilepsy surgery case conference attended by neurologists, neurosurgeons, neuroradiologists, and nuclear medicine specialists; the assessments of neuropsychologists and psychiatrists were taken into consideration before surgery to evaluate coexisting psychiatric conditions and corroborate the localization of epilepsy and resulting deficits. Patients with concordance of video EEG localization of the region of onset of the seizure (ictal-onset zone) and the location of the lesion on MRI underwent resection of that region of cortex or of the lesion or malformed cortex; those with multiple, subtle, or no lesions underwent resection of the region that was concordant between video EEG results and localization on PET, SPECT, or MEG. Patients who had multiple seizure types (including drop attacks) and multiple bilateral lesions and seizure foci underwent corpus callosotomy. Patients who had extensive lesions confined to one hemisphere with significant weakness of limbs (weak pincer grip or worse) opposite to the involved hemisphere underwent hemispherotomy.

Patients were not included in the trial if there was no consensus regarding the location of an epileptic focus and were excluded if there were metabolic abnormalities (genetic or acquired) or cardiac, renal, or any other systemic illness or a history of status epilepticus. In all the patients in the surgery group, postsurgery MRI was performed with a high-field 1.5 Tesla system in the operating room to ensure the adequacy of the planned excision.

RANDOMIZATION AND BLINDING

Randomization was performed with the use of computer-generated, nonstratified sequences, and assignments were prepared in sequentially numbered, sealed, opaque envelopes by persons not involved in the trial. Patients who were assigned to the surgery group underwent the procedure within a month after randomization; those who were assigned to the medical-therapy group remained on the waiting list, with surgery planned for 1 year or longer after randomization, which represented the standard of care at our center, since the waiting list is typically 12 months or longer. All the patients continued to receive antiepileptic drugs, and changes were made by the treating clinicians as necessary to manage seizures. In the surgery group, patients who became seizure-free underwent tapering of antiepileptic drugs, starting 1 year after surgery.

OUTCOMES

The primary outcome was freedom from seizures, which was defined as class 1 (no seizures or auras) on the International League Against Epilepsy scale[11] at 12 months. Other categories on the scale are as follows: auras only with no other seizures (class 2), 1 to 3 seizure days per year (class 3), from 4 seizure days per year to a number of seizure days that represents a 50% reduction in the number of days from baseline (class 4), from less than a 50% reduction in the number of seizure days to a 100% increase in the number of seizure days from baseline (class 5), and more than a 100% increase in the number of seizure days from baseline (class 6).

Secondary outcomes, which were evaluated at 12 months after the date of surgery or randomization and were compared with baseline scores, included any occurrence of seizures, the score on the Hague Seizure Severity scale (ranging from 13 to 54, with higher scores indicating greater severity), the Binet–Kamat intelligence quotient or the social quotient on the Vineland Social Maturity Scale (normal range, 85 to 110 on both scales, with higher scores indicating higher levels of function), the T score on the Child Behavior Checklist (normal score, <60; borderline, 60 to 63; and clinically impaired, >63), and the score on the Pediatric Quality of Life Inventory (ranging from 0 to 100, with higher scores indicating a better quality of life). The Binet–Kamat test was administered to children with adequate verbal responses, and the Vineland Social Maturity Scale was administered to children younger than 2 years of age and to older children whose verbal response was inadequate for the completion of the Binet–Kamat test. (Details regarding the evaluation scales and testing procedures are provided in Section 1 in the Supplementary Appendix, available at NEJM.org.)

The primary outcome measure of freedom from seizures was assessed in a blinded manner on the basis of seizure diaries, as reported by telephone at 6 months and 12 months (see Section 2 in the Supplementary Appendix) and verified from seizure diaries. Diaries were coded with unique identification numbers and sent to the assessor by a person uninvolved in the trial. Secondary outcomes of seizure occurrence during the 12-month period and psychosocial measures

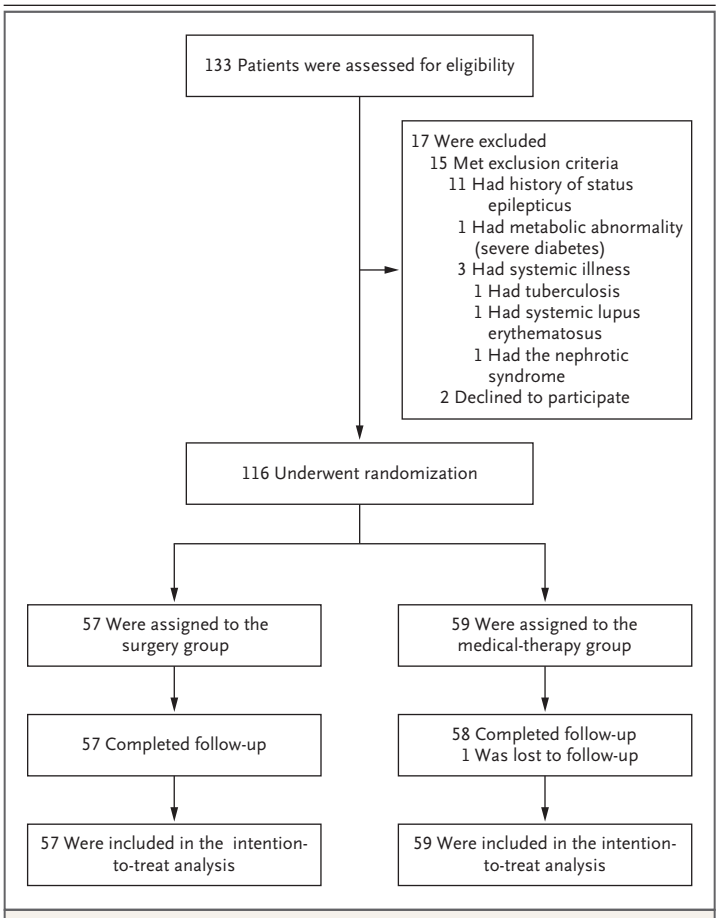

Figure 1. Enrollment and Outcomes.

were assessed by the treating epileptologist and psychologist (both of whom were aware of study-group assignments) during clinical visits and with the use of the seizure diary. All the patients were seen at the epilepsy clinic every 3 months or more frequently as required for clinical care.

ADVERSE EVENTS

Adverse events that were classified as serious were assessed in a blinded manner during a telephone checklist discussion. (Details are provided in Section 2 in the Supplementary Appendix.) Serious adverse events included death, hospital admission or prolongation of an existing hospital stay, and events that resulted in persistent or substantial disability or incapacity or that were considered to be life-threatening.[12] All other adverse events were recorded as nonserious.

STATISTICAL ANALYSIS

Power calculations were based on the results of the study by Widjaja et al., in which the seizure-free rate after surgery was 60%.[13] We calculated that the enrollment of 116 patients would provide a power of 90% to determine an absolute between-group difference of 40 percentage points in the rate of freedom from seizures (and a superiority margin of 15% in the surgery group) at 12 months at a two-sided alpha level of 5% and assuming that 5% of the patients would be lost to follow-up.

We used the chi-square test and Fisher's exact test to compare categorical characteristics at baseline; we used Student's t-test to compare normally distributed continuous variables and the Wilcoxon rank-sum test to compare nonparametric continuous data. Intention-to-treat analyses were performed for both primary and secondary outcomes. Patients who did not complete follow-up at 12 months were not considered to be seizure-free in the primary analysis; for the secondary outcomes, the last observation was carried forward.

The primary outcome of complete freedom from seizures at 12 months was analyzed with the use of the z-test and was reported as the difference in proportions and relative risk with 95% confidence intervals. We used the Kaplan–Meier method and log-rank test to analyze the secondary outcome of seizure during the 12-month period and a Cox proportional-hazards model to calculate hazard ratios and 95% confidence intervals. We used Student's t-test to analyze other secondary outcomes and the paired t-test to analyze the change from baseline to last follow-up. A P value of less than 0.05 was considered to indicate statistical significance. All the statistical analyses were performed with the use of Stata software, version 11.0.

RESULTS

PATIENTS

A total of 133 children underwent screening; 2 of the children were eligible but did not provide informed consent and 116 met the inclusion criteria (57 in the surgery group and 59 in the medical-therapy group) (Fig. 1). One patient in the medical-therapy group did not return for the last follow-up visit. There were no significant

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Surgery Group (N=57)	Medical-Therapy Group (N=59)
Median age (range) — yr	9.0 (0.8–17.0)	10.0 (2.0–17.0)
Female sex — no. (%)	23 (40)	19 (32)
Family history of epilepsy — no. (%)	3 (5)	6 (10)
Median age at onset of seizures (range) — yr†	1.5 (0.1–9.0)	3.0 (0.1–10.0)
Median duration of epilepsy (range) — yr	4.9 (0.4–16.3)	5.0 (0.5–16.0)
Type of seizures — no. (%)		
Focal	43 (75)	43 (73)
Secondary generalized	14 (25)	16 (27)
Frequency of seizures 6 mo before randomization		
≥1 Per day	48 (84)	40 (68)
≥1 Per week	5 (9)	10 (17)
≥1 Per mo	4 (7)	6 (10)
≥1 Per 3 mo	0	3 (5)
Median number of previous antiepileptic medications (range)	3 (2–6)	3 (2–6)
Score on Hague Seizure Severity scale‡	37.9±4.2	37.4±4.3
Intelligence quotient on Binet–Kamat test§	63.9±19.3	62.8±21.4
Social quotient on Vineland Social Maturity Scale§	38.6±24.2	41.8±20.9
Total score on Child Behavior Checklist¶	69.5±6.3	67.8±5.1
Total score on Pediatric Quality of Life Inventory‖	53.4±15.4	53.2±16.4

* Plus–minus values are means ±SD. There were no significant differences between the groups.
† The earliest onset was between 2 and 4 days after birth.
‡ Scores on the Hague Seizure Severity scale range from 13 to 54, with higher scores indicating greater seizure severity.
§ Average scores on the tests of intelligence quotient and social quotient range from 85 to 110, with higher scores indicating higher levels. Intelligence quotient was tested in 30 patients in the surgery group and 33 in the medical-therapy group; social quotient was tested in 27 patients in the surgery group and 26 in the medical-therapy group.
¶ The normal T score on the Child Behavior Checklist is less than 60, with higher scores indicating greater behavioral problems.
‖ Scores on the Pediatric Quality of Life Inventory range from 0 to 100, with higher scores indicating a better quality of life.

differences in the baseline characteristics between the two groups (Table 1). The following surgical procedures were carried out: temporal lobe resections in 14 patients, resection of lesion in a lobe other than temporal in 12, hemispherotomy in 15, corpus callosotomy in 10, and disconnection or resection of hypothalamic hamartoma in 6. (Details regarding the surgical procedures are provided in the Supplementary Appendix, Section 1, Tables S7 and S8.)

PRIMARY OUTCOME

At 12 months, complete freedom from seizures was reported in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group (absolute difference, 70.4 percentage points; 95% confidence interval [CI], 57.8 to 83.1; P<0.001) (Table 2). The relative risk of seizure recurrence was 4.09 (95% CI, 2.52 to 6.62) in the medical-therapy group as compared with the surgery group.

At the last follow-up, all the patients who had undergone temporal lobectomy or hypothalamic hamartoma surgeries were seizure-free. Of those who had undergone extratemporal resection or hemispherotomy, 11 of 12 patients (92%) and 13 of 15 (87%), respectively, had complete freedom from seizures (Supplementary Appendix, Section 1, Table S2). In the medical-therapy group, 2 of 15 patients (13%) who were on the waiting list for a temporal lobectomy were seizure-free at 12 months, along with 1 of 19 patients (5%) who were on a waiting list for an extratemporal resection and 1 of 16 (6%) who were waiting

Table 2. Primary and Secondary Outcomes at 1 Year.*

Outcome	Surgery Group (N=57)	Medical-Therapy Group (N=59)	Absolute Difference		Difference in Change from Baseline	
			Value (95% CI)	P Value	Value (95% CI)	P Value
Primary outcome: freedom from seizures — no. (%)	44 (77)	4 (7)	70.4 (57.8 to 83.1)†	<0.001	NA	NA
Secondary outcomes						
Score on Hague Seizure Severity scale	15.4±5.5	34.3±11.8	18.9 (15.5 to 22.3)	<0.001	19.4 (15.8 to 23.1)	<0.001
Intelligence quotient on Binet–Kamat test	62.7±18.5	58.9±22.1	3.7 (−6.6 to 14.0)	0.47	2.5 (−0.1 to 5.1)	0.06
Social quotient on Vineland Social Maturity Scale	41.5±23.1	39.9±19.7	1.6 (−10.3 to 13.4)	0.79	4.7 (0.4 to 9.1)	0.03
Total score on Child Behavior Checklist	57.2±6.7	68.6±7.6	11.4 (8.8 to 14.0)	<0.001	13.1 (10.7 to 15.6)	<0.001
Total score on Pediatric Quality of Life Inventory	76.1±13.1	53.9±18.5	22.1 (16.2 to 28.1)	<0.001	21.9 (16.4 to 27.6)	<0.001

* Plus–minus values are means ±SD. NA denotes not applicable.
† The absolute between-group difference for the primary outcome is provided in percentage points.

for a corpus callosotomy; among those with a planned hemispherotomy or intervention for hypothalamic hamartoma, none of the patients were seizure-free (Supplementary Appendix, Section 1, Table S3).

SECONDARY OUTCOMES

Estimates of the probability of being seizure-free at 12 months on Kaplan–Meier analysis were 36.7% in the surgery group and zero in the medical-therapy group (hazard ratio for freedom from seizures in the surgery group, 6.2; 95% CI, 4.6 to 8.2; P<0.001) (Fig. 2). (Although 77% of the patients in the surgery group were seizure-free at the 12-month follow-up, the postoperative seizures that had occurred during the first 6 months were included in the Kaplan–Meier analysis.) The reduction from baseline in the score on the Hague Seizure Severity scale at 1 year was significantly greater in the surgery group than in the medical-therapy group (between-group difference in the change from baseline, 19.4; 95% CI, 15.8 to 23.1; P<0.001) (Table 2). The Binet–Kamat test was administered to 63 patients (30 in the surgery group and 33 in the medical-therapy group). The reduction from baseline in the mean (±SD) intelligence quotient was not significant in the surgery group (–1.3±6.5, P=0.29) and was significant in the medical-therapy group (–3.8±3.6, P<0.001); however, the between-group difference in change from baseline to 12 months was not significant (difference, 2.5; 95% CI, −0.1 to 5.1; P=0.06). The Vineland Social Maturity Scale test was administered to 53 children (27 in the surgery group and 26 in the medical-therapy group). There was no significant change from baseline in the mean social quotient in either group (2.9±7.9 in the surgery group, P=0.07; and –1.8±7.7 in the medical-therapy group, P=0.24), but the between-group difference in the change from baseline significantly favored the surgery group (difference, 4.7; 95% CI, 0.4 to 9.1; P=0.03) (Table 2).

At 12 months, the change from baseline in the mean T score on the Child Behavior Checklist was significant in the surgery group (–12.3±6.2, P<0.001) but not in the medical-therapy group (–0.86±7.2, P=0.36), which resulted in a significant between-group difference that favored the surgery group (difference, 13.1; 95% CI, 10.7 to 15.6; P<0.001). On the Pediatric Quality of Life Inventory, the mean total score increased sig-

nificantly in the surgery group (22.7±14.3; 95% CI, 18.9 to 26.5; P<0.001) but not in the medical-therapy group (0.70±16.0; 95% CI, 3.5 to 4.9; P=0.74), which also resulted in a significant between-group difference in the change from baseline that favored the surgery group (difference, 21.9; 95% CI, 16.4 to 27.6; P<0.001). (Details regarding the subscales on the Child Behavior Checklist and Pediatric Quality of Life Inventory at baseline and 12 months are provided in the Supplementary Appendix, Section 1, Tables S5 and S6.)

ADVERSE EVENTS

There were no deaths in either group. Serious adverse events occurred in 19 patients (33%) in the surgery group and none in the medical-therapy group. These events included monoparesis in 2 patients who had undergone temporal lobectomy or resection of parietal focal cortical dysplasia, hemiparesis in 15 patients who had undergone hemispherotomy, and generalized hypotonia and language deficits in 1 patient each who had undergone frontal lobectomy. Of the 17 patients with monoparesis or hemiparesis, 15 (with the exclusion of 2 of those with hemiparesis) were able to move all major joints against gravity or better at 12 months. In the child with generalized hypotonia and the one with language deficits after surgery, both reached baseline levels of motor and language functions, respectively, at 12 months. In the medical-therapy group, 10 had physical injuries associated with seizures (cuts, burns, and fractures), 1 had an adverse event associated with an antiepileptic drug, and autistic features developed in another. (Details regarding adverse events are provided in the Supplementary Appendix, Section 1, Tables S7 and S9.)

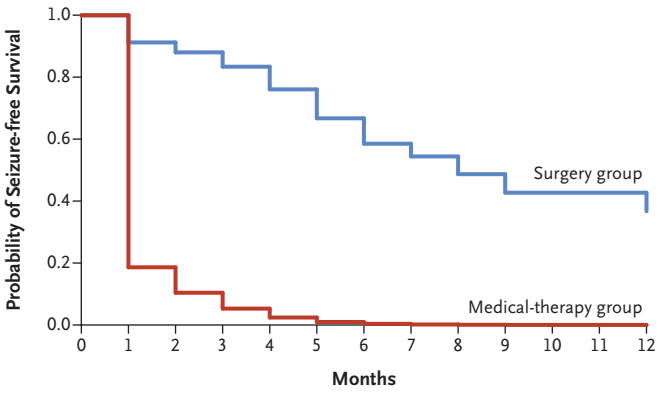

Figure 2. Probability of Seizure-free Survival at 1 Year.

Shown are Kaplan–Meier estimates of the probability of being seizure-free at 1 year in the two study groups. The rate of seizure-free survival was 36.7% in the surgery group and zero in the medical-therapy group (hazard ratio for freedom from seizures in the surgery group, 6.2; 95% confidence interval, 4.6 to 8.2; P<0.001).

DISCUSSION

In this single-center, randomized, controlled trial, seizure outcomes 1 year after epilepsy surgery were significantly better than after continued medical therapy alone. Of the 57 patients who underwent surgery, 44 (77%) became seizure-free and 13 (23%) had ongoing seizures of varying degrees (class 2 to class 5 on the International League Against Epilepsy scale) (Supplementary Appendix, Section 1, Tables S1 and S2). In comparison, 93% of those receiving medical therapy alone continued to have seizures. In the surgery group, 21 patients (37%) were completely seizure-free during the entire 12-month period, whereas during the first weeks after surgery, the other 23 patients continued to have seizures; these episodes subsequently decreased in frequency, a feature that has been observed in other series of epilepsy surgery.[14] A substantial proportion of the children in the surgery group had anticipated major postoperative motor, sensory, or cognitive deficits that were related to the area of the brain that was resected or disconnected.

Complete freedom from seizures occurred in all the patients in our trial who had undergone temporal lobectomy, as compared with only 38% of those who had undergone the same surgery in another randomized trial of epilepsy surgery that included only adults with a longer duration of epilepsy than the children in our trial. The difference in ages and duration of epilepsy between the two trials may explain the difference in results.[4]

The between-group difference in the change from baseline to 12 months in the mean intelligence quotient was not significant in our trial, and it is possible that the 12-month interval of observation was too brief to observe a change in this measure. The improvements that were observed in other cognitive, behavioral, and quality-of-life scores in the surgery group may have been due to a reduction in the frequency of

seizures; conversely, the deterioration in these measures in the medical-therapy group may be attributed to a continuation of seizures, which has been associated with poor cognitive functioning in children.[15-24] In two nonrandomized trials, overall quality-of-life scores were significantly better among children who had undergone epilepsy surgery than among those who had received only medical therapy after 2 years or more of follow-up.[25,26] An observational study comparing surgical versus medical treatment in children with epileptic encephalopathy in infancy and early childhood showed that surgery resulted in better seizure control and a better developmental quotient than did medical therapy.[27]

Our trial has some limitations. First, we included patients undergoing many types of epilepsy surgeries that were directed at several underlying pathological causes of seizures. However, the patients who were included in the trial reflect the populations encountered at a referral center for pediatric epilepsy. Second, there was an overrepresentation of hypothalamic hamartomas in our trial as compared with some other series. And third, our statistical analysis plan called for an outdated approach of last observation carried forward for missing data of secondary outcomes, although the effect was relatively minor, since information was missing in only one patient.

Serious adverse events due to the surgery included major motor, sensory, and cognitive deficits that were related to the area of the brain that was resected or disconnected. Despite these deficits, quality-of-life measures were significantly better in the surgery group, possibly because of better seizure control.

In conclusion, surgery in children with drug-resistant epilepsy resulted in higher rates of cessation of seizures at 1 year and better scores on some measures of behavior and quality of life than continued medical therapy alone. Some patients in the surgery group had anticipated serious neurologic consequences, including hemiparesis, some of which improved over time.

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No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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RESEARCH ARTICLE

Safety, Efficacy, and Tolerability of Modified Atkins Diet in Persons With Drug-Resistant Epilepsy

A Randomized Controlled Trial

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Abstract

Background and Objectives

Modified Atkins diet (MAD) has emerged as an adjuvant therapy in drug-resistant epilepsy (DRE). Most studies are in children; there is limited evidence for DRE in adults. This study aimed to investigate whether MAD along with standard drug therapy (SDT) was indeed more effective than SDT alone in reducing seizure frequency and improving psychological outcomes at 6 months in adolescents and adults with DRE (nonsurgical).

Methods

A prospective randomized controlled trial was conducted at tertiary care referral center in India. Persons with DRE aged 10–55 years attending outpatient epilepsy clinics between August 2015 and April 2019, who had more than 2 seizures per month despite using at least 3 appropriate antiseizure medications (ASMs) at their maximum tolerated doses and had not been on any form of diet therapy for the past 1 year, were enrolled. Patients were assessed for the eligibility and randomly assigned to receive SDT plus MAD (intervention arm) or SDT alone (control arm). The primary outcome was >50% reduction in seizure frequency, and the secondary outcomes were quality of life (QOL), behavior, adverse events, and rate of withdrawal at 6 months. Intention-to-treat analysis was performed.

Results

A total of 243 patients were screened for eligibility; 160 patients (80 adults and 80 adolescents) were randomized to either the intervention or control arm. Demographic and clinical characteristics in both groups were comparable at baseline. At 6 months, >50% seizure reduction was seen in 26.2% in the intervention group vs 2.5% in the control group (95% CI 13.5–33.9; $p < 0.001$). Improvement in QOL was 52.1 ± 17.6 in the intervention group vs 42.5 ± 16.4 in the control group (mean difference, 9.6; 95% CI 4.3 to 14.9, $p < 0.001$). However, behavior scores could be performed in 49 patients, and improvement was seen in the intervention vs control group (65.6 ± 7.9 vs 71.4 ± 8.1, $p = 0.015$) at the end of the study. One patient had weight loss; 2 patients had diarrhea.

Discussion

The MAD group demonstrated improvement in all aspects (reduction in seizure frequency and behavioral problems) compared with the control group at the end of the study. MAD is an effective modality in controlling seizures; further research is required to assess its efficacy in terms of biomarkers along with descriptive metabolomics studies.

Trial Registration Information

The clinical trial registry of India: CTRI/2015/07/006048.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Infographic
links.lww.com/WNL/C685

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AIIMS = All India Institute of Medical Sciences; **ASMs** = antiseizure medications; **DRE** = drug-resistant epilepsy; **ILAE** = International League Against Epilepsy; **ITT** = intention to treat; **MAD** = modified Atkins diet; **PP** = per protocol; **QOL** = quality of life; **RCTs** = randomized controlled trials; **SDT** = standard drug therapy.

Classification of Evidence

This study provides Class III evidence that the MAD increases the probability of seizure reduction in adolescents and adults with DRE.

Epilepsy affects more than 70 million people worldwide, and one-third of persons with epilepsy are resistant to antiseizure medications (ASMs).[1]

Drug-resistant epilepsy (DRE) is defined by the International League Against Epilepsy as "failure of adequate trials of 2 tolerated, appropriately chosen, and used ASM schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom."[2] Many patients who are not suitable surgical candidates or decline surgery[3] have benefited from dietary interventions.[4,5]

Modified Atkins diet (MAD) aims to provide increase palatability and flexibility with a 1:1 ratio of fat to carbohydrates and protein, as it has around 65% fat, 25% protein, and 10% carbohydrates.[6] MAD and low glycemic index diet (LGIT) are hence less restrictive alternatives to the ketogenic diet (KD), as protein and calories are not restricted.[7]

In previous studies, nearly half the patients with DRE showed >50% seizure reduction on the KD, and about 15%–20% became seizure-free.[8] A meta-analysis showed that the combined efficacy rates for freedom from seizures, reduction of seizures by 50% or more, and reduction of seizures below 50% in adults with difficulty to treat epilepsy was 13%, 53%, and 27%, respectively.[9] Several studies have shown an efficacy of MAD of at least in 30% of the study patients having >50% reduction in seizure.[10-14] The efficacy of MAD has been established and well tolerated in children with DRE.[13,15,16] Evidence suggests that MAD may have comparable efficacy but a higher rate of compliance as compared to KD in adults with DRE.[17-20] There is an uncertainty as to the best dietary treatment because of a low number of trials in adults with DRE.[21,22] Therefore, we chose MAD because of its ease of applicability and better compliance than the KD and the need for randomized controlled trials (RCTs) for assessing long-term outcomes with regard to the response to MAD in a larger cohort, including adolescents and adults with DRE, which are still lacking.

We therefore performed a RCT. Our primary research question was to investigate "whether the addition of MAD (dietary intervention) with on-going standard drug therapy (SDT) is more efficacious in terms of seizure control at 6 months in the nonsurgical patients with DRE?" The secondary objectives were to determine the quality of life, behavior, tolerability of MAD, and their adverse effects at 6 months among adolescents and adults with DRE.

Methods

Trial Design and Oversight

A prospective randomized open-label, blinded endpoint controlled trial with 2 parallel arms design was conducted in the pediatric and adult neurology clinic, All India Institute of Medical Sciences (AIIMS), a tertiary care referral center in New Delhi, India. Eligible participants were randomly assigned to receive the SDT plus MAD or SDT alone in a 1:1 ratio. All the patients underwent clinical evaluations at baseline, 3 months, and 6 months, and outcome assessment was performed at 6 months. Structured formats of seizure-log, ketone-log, food-log, adverse event diary, and schedule of enrollment and timeline of clinical evaluations (eFigure 1A, 1B) are provided in eAppendix 1 (links.lww.com/WNL/C564).

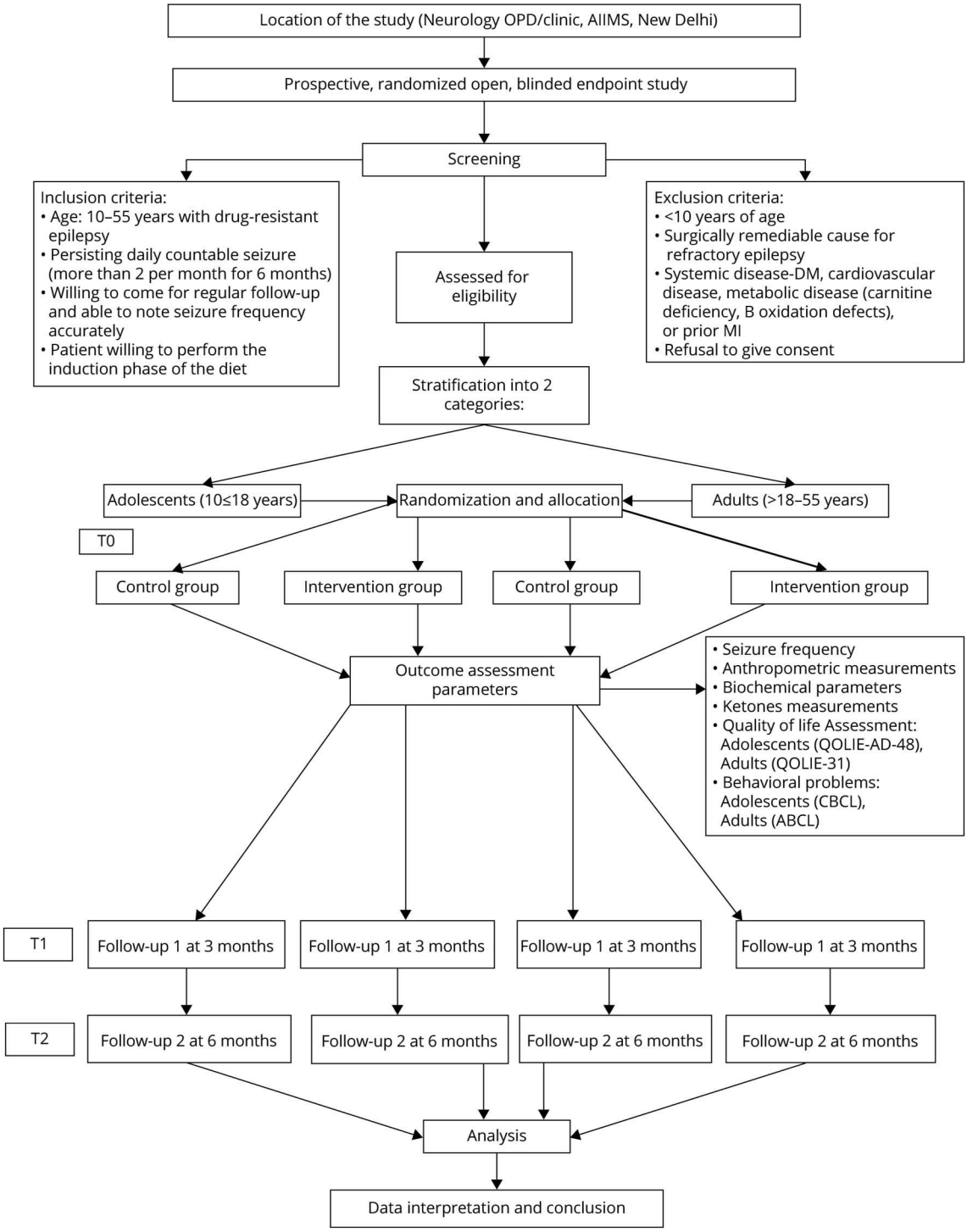
Standard Protocol Approvals, Registrations, and Patient Consents

The institutional ethics committee approved this trial, and written informed consent was obtained from adults, parents, or the legally authorized representatives of the adolescent patients with DRE, before recruitment. This trial was registered with the Clinical Trial Registry of India [(CTRI); ref no. CTRI/2015/07/006048]. The report of the study follows the CONSORT guidelines.[23]

Participants

The detailed study flowchart is presented in Figure 1. Potential candidates were recruited from the pediatric and neurology epilepsy clinic of tertiary care referral center, New Delhi. We enrolled patients who met the following inclusion criteria: (1) age [10–55 years; adolescents (10 to ≤18 years) and adults (>18–55 years)], (2) DRE who had more than 2 seizures per month despite using at least 3 appropriate ASMs at their maximum tolerated doses,[21] and (3) agreed to regular follow-up and maintain their seizure-log. Patients were excluded in the following conditions: (1) surgical candidates, (2) an inborn error of metabolism, clinical suspicion of metabolic disorder[4]

Figure 1 Study Flowchart



ABCL = Adult Behavior Checklist; CBCL = Child Behavior Checklist.

known as chronic systemic disorder, (3) intake of any dietary therapy in the past, and (4) refusal to give consent. The screening procedure was performed with the assistance of the concerned clinicians (M.T. and S.G.). All patients underwent a 4-week observation period (week -4 to week 0 [the weeks are labeled -4 to 0] [run-in period]). Parents/caregivers were asked to maintain a daily seizure-log by recording the seizure type, duration, and frequency before enrollment. In the run-in period, no special dietary restrictions were advised. All baseline demographic details, biochemical investigations, and clinical details were collected in the paper-based standard case report form and then entered in an excel datasheet after the run-in period.

Randomization and Blinding

Patients were randomly assigned to either of the 2 groups—SDT plus MAD (intervention arm) or SDT alone (control arm). Computer-generated permuted blocks stratified by age group were used to generate a randomization list. Allocation concealment was performed using sealed and serially numbered opaque envelopes. These envelopes were prepared by a person not involved in the study (R.D.). A dietician (M.M.) was directly involved with the diet prescription, and patients and their caregivers were not blinded to the treatment, seizure frequency, and adverse events related to the treatment. The primary outcome assessor (K.K.) was blinded to the treatment allocation. Secondary outcome assessors (S.S. and A.N.), clinicians (M.T. and S.G.), other personnel (R.D.), and statisticians (R.M.P. and A.U.) were also blinded to the group allocation.

Intervention and Control

After the run-in period (−4 weeks), MAD therapy was started on an outpatient basis. Carbohydrate intake was restricted to 20 g/d. The detailed MAD protocol, a standard food exchange list, sample menu, and recipe booklet of standardized recipes including Indian recipe with either 2.5 g or 5 g carbohydrate are provided in eAppendix 2, links.lww.com/WNL/C564. High-fat and low-carbohydrate foods were encouraged; however, proteins were unrestricted. The diet was supplemented with multivitamins and minerals. Parents and caregivers were taught to maintain a daily-log of seizure count, meals consumed in a day, dietary intolerance, and urine ketones (thrice a day) using color-coded keto dipsticks. Average ketosis was calculated after 24 weeks of diet. Any adverse effects (i.e., constipation, diarrhea, weight loss, anorexia, lethargy, vomiting, sleep, disturbance, and hospitalization due to MAD) were noted as per parental/caregivers' interview at each visit at 15 days after the diet initiation, 3 months, and 6 months. Diet compliance was assessed based on carbohydrate consumption recorded in the daily food-log. Consumption of carbohydrates was calculated by using DietCal software.[24] Regular telephonic consultation was given weekly to ensure adherence to the diet.

The control group received a normal diet with no specific dietetic inputs. A trained dietician (M.M.) provided counseling to the caregivers along with age and weight-specific dietary charts based on the Recommended Dietary Allowance without any carbohydrate restriction. Prescribed ASMs were not changed during the study period in both the groups. The complete blood count and fasting lipid profile at baseline and follow-up at 6 months were measured. After 6 months, MAD was offered to those who wanted to follow the therapy.

Outcome Measurements

The primary outcome measure was the proportion of patients with greater than 50% seizure reduction (seizure frequency) from baseline to 6 months of follow-up in both groups. Seizure frequency was measured as the average seizures/week in the preceding 4-week period. Secondary outcome measures included tolerability and adverse effects of the diet as per parental/caregivers' reports. We also compared changes in biochemical parameters, QOL, and behavior from baseline to 6 months using QOL in Epilepsy Inventory for Adolescents-48 and QOL in Epilepsy Inventory-31 for adults. Both scales contain questions about health-related quality of life. Child Behavior Checklist and Adult Behavior Checklist scales were used for the behavioral assessments, which were completed by parents/caregivers in each visit. Patients were followed up and assessed using daily seizure-log, food-log, and ketone-log at 1 month, 3 months, and 6 months.

Safety

An independent, external data safety monitoring board (DSMB) (Acknowledgement section) reviewed all the patients' case record files periodically for their safety, efficacy, and adverse events. We followed DSMB guidelines.[25]

Statistical Analysis

The sample size was calculated based on an anticipated decrease of >50%[13,17] for the SDT plus MAD group as compared to the SDT group. Expecting a 30% response rate in the intervention arm and 10% in the control arm, power of 80%, and level of significance 5%, a sample size of 144 (72 each group) was calculated. Considering that 10% of patients might be lost to follow-up at 6 months, 160 patients were enrolled in total.

All statistical analyses were conducted using STATA (Version 14, Stata Corp; College Station, TX). Variables were checked for normal distribution, and frequency (percentage), mean, or median values were used as appropriate. Categorical and continuous variables were computed using the χ^2 test/Fisher exact and unpaired *t* test or the Wilcoxon-Mann-Whitney test. Owing to skewness, the variables (i.e., SGPT and triglycerides) were log-transformed and appropriate test applied. Log-binomial regression was used to see the effect of intervention after adjusting the variables, which were not comparable at baseline. For the primary outcome, percentage reduction on seizure frequency at 6 months was analyzed using effect size (mean or median difference) with 95% CI, and relative risk (RR with 95% CI) was also analyzed to see the risk between the 2 treatment groups. Intention-to-treat (ITT) analysis was performed by including all patients who were enrolled and assigned to an intervention. Patients who could not be contacted at 6 months and their outcome data were missing; the last observation carried forward method was used for primary and secondary outcome analyses. Per-protocol (PP) analysis was performed for patients who assigned the allocation and who adhered to the protocol at 6 months. The effect of diet on seizure reduction was analyzed using worst-case scenario analysis. Adverse effects of the intervention were summarized as number (percentage), and $p < 0.05$ was considered statistically significant.

The study protocol and statistical analysis plan are available in eSAP 1, links.lww.com/WNL/C563.

Results

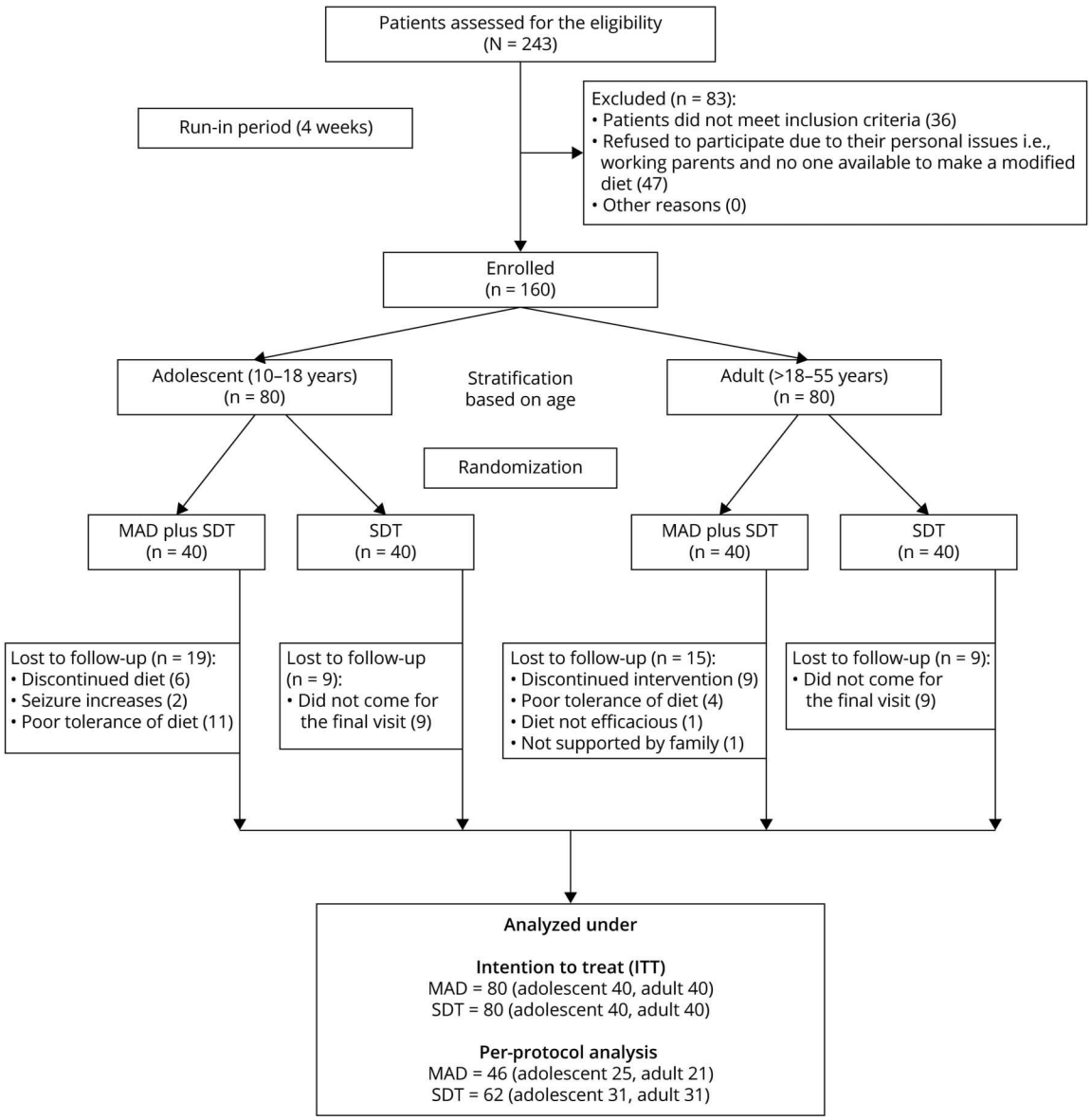
Baseline Characteristics

A total of 243 patients with DRE were screened for eligibility between August 2015 and April 2019; 160 patients were enrolled and randomly assigned to the intervention (n = 80) or control (n = 80) group. Fifty-two patients withdrew from the study, and the remaining 108 patients (46: intervention and 62: control) who completed 6 months of follow-up were included for the per-protocol analysis. The reasons for the patient's withdrawal and exclusion from the study are given in the CONSORT chart (Figure 2).

The demographic and clinical characteristics of the patients were comparable at baseline except for gender (p = 0.006) (Table 1). The median of the baseline seizure frequency was similar in both groups (intervention: 16.5 and control: 24.0; p = 0.88). Most of the patients had epilepsy of structural (MAD: 52.5%, SDT: 57.5%) or unknown etiology (MAD: 45.0%, SDT: 40.0%). Most patients were on at least 4 or more ASMs, the frequent of these being levetiracetam (MAD: 60.0%, SDT: 70.0%), valproate (MAD: 75.0%, SDT: 75.0%), and clobazam (MAD: 62.5%, SDT: 55.0%) (eFigure 2, links.lww.com/WNL/C564). Nonvegetarians were higher in both groups (MAD: 65.0%, SDT: 58.7%) as compared to vegetarians (MAD: 35.0%, SDT: 41.2%) (eFigure 3, links.lww.com/WNL/C564).

Urine ketone levels were moderate to high (40–80 mg/dL) throughout the study period. The mean morning and evening levels of urine ketosis among the patients in the diet group were

Figure 2 CONSORT Flowchart of the Study



MAD = modified Atkins diet; SDT= standard drug therapy.

Table 1 Baseline Demographic and Clinical Details of All Patients With DRE

Baseline characteristics	Intervention group (n = 80)	Control group (n = 80)	*p* Value
Age at enrollment (in years)[a]	19.5 ± 7.4	19.4 ± 7.1	0.92
Gender, n (%)			0.006
Male	64 (80)	48 (60)	
Female	16 (20)	32 (40)	
Weight (in kg)	58.9 ± 19.8	59.6 ± 19.9	0.81
BMI (kg/m^2)	22.5 ± 5.8	23.5 ± 6.2	0.28
Age at first seizure (in years) [median (IQR)]	5.5 (2.0–8.5)	6.5 (3–10)	0.28
Duration of epilepsy (in years)[a]	12.9 ± 6.3	11.7 ± 5.7	0.24
No. of seizures per month [median (IQR)]	37.5 (11.0–75.0)	26.5 (6.5–72.5)	0.10
No. of ASMs tried in the past months [median (mean ± SD)][a]	4 (4.0 ± 0.9)	4 (4.1 ± 0.9)	0.86
Seizure type (%)			0.31
Tonic	2 (2.5)	5 (6.3)	
Atonic	3 (3.7)	1 (1.2)	
Focal seizures	33 (41.3)	43 (53.8)	
Generalized tonic-clonic seizures	27 (33.7)	23 (28.7)	
Myoclonic jerks	10 (12.5)	5 (6.3)	
Multiple seizure types	5 (6.3)	3 (3.7)	
Etiology, n (%)			0.86
Structural	42 (52.5)	46 (57.5)	
Infectious	2 (2.5)	2 (2.5)	
Unknown	36 (45.0)	32 (40.0)	
Levels of biochemical parameters[a]			
Uric acid, μmol/L	4.3 ± 1.4	4.3 ± 1.3	0.99
SGOT, mmol/L	26.7 ± 9.9	26.1 ± 8.3	0.93
SGPT, mmol/L	30.6 ± 18.6	26.1 ± 10.5	0.13
Total cholesterol, mmol/L	170.0 ± 41.5	171.7 ± 40.5	0.79
LDL, mmol/L	103.3 ± 36.4	105.3 ± 35.6	0.73
HDL, mmol/L	49.7 ± 10.4	47.8 ± 16.5	0.39
Triglycerides, mmol/L	106.9 ± 54.3	115.4 ± 52.2	0.18
Quality of life[a]	44.1 ± 15.6	46.7 ± 15.2	0.29
Behavior problems (T scores)[a] (n = 49)	71.2 ± 6.3 (n = 23)	69.8 ± 9.1 (n = 26)	0.56

Abbreviations: IQR = interquartile range; intervention group = standard drug therapy (SDT) plus modified Atkins diet (MAD); control group = SDT alone; ASMs = antiseizure medications; BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
[a] Data are represented as mean ± SD.

58.3 ± 8.0 mg/dL and 62.2 ± 22.6 mg/dL, respectively, indicating satisfactory adherence to the diet. Baseline demographic and clinical details were obtained for adolescents and adults (eTables 1 and 2, links.lww.com/WNL/C564).

Primary and Secondary Outcomes

At the end of the study period, the proportion of patients with >50% seizure reduction from baseline was significantly higher in the intervention group (Table 2) as per both ITT

Table 2 Efficacy of Diet in Seizure Frequency at the End of Treatment (6 Months) in All Patients

Seizure reduction	Intervention group	Control group	Proportion difference (95% CI)	RR (95% CI)	*p* Value
A) ITT analysis [SDT plus MAD group (n = 80) and SDT group (n = 80)]					
[c]More than 50%	21 (26.2%)	2 (2.5%)	23.7 (13.5, 33.9)	10 (2.54, 43.3)	<0.001[a]
More than 90%	6 (7.5%)	0	7.5 (1.7, 13.3)	Undefined	0.028[b]
Complete seizure-free	4 (5%)	0	5.0 (0.2, 9.7)	Undefined	0.116
B) PP analysis [SDT plus MAD group (n = 46) and SDT group (n = 62)]					
[c]More than 50%	21 (45.7%)	2 (3.2%)	42.0 (27.3, 57.4)	14.2 (3.94, 57.35)	<0.001[a]
More than 90%	6 (13%)	0	13 (3.3, 22.7)	—	0.005[b]
Complete seizure-free	4 (8.7%)	0	8.7 (0.5, 16.8)	—	0.03[b]

[a] p Value < 0.005.
[b] $p < 0.05$.
[c] Primary outcome >50% seizure reduction.
Abbreviations: intervention group = standard drug therapy (SDT) plus modified Atkins diet (MAD); control group = SDT alone; ITT = intention to treat; PP = per protocol; RR = relative risk.

[intervention: 26.2%; control: 2.5%, p value: 0.001] and per-protocol analysis (intervention: 45.7%; control: 3.2%, p value: 0.001). It was also observed that >50% seizure reduction in the intervention group was 10 times more as compared to the control group (RR = 10; 95% CI 2.54, 43.3, $p = 0.001$). In the intervention group, 5.0% (ITT analysis) and 8.7% (PP analysis) of patients were seizure-free at the end of follow-up, whereas none of the patients were seizure-free in the control group. These differences in the seizure freedom rate were statistically significant as per the PP analysis ($p = 0.03$) and the ITT analysis (Table 2). The median (IQR) percentage reduction in seizure frequency from baseline was found to be significant ($p = 0.001$) in the intervention group [12.4 (−0.94–50.70)] as compared to the control group [0 (−56.08, 9.45)]. On adjusting variables (i.e., gender), there was 13.8 (95% CI 3.1, 62.6; $p = 0.001$; ITT analysis) and 24.4 (95% CI 5.24, 113.8, $p = 0.001$; PP analysis) times more seizure reduction (>50%) observed in the intervention group as compared to the control group. Furthermore, as per ITT analysis, the proportion of adult and adolescent patients having >50% seizure reduction and percentage change in seizure frequency was significantly higher ($p = 0.001$) in the intervention group as compared to the control group (eFigure4–7, links.lww.com/WNL/C564). As per PP analysis, significant improvement (57.1%; $p = 0.001$) in seizure reduction was most notable in the adult population of the intervention group vs control group (eTable 3, links.lww.com/WNL/C564).The worst-case scenario analysis revealed no significant improvement (>50% seizure reduction) between the intervention and control groups (eTable 4, links.lww.com/WNL/C564).

There were no significant differences ($p > 0.05$) in the mean scores of body weight, weight loss (eTable 5, links.lww.com/WNL/C564), and biochemical profiles between the 2 groups at 6 months (Table 3). There was no change in most biochemical parameters at 6 months on the diet when compared with the baseline in both groups (eFigure 8, A–G). The difference in the QOL and behavior scores was statistically significant ($p = 0.0005$ and $p = 0.015$, respectively) in the intervention group as compared to the control group at 6 months (Table 3).

A significant improvement (eTable 6, links.lww.com/WNL/C564) from baseline was noted in the mean score of QOL (baseline: 52.7 ± 11.6 and last follow-up: 58.7 ± 14.2; $p = 0.001$ [adult]; 35.5 ± 14.3 (baseline) and 45.4 ± 18.3 (follow-up); $p = 0.001$ [adolescent]) in the intervention group. No significant difference in QOL from baseline was found in adult patients of the control group, whereas significant deterioration was observed in adolescents (baseline: 41.3 ± 15.0 and 6-month follow-up: 33.8 ± 15.3; $p = 0.0001$). Most of the patients in the intervention group had clinically meaningful increase (6.0 points: adults and ~10 points: adolescents) in their overall QOL.

Total T scores on the Child Behavior Checklist/Adult Behavior Checklist scales indicated the possible behavior problems at the end of treatment. However, we obsedverd that the behavior problems normalized in the intervention compared to controls. The difference of the mean total behavior T score from baseline to follow-up [8.3, $p = 0.0069$ (adults); 3.7, $p = 0.03$ (adolescents)] in the intervention group while in the control group [−3.5, $p = 0.0179$ (adults); −0.06, $p = 0.95$ (adolescents)] (eTable 7, links.lww.com/WNL/C564).

Dietary adherence/compliance [median percentage (range)] was 91.07 (87.5–92.85) in the MAD group at 6 months (eFigure 9 and eTable 8, links.lww.com/WNL/C564). No significant adverse effects were observed in patients receiving MAD. However, 1 patient had weight loss; 2 patients had diarrhea (4.3%). The most common adverse effects were constipation, vomiting, diarrhea, lethargy, and anorexia, which resolved by dietary modifications (eTable 9, links.lww.com/WNL/C564).

This study provides Class III evidence that the MAD increases the probability of seizure reduction in adolescents and adults with DRE.

Table 3 Treatment Effect on the Secondary Outcome Variables at the End of the 6 Months in All Patients

Outcome	Intervention group (n = 80)	Control group (n = 80)	Difference (95% CI)	*p* Value
BMI (kg/m^2)	22.5 ± 5.3	23.6 ± 5.8	−1.13 (−2.86, 0.60)	0.19
Body weight (kg)	58.8 ± 18.5	59.9 ± 18.8	−1.10 (-6.94, 5.46)	0.70
Weight loss[d]	1.9 ± 0.1	1.9 ± 0.1	−0.01 (−0.05, 0.03)	0.56
Uric acid, μmol/L	4.6 ± 1.5	4.3 ± 1.4	0.35 (−0.11, 0.80)	0.13
SGOT, mmol/L	27.5 ± 11.6	27.0 ± 10.5	0.62 (−2.22, 3.47)	0.66[a]
SGPT, mmol/L	33.8 ± 25.3	28.5 ± 16.5	5.34 (−1.34, 12.02)	0.13[a]
Total cholesterol, mmol/L	177.3 ± 35.3	173.6 ± 37.1	3.73 (−7.56, 15.04)	0.51
LDL, mmol/L	110.4 ± 34.0	108.0 ± 29.8	2.37 (−7.62, 12.36)	0.63
HDL, mmol/L	50.5 ± 14.2	49.4 ± 15.0	1.06 (−3.49, 5.63)	0.64
Triglycerides, mmol/L	108.3 ± 58.1	112.1 ± 45.4	−3.81 (−20.10, 12.46)	0.19
Quality of life	52.1 ± 17.6	42.5 ± 16.4	9.59 (4.26, 14.92)	**0.0005**[c]
Behavior problems (T scores)	65.6 ± 7.9	71.4 ± 8.1	−5.77 (−10.39, −1.16)	**0.015**[b]

[a] *p* Value given using the nonparametric test.
[b] *p* Value < 0.05.
[c] *p* Value < 0.0005.
[d] Categorical variables.
Data are represented as mean ± SD.
Abbreviations: intervention group = standard drug therapy (SDT) plus modified Atkins diet (MAD); control group = SDT alone; BMI = body mass index; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Discussion

In this RCT, we investigated the effect of an add-on MAD therapy on seizure reduction in adolescents and adults with DRE. MAD was found to be more efficacious for reducing seizure frequency than SDT alone. 26.2% of patients had >50% seizure reduction in the intervention group compared with the control group. The result of the present RCT agrees with previous findings,[13,15,21,16] and the observed seizure reduction was comparable with previously published reports on MAD with DRE,[18,17,26,27] which suggest that MAD for DRE in adults and adolescents is well tolerated; however, data on MAD treatment in adults are limited.[21,22] The present cohort demonstrated a lesser reduction in seizure frequency on MAD as compared to another study.[17] in adults and in children.[13,15,16] This difference could be partially accounted for by the fact that the MAD was started late in our clinical setting. In our study, patients had a duration of epilepsy of more than 10 years on an average and had a median of 37.5 seizures per month in the intervention group and 26.5 in the control group; after having tried an average of 4 different ASMs, most presented with structural (bilateral hypoxic ischemic changes) etiology.

An RCT performed in adults in Iran reported a 35.5% responder (>50% seizure reduction) vs no responder in the control group.[21] Another study could not detect a decrease in seizure frequency.[22] Both these studies had a relatively low number of participants and a shorter follow-up period.

Our study was conducted in a larger cohort, including adolescents and adults, with a 6-month follow-up. On subgroup analysis, >50% seizure reduction was found in 32.5% of the adult population. Use of exchange list and recipe booklet helped in the initiation of MAD with the flexibility of meal choices and ease of administration, hence an ideal treatment option for low-resource settings.

On PP analysis, we have found similar efficacy of MAD on seizure reduction (45.7%), which is comparable with the observational study[10] in contrast to other studies reported.[11,21] Worst-case scenario analysis for the missing data was performed, and we observed that there was no significant difference between intervention and control groups for favorable outcome (>50% seizure reduction) and unfavorable outcome (≤50% seizure reduction). The analysis was performed because of the higher dropouts in our study.[28,29]

Reduction in seizure frequency and QOL improved significantly for the entire population in adults and adolescents in the intervention group. Improvement in nonseizure domains (QOL) was observed in the intervention group as compared to the control group (r = 0.17, p = 0.027), which was significant. The reasons may be probably fewer and lower frequency of seizures that visibly enhanced quality of life. Many other investigators have reported a better QOL without any standard scales, including recent studies on a diet.[30-32]

Of interest, we have not found a significant difference in weight loss (>10%) in the diet group, which is supported by previous

studies.[21,18] However, weight loss is more common in adults as reported elsewhere.[17] In our study, there was no change in most biochemical parameters at 6 months on the diet when compared with the baseline. None of the patients had hyperuricemia. However, one study reported an increase in the lipid profile over the first 3 months of the diet; these values normalized within a year of treatment, including in patients treated with MAD for more than 3 years.[33] Longer follow-up data are required to assess the change in the lipid profile in adults on MAD. Other studies have reported some side effects (i.e., gastrointestinal complaints, dyslipidemias, constipation, and weight loss).[21,34,27] Kidney stones[31] are a common diet-induced problem in children in the case of diets. None in our study reported renal stones possibly because of adequate liquid consumption during the dietary intervention. Increased seizure frequency was reported in 1 patient. The seizure aggravation in this patient is hard to explain. Others have reported an aggravated seizure frequency when on diet.[22,27]

We found 32.5% dropouts because of lack of efficacy, nonacceptability of diet, and inability to follow-up (around COVID time). Other reports also show a variation in the dropout rate between 7% and 50%.[13,15,21,35,36] We also assessed QOL and behavior using structural scales in the whole cohort along with diet compliance by an expert dietician (M.M.), which added strength to our study. Our study has few limitations; blinding could not be performed with the individuals and dieticians because it required close interaction with patients. Because of resource constraints, the behavior could be assessed only in a subset of patients and not the entire cohort. Compliance to diet is more challenging in long term, especially in adults. However, the tolerance of MAD is much better than high-fat diet (classical KD).[15] Daily-logs maintained by caregivers could have missed some seizures, including nocturnal seizures, and runs the risk of introducing subjective errors. A multicentric trial including all primary dietary options such as KD, MAD, and LGIT in older adults with DRE having outcomes of seizure reduction, adverse events, and cognitive effects is required to further validate the results. In addition, a selection bias cannot be ruled out because this was a single-center study.

MAD therapy was efficacious, feasible, and well tolerated, with better compliance along with seizure reduction in adolescents and adults with DRE. Reduction of seizure frequency reflected in the improvement of the quality of life in all patients in the intervention group as compared to the control group. Future studies would be needed to identify neurophysiologic and genetic biomarkers associated with MAD response, which may have implications for clinical care by encouraging targeted and earlier use of the MAD and also individualized risk-benefit analysis of the therapeutic diet, which can provide alternative therapy to standard care treatment.

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Mala Manral, PhD	Department of Neurology, All India Institute of Medical Sciences, New Delhi	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Rekha Dwivedi, PhD	Department of Neurology, All India Institute of Medical Sciences, New Delhi	Drafting/revision of the manuscript for content, including medical writing for content
Sheffali Gulati, MD, DM	Department of Paediatrics, All India Institute of Medical Sciences, New Delhi	Drafting/revision of the manuscript for content, including medical writing for content; helped in writing of the manuscript
Kirandeep Kaur, PhD	Department of Neurology, All India Institute of Medical Sciences, New Delhi	Drafting/revision of the manuscript for content, including medical writing for content
Ashima Nehra, PhD	Department of Neuropsychology, All India Institute of Medical Sciences, New Delhi	Drafting/revision of the manuscript for content, including medical writing for content
Ravindra Mohan Pandey, PhD	Department of Biostatistics, All India Institute of Medical Sciences, New Delhi	Analysis or interpretation of data; revision of manuscript writing
Ashish Datt Upadhyay, PhD	Department of Biostatistics, All India Institute of Medical Sciences, New Delhi	Analysis or interpretation of data; revision of manuscript writing

Appendix *(continued)*

Name	Location	Contribution
Savita Sapra, PhD	Department of Paediatrics, All India Institute of Medical Sciences, New Delhi	Drafting/revision of the manuscript for content, including medical writing for content; revision of the manuscript
Manjari Tripathi, MD, DM	Department of Neurology, All India Institute of Medical Sciences, New Delhi	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; support for research grant

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