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Real-World Preliminary Experience With Responsive Neurostimulation in Pediatric Epilepsy: A Multicenter Retrospective Observational Study

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BACKGROUND: Despite the well-documented utility of responsive neurostimulation (RNS, NeuroPace) in adult epilepsy patients, literature on the use of RNS in children is limited.
OBJECTIVE: To determine the real-world efficacy and safety of RNS in pediatric epilepsy patients.
METHODS: Patients with childhood-onset drug-resistant epilepsy treated with RNS were retrospectively identified at 5 pediatric centers. Reduction of disabling seizures and complications were evaluated for children (<18 yr) and young adults (>18 yr) and compared with prior literature pertaining to adult patients.
RESULTS: Of 35 patients identified, 17 were <18 yr at the time of RNS implantation, including a 3-yr-old patient. Four patients (11%) had concurrent resection. Three complications, requiring additional surgical interventions, were noted in young adults (2 infections [6%] and 1 lead fracture [3%]). No complications were noted in children. Among the 32 patients with continued therapy, 2 (6%) achieved seizure freedom, 4 (13%) achieved ≥90% seizure reduction, 13 (41%) had ≥50% reduction, 8 (25%) had <50% reduction, and 5 (16%) experienced no improvement. The average follow-up duration was 1.7 yr (median 1.8 yr, range 0.3-4.8 yr). There was no statistically significant difference for seizure reduction and complications between children and young adults in our cohort or between our cohort and the adult literature.
CONCLUSION: These preliminary data suggest that RNS is well tolerated and an effective off-label surgical treatment of drug-resistant epilepsy in carefully selected pediatric patients as young as 3 yr of age. Data regarding long-term efficacy and safety in children will be critical to optimize patient selection.

KEY WORDS: Brain stimulation, Children, Closed-loop, Eloquent cortex, Multifocal epilepsy, Neuromodulation

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Drug-resistant epilepsy (DRE) impacts ~1/3 of patients who experience partial-onset seizures.[1] The responsive neurostimulation system (RNS, NeuroPace, Mountain View, California) is a cranially implanted, closed-loop, brain-responsive stimulation system, currently approved by the U.S. Food and Drug Administration for patients with DRE despite an adequate trial of ≥2 antiepileptic medications who are ≥18 yr of age and have 1 or 2 unresectable seizure foci. The system has 2 ports allowing connection of two 4-contact leads (depth and/or subdural cortical strip leads). Additional leads may be implanted and left unconnected for future use. The system continues to sense electrocorticographic activities and can be programmed to deliver stimulation customized along multiple parameters in response to specific electrocorticographic patterns. Prior studies demonstrated the benefits and safety of RNS in patients of age 18 to 70 yr.[2-6]

Despite well-documented utility in adult epilepsy patients, literature on the use of RNS

ABBREVIATIONS: DRE, drug-resistant epilepsy; **RNS,** responsive neurostimulation; **SEEG,** stereoelectroencephalography; **VNS,** vagus nerve stimulation

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(NeuroPace) in children is limited.[7-9] We undertook a multicenter study to retrospectively assess the efficacy and safety of RNS at multiple pediatric epilepsy centers in a diverse, real-world pediatric population.

METHODS

Study Design and Setting

This study was a multicenter retrospective cohort study across 5 academic pediatric epilepsy centers in the United States. The study centers include (1) UCLA Mattel Children's Hospital in Los Angeles, California; (2) Primary Children's Hospital in Salt Lake City, Utah; (3) Lucille Packard Children's Hospital Stanford in Palo Alto, California; (4) Nicklaus Children's Hospital in Miami, Florida; and (5) Children's Hospital Colorado in Aurora, Colorado. This study was approved by the institutional review board at each participating center with a waiver of informed consent.

Participants and Perioperative Management

We included consecutive patients who underwent RNS (NeuroPace) implantation at the participating pediatric epilepsy centers. All patients with a history of childhood-onset DRE who underwent RNS implantation before April 2020 were identified. Patients who had a history of prior epilepsy surgery and/or who had concurrent partial resection of a presumed epileptogenic zone were considered eligible for the study. Patients who had 1 functional/connected RNS lead targeting the thalamus were also considered eligible, but those who had both functional/connected leads targeting the thalamus (ie, an RNS system used in place of a deep brain stimulation device) were excluded. All identified patients underwent RNS implantation after a standard presurgical evaluation and discussion in a multidisciplinary epilepsy conference.

Despite relatively minor institutional differences (eg, duration of perioperative antibiotics), all patients in this study, both children (<18 yr) and young adults (>18 yr), were managed similarly during the perioperative period at each participating center, without any differences in the technical aspects of RNS implantation (eg, 4 centers delayed RNS implantation following stereoelectroencephalography [SEEG] evaluation; 3 centers used intraoperative Bacitracin irrigation and 2 centers used intraoperative Vancomycin powder; all centers implanted the entire RNS system [leads and generator] during 1 surgery). In general, no special precautions (other than avoiding contact sports) were taken postoperatively to reduce the risk of device damages.

Variables and Outcomes

The following clinical variables were collected: clinical history, results of presurgical workups, surgical details, complications (ie, procedure- or device-related adverse events resulting from RNS implantation or use and resulting in previously unplanned surgery), latest stimulation parameters, side effects from RNS therapy, and seizure outcomes at the time of last follow-up.

Two complementary methods were used to estimate seizure outcome: estimated seizure reduction and categorical outcome. Baseline seizure frequency and seizure outcome were defined as the number of disabling seizures occurring in the 3-mo period before RNS intervention or in the 3-mo period before most recent follow-up, respectively (% reduction = [# seizures before RNS implantation – # seizures after RNS implantation]/# seizures before RNS implantation *100). Each patient was placed into 1 of 5 categorical outcomes: (1) free of disabling seizures; (2) ≥90% reduction of disabling seizures; (3) ≥50% but <90% reduction of disabling seizures; (4) <50% but some noticeable reduction of disabling seizures; or (5) no improvement. Collectively, "responders" were defined as patients with ≥50% reduction of disabling seizures (categories 1-3), and "super-responders" as those with ≥90% reduction of disabling seizures (categories 1 and 2). Additionally, qualitative improvement in disabling seizures was noted.

Study Size

Given the rarity of RNS use in pediatric patients, we aimed to recruit as many participants as possible from the participating centers. No sample size calculation was performed.

Statistical Methods

The baseline characteristics of the participants were summarized using descriptive statistics. Continuous variables were reported using means, standard deviations, and ranges. Categorical variables were presented using frequencies and percentages. Participants were stratified into 1 of the 2 cohorts according to age at the time of RNS implantation (<18 yr and ≥18 yr) and compared accordingly. The Wilcoxon-Mann-Whitney test was used to assess differences in continuous variables. The Fisher exact test was used to identify significant differences in binomial categorical variables, while the chi-squared test was used for the assessment of multinomial categorical variables. When comparing the results with published literature, an unpaired *t*-test was used for continuous variables and the Fisher exact was used for categorical variables. A 2-sided *P*-value ≤ .05 was used as the threshold for statistical significance in all analyses. All statistical analyses were performed in RStudio (RStudio Inc., Version 1.2.1335).

RESULTS

Participants and Descriptive Data

A total of 35 patients (mean age at RNS (NeuroPace) implant 16.6 ± 5 yr, range 3-25 yr; 34% female) were included in the study (Figure 1, Table 1), including 17 patients <18 yr at the time of RNS implantation (mean age 12.6 ± 3.9 yr, range 3-17 yr; 24% female) (Figure 2). The average duration of epilepsy before RNS implantation was 9.9 ± 5.4 yr. Previous interventions included focal resection in 10 patients (28.6%) and vagus nerve stimulation (VNS) therapy in 4 patients (11.4%), with the

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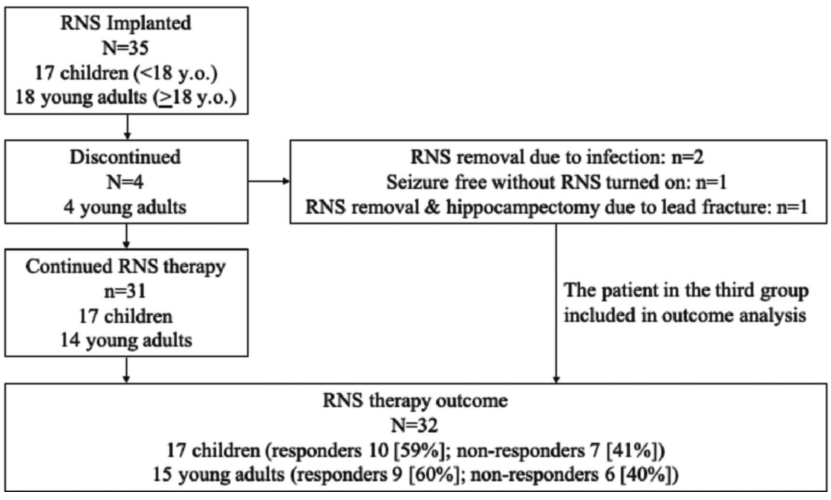

FIGURE 1. *Patient flow chart. A total of 35 patients underwent RNS (NeuroPace) implantation in this series. The outcome of RNS therapy was assessed for 32 patients who received RNS therapy, excluding 2 patients with wound infection requiring RNS removal and 1 patient who achieved seizure freedom without RNS therapy. The outcome for a patient who initially received RNS therapy but subsequently underwent RNS removal and hippocampectomy due to a lead fracture was assessed at the time of the most recent follow-up before the RNS removal.*

low rate of prior VNS therapy partially reflecting the focal (up to 2) nature of epilepsy in these patients (thus candidates for RNS therapy).

All patients underwent invasive intracranial recordings before RNS implantation: SEEG alone in 15 patients (42.9%), craniotomy for placements of subdural cortical electrodes with/without depth electrodes in 14 patients (40.0%), and both methods in separate monitoring sessions in 6 patients (17.1%). Eighteen patients (51.4%) had an RNS system implanted at completion of the invasive recording, typically concurrent with the reoperative craniotomy and electrode removal.

The most common indication for use of RNS (Table 1) was an epileptogenic zone involving primary motor/sensory area (13 patients, 37.1%). Some patients had multiple indications. The number of electrodes placed ranged from 2 to 4 (mean 2.7, median 2); bilateral electrodes were placed in 7 cases (20.0%). The average follow-up duration was 1.7 ± 1.0 yr (0.3-4.8 yr). There were no significant differences in the evaluated variables between the age subgroups.

Adverse Events and Complications

There were 9 adverse events and complications (Table 2). Five patients experienced side effects related to stimulation (see Table 2 for details). Two patients required surgical wound washout and removal of the RNS system because of infection. Lead fracture occurred in 2 patients (5.7%): in 1 patient, ≥50% seizure reduction was achieved initially, but lead fracture occurred ~2 yr after surgery, presumably as a result of a fall unrelated to seizures. Because of progressively diminishing verbal memory, removal of the RNS and left hippocampectomy were eventually performed. The second patient with a lead fracture achieved seizure freedom; high impedance was noted in the less active lead 7 mo after the implant, without requiring a surgical intervention. There were no statistically significant differences in the incidence of adverse events and complications between the age subgroups. No patients under 18 yr of age experienced complications requiring additional surgical interventions.

Outcome Data

One patient who underwent right frontal resection at the time of RNS placement with 2 strip electrodes placed over the ipsilateral primary motor area achieved seizure freedom without having the RNS system turned on. This patient and 2 patients explanted due to device infection were excluded from the outcome analysis (Table 3). Of the 32 patients (91.4%), 2 patients (6%) achieved freedom from disabling seizures, 4 patients (13%) achieved ≥90% freedom, 13 patients (41%) had ≥50% freedom, 8 patients (25%) had <50% reduction of disabling seizures, and 5 patients (16%) experienced no improvement. For the subgroup of 17 patients under the age of 18 yr, 1 patient (6%) achieved freedom from disabling seizures, 3 patients (18%) achieved ≥90% freedom, 6 patients (35%) had ≥50% freedom, 3 patients (18%) had <50% reduction of disabling seizures, and 4 patients (24%) experienced no improvement. Many patients and/or family members noted qualitative improvement in the nature of their seizure events (decreased intensity or decreased

TABLE 1. Baseline and Demographic Characteristics

Characteristic	All patients (n = 35)	Patients <18 yr (n = 17)	Patients ≥ 18 yr (n = 18)	*P*-value
Age at time of RNS (yr)	16.6 ± 5 (3-25)	12.6 ± 3.9 (3-17)	20.3 ± 2 (18-25)	<.001[a]
Age at seizure onset (yr)	6.7 ± 4.5 (0.5-18)	5.7 ± 3.2 (2-13)	7.6 ± 5.4 (0.5-18)	.371
Epilepsy duration before RNS (yr)	9.9 ± 5.4 (1-20)	7.0 ± 4.0 (1-13.5)	12.7 ± 5.3 (4-20)	.003[a]
Female	12 (34%)	4 (24%)	8 (44%)	.289
Patient weight at time of RNS (kg)	59.8 ± 19.4 (17.5-102.9)	53.8 ± 25.4 (17.5-102.9)	65.4 ± 8.6 (52.2-87.7)	.049[a]
Epilepsy syndrome				.486
Multifocal	10 (29%)	6 (35%)	4 (22%)	
Focal	23 (66%)	11 (65%)	12 (67%)	
Generalized	1 (3%)	0	1 (6%)	
Known genetic abnormality, name (n)[b]				.405
CHRNB2	1 (2.9%)	1 (5.9%)	0	
Lennox-Gastaut	1 (2.9%)	0	1 (5.6%)	
Pierre-Robin	1 (2.9%)	1 (5.9%)	0	
RELN + CACNA1H	1 (2.9%)	0	1 (5.6%)	
Hx of infantile spams	2 (6%)	0	2 (11%)	.486
AEDs trialed				
Previously trialed and discontinued	4.4 ± 2.9 (1-11)	4.1 ± 2.7 (1-10)	4.7 ± 3.2 (1-11)	.581
In use at time of RNS	2.9 ± 1.2 (1-6)	2.7 ± 1.4 (1-6)	3.1 ± 1.1 (1-5)	.111
Structural abnormality on MRI[c]				.708
Cortical dysplasia	6 (17%)	4 (24%)	2 (11%)	
Mesial temporal sclerosis	3 (9%)	1 (6%)	2 (11%)	
Gliosis	2 (6%)	1 (6%)	1 (6%)	
Focus of T2 signal change	5 (14%)	2 (12%)	3 (17%)	
Other	1 (3%)	0	1 (6%)	
Other phase I workups performed				
vEEG	35 (100%)	17 (100%)	18 (100%)	1.000
PET	30 (86%)	15 (88%)	15 (83%)	1.000
MEG	10 (29%)	5 (29%)	5 (28%)	1.000
Concordance if ≥ 2 used	22 (67%)	9 (56%)	13 (77%)	.282
Prior therapeutic surgery				
Focal resection	10 (29%)	2 (12%)	8 (44%)	.059
Vagus nerve stimulation	4 (11%)	0	4 (22%)	.104
Corpus callosotomy	1 (3%)	0	1 (6%)	1.000
Other	1 (3%)	0	1 (6%)	1.000
Phase II monitoring				
SEEG	15 (43%)	9 (53%)	6 (33%)	.314
Craniotomy (cortical with/without depth electrodes)	14 (40%)	4 (24%)	10 (55%)	.086
Both	6 (17%)	4 (24%)	2 (11%)	.402
Important technical differences				
Resection at the time of RNS	4 (11%)	0	4 (22%)	.104
RNS at the time of SEEG and/or subdural electrode removal	18 (51%)	7 (41%)	11 (61%)	.318
Days of IC monitoring just prior to RNS[d]	6.4 ± 3.1 (3-14)	7.3 ± 3.9 (4-14)	5.8 ± 2.5 (3-11)	.513
Indication for RNS				
Bitemporal	5 (14%)	2 (12%)	3 (17%)	1.000
Multifocal	9 (26%)	5 (29%)	4 (22%)	.711
Primary motor/sensory	13 (37%)	5 (29%)	8 (44%)	.489
Language	4 (11%)	2 (12%)	2 (11%)	1.000
Preserved memory	7 (20%)	4 (24%)	3 (17%)	.691
Difficult-to-access region (eg, insula)	1 (3%)	0	1 (6%)	1.000
Total RNS leads (per patient): implanted/connected	2.7 ± 0.9 (2-4)/2 ± 0	2.5 ± 0.8 (2-4)/2 ± 0	2.8 ± 0.9 (2-4)/2 ± 0	.220/1.000
Depth implanted	1.2 ± 1.1 (0-4)	1.3 ± 1.1 (0-4)	1.2 ± 1.2 (0-4)	.726

TABLE 1. Continued

Characteristic	All patients (n = 35)	Patients <18 yr (n = 17)	Patients ≥ 18 yr (n = 18)	*P*-value
Depth connected	1.1 ± 0.9 (0-2)	1.1 ± 0.9 (0-2)	1.1 ± 0.9 (0-2)	1.000
Strip implanted	1.4 ± 1.4 (0-4)	1.2 ± 1.2 (0-4)	1.7 ± 1.6 (0-4)	.400
Strip connected	0.9 ± 0.9 (0-1)	0.9 ± 0.9 (0-2)	0.9 ± 0.9 (0-2)	1.000
Unilateral (vs bilateral)	28 (80%)	14 (82%)	14 (78%)	1.000
Follow-up duration (yr)	1.7 ± 1.0 (0.3-4.8)	1.3 ± 0.7 (0.3-2.6)	2.0 ± 1.2 (0.3-4.8)	.133

RNS, responsive neurostimulation; IC, intracranial monitoring; vEEG, video electroencephalography; MEG, magneto encephalography; PET, positron emission tomography; SEEG, stereo-EEG; AED, antiepileptic drug.

[a]Statistically significant with *P*-value ≤ 0.05.

[b]Genetic testing was not performed on all patients; however, 4 patients were found to harbor single nucleotide polymorphisms or demonstrate a clinical syndrome associated with epilepsy.

[c]Structural abnormalities noted on MRI did not necessarily localize to the suspected epileptogenic cortex and did not include MRI changes that were postsurgical in nature. "Other" refers to one patient with a convexity arachnoid cyst remote from the suspected region of seizure onset.

[d]The number of days for intracranial monitoring prior to RNS implantation surgery is reported as a possible risk factor for infection. This refers to cases in which RNS was implanted at the time of removal of intracranial electrodes after completion of phase II intracranial monitoring in the same operation. There was a trend toward increased utilization of craniotomy during phase II monitoring in young adults (55%) vs children (24%). Subsequently, to avoid performing multiple craniotomies, RNS implantation at the time of electrode removal was performed more often in young adults (61%) vs children (41%).

Data reported as mean ± SD (min–max) or n (%).

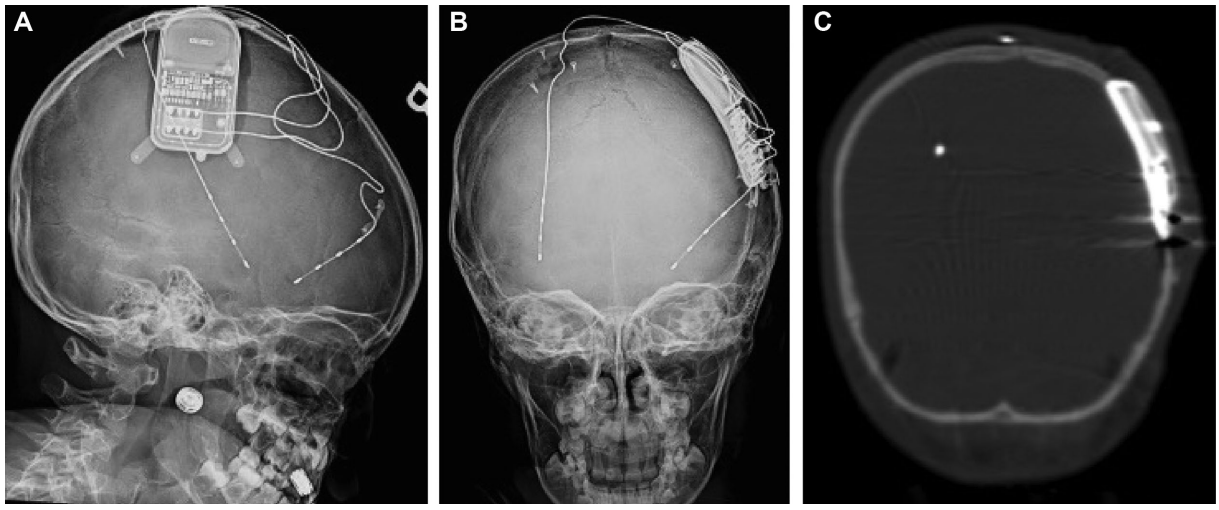

FIGURE 2. A-C, *RNS (NeuroPace) placement in a 3-yr-old patient with multifocal seizure foci. The patient, who had been noted to have seizure foci involving the right insula and left inferior frontal area, underwent uncomplicated RNS placement with 2 depth leads targeting those areas.* **A**, *Lateral and* **B**, *anterior-posterior postoperative X-ray films show appropriate placement of the RNS device.* **C**, *Coronal postoperative CT demonstrated appropriate placement of the RNS neurostimulator device along the contour of the left parietal area.*

duration). There was no significant difference in quantitative and qualitative effectiveness of RNS therapy between the age subgroups (Table 3).

Comparison With Previous Studies

The baseline characteristics, adverse events and complications, and seizure outcomes from this series were compared with the results from the landmark randomized trial performed on an adult population by Heck et al[2] (Table 4). There were statistically significant differences in the variables expected based on the age differences (eg, age at RNS implantation, epilepsy duration), as well as the percentage of the patients who underwent intracranial recordings before RNS implantation ($P < .001$). However, there were no statistically significant differences in the risks of adverse events and complications or in seizure outcome.

TABLE 2. Adverse Events and Complications That Resulted from Implantation and/or Use of RNS (NeuroPace) System

	All patients (n = 35)	Patients <18 yr (n = 17)	Patients ≥ 18 yr (n = 18)	*P*-value
Adverse events				
Bothersome side effects related to stimulation[a]	5 (14%)	3 (18%)	2 (11%)	.658
Lead fracture not requiring revision	1 (3%)	1 (6%)	0	.486
Complications (events resulting in unplanned surgical intervention)				
Infection[b]	2 (6%)	0	2 (11%)	.486
Hematoma evacuation	0	0	0	1.000
Hardware revision				
Hardware failure[c]	1 (3%)	0	1 (6%)	1.000
Lead revision due to misplacement	0	0	0	1.000

RNS, responsive neurostimulation.

[a]One patient experienced intermittent, at times painful muscle spasms and dysesthetic pain in the right upper extremity. Two patients could not tolerate higher current on depth electrode stimulation without a painful sensation. One patient experienced tingle and vibration to right foot, a lower-extremity burning sensation, and occasional shock-like sensation in the right arm and leg. One patient experienced left eye twitching.

[b]Both cases of infection required hardware removal with antibiotic treatment. No cases of infection were treated with antibiotics alone without hardware removal. Both these 2 patients with infection requiring hardware removal were ≥ 18 yr old. Both patients underwent craniotomy for electrode placement. One of these patients underwent 9 d and the other 4 d of intracranial monitoring just prior to RNS implantation.

[c]There was one instance of lead fracture 2 yr after implantation likely secondary to head trauma from an accidental mechanical fall, not related to seizures. Since the time of implantation, the patient's verbal memory had declined, so the decision was made to remove the RNS system and perform a hippocampectomy.

TABLE 3. Outcomes for Patients Comparing a 3-Month Follow-up Period After RNS (Neuropace) With a 3-Month Presurgical Period

Description	All patients (n = 32)	Patients <18 yr (n = 17)	Patients ≥ 18 yr (n = 15)	*P*-value
Estimated % reduction in seizures	54.7 ± 33.4 (0-100)	54.4 ± 36.1 (0-100)	55.2 ± 31.2 (0-86)	.894
Qualitative outcome				
Decreased intensity	16 (50%)	11 (65%)	7 (47%)	.477
Decreased duration	13 (41%)	9 (53%)	6 (40%)	.502
Less frequent	20 (63%)	9 (53%)	12 (80%)	.148
Lower incidence of secondary generalization	10 (31%)	5 (29%)	6 (40%)	.712
Seizure outcome category[a]				
Free of disabling seizures	2 (6%)	1 (6%)	1 (7%)	1.000
≥90% reduction	4 (13%)	3 (18%)	1 (7%)	.603
≥50% but < 90% reduction	13 (41%)	6 (35%)	7 (47%)	.720
<50% but some reduction	8 (25%)	3 (18%)	5 (33%)	.424
No improvement	5 (16%)	4 (24%)	1 (7%)	.338
Stimulation parameters[b]				
Current (mA)	4 ± 2.1 (0.5-7)	3.7 ± 2.2 (0.5-7.0)	4.4±2 (1-7)	.359
Frequency (Hz)	189.7 ± 31.7 (75-200)	185.7 ± 38.7 (75-200)	194 ± 20.8 (125-200)	.648
Pulse width (μS)	160 ± 0	160 ± 0	160 ± 0	1.000
Burst duration (mS)	100 ± 0	100 ± 0	100 ± 0	1.000
Charge density ($\mu C/cm^2$)	2.2 ± 0.9 (0.5-3.5)	2 ± 1 (0.5-3.5)	2.4 ± 0.8 (1-3.5)	.214

RNS, responsive neurostimulation.

[a]This categorical outcome is determined by the treating physician for each patient even if the information available is not sufficient to count the recent and baseline seizures over 3 mo and calculate % seizure reduction.

[b]Stimulation parameters are taken from the most recent clinical visit. Complete data for stimulation parameter were available for 29 out of 32 patients.

Mean ± SD (min–max) or n (%).

DISCUSSION

Key Results

The efficacy and safety of RNS (NeuroPace) have been well described in adults (≥18 yr),[2-5] but the literature describing the safety and efficacy in children is limited.[7-9] With the growing use of RNS in pediatric centers, there is a critical need to understand the efficacy and safety of RNS therapy in children. Our collective preliminary experience suggests that RNS is effective in reducing the number of disabling seizures in the majority of pediatric patients, is well tolerated, and can be performed with acceptable safety. The efficacy and safety profiles

TABLE 4. Comparison With Published Literature

	Heck et al cohort	This cohort	*P*-value
Baseline characteristics			
Number of patients included	97	35	
Age in years at time of RNS	34.0 ± 11.5 (18-60)	16.6 ± 5 (3-25)	<.001[a]
Epilepsy duration in years before RNS	20.0 ± 11.2 (2-57)	6.7 ± 4.5 (0.5-18)	<.001[a]
Female	47 (48%)	12 (34%)	.169
AEDs at time of RNS	2.8 ± 1.3 (1-8)	2.9 ± 1.2 (1-6)	.691
Prior therapeutic surgery	34 (35%)	13 (37%)	.839
Prior EEG monitoring with intracranial electrodes	63 (65%)	35 (100%)	<.001[a]
Adverse events			
Number of patients included	191	35	
Infection	7 (4%)	2 (6%)	.633
Device lead revision	7 (4%)	1 (3%)	1.000
Device lead damage	5 (3%)	2 (6%)	.297
Outcomes			
Number of patients included	183	32	
Free of disabling seizures	16 (9%)	2 (6%)	1.000
50% or greater reduction of disabling seizures ("responders")	99 (54%)	19 (59%)	.701
Some reduction of disabling seizures	150 (82%)	25 (78%)	.624

RNS, responsive neurostimulation.
[a]Statistically significant with *P*-value ≤ .05.
Data reported as mean ± SD (min-max) or n (%).

noted in this study are comparable with those in the adult literature.

Interpretation

With respect to the efficacy of RNS, the number of disabling seizures was reduced in 27 of 32 patients (84.4%). In particular, 19 of 32 patients (59.4%) achieved ≥50% reduction ("responders"), including 6 patients (18.8%) who achieved ≥90% reduction ("super-responders"). For the subgroup of the 17 patients under the age of 18 yr, the responder rate and super-responder rate were 58.8% and 23.5%, respectively. The responder rate in this pediatric series with the median follow-up duration of 1.8 yr is comparable with the results from the initial randomized study of the RNS system in adults (ie, 44% at 1 yr and 55% at 2 yr).[2] The responder rate was not as high as the rates reported in a more recent multicenter adult RNS series (ie, 66% at 1 yr and 77% at 2 yr),[10] which could be at least partially explained by limited experience with pediatric RNS, the small number of patients included in the current study, and the diversity and complexity unique to pediatric epilepsy (eg, all the patients in this study required intracranial recordings, more extratemporal cases, diverse pathologies). Given the known improvement of seizure control over time with programming optimization and likely neuromodulatory effects of long-term stimulation therapy,[2,5,10] seizure control may continue to improve in our cohort with longer follow-ups.

The rate of adverse events and complications in this series was comparable with those reported in the prior adult RNS studies. Three patients experienced clinically significant complications (2 patients with infection and 1 patient with a lead fracture) requiring surgical interventions. These 3 patients were all ≥18 yr at the time of RNS implant. None of the patients under 18 yr of age experienced complications.

Complexity and Diversity of Pediatric RNS

In prior adult studies, 59% to 82% of the patients underwent preoperative workups with intracranial recording,[2,3,5,10] whereas all the patients in our series underwent intracranial recording. However, the type of intracranial recording used was variable across the institutions. In addition, the number of RNS leads placed was variable across the institutions, with some using 2 leads only and the others using a variable number of leads between 2 and 4. The strength of a multi-institutional cohort design is that the flexibility in clinician treatment strategies and variability in clinical pathologies are reflected, better approximating the true diversity seen in a pediatric population and increasing the generalizability of these results.

Unique Considerations in Pediatric RNS

As we expand use of RNS to the pediatric population, it is critical to consider how to determine the lower age limit. Considering this procedure invariably involves a craniectomy for device implantation, the benefits and potential harm based on the variable skull development in individual patients should be considered. Children experience rapid skull growth within the first 2 yr and reach ~90% of the adult skull volume by 7 yr.[11] There were 2 patients under 7 yr at the time of RNS implantation included in this study. The youngest was 3 yr of age at the time of RNS implantation, which is the youngest reported patient to undergo RNS implantation (personal

communication, NeuroPace). In cases of severe, refractory epilepsy, the benefits of neuromodulation may outweigh the potential harm in patients who are <7 yr old. Theoretically, once skull growth nears maturity, there is likely less concern for future complications. Open sutures in infants would be a contraindication due to the small head size and the difficulty in securing the device. Although skull immaturity may be considered a relative contraindication in very young patients, this must be determined on a case-by-case basis, given the variability in skull growth and skull thickness in individual patients (eg, 4-mm thickness of the skull at the site of RNS implant in our 3-yr-old patient). Variable skull thickness can be assessed with use of computed tomography (CT) scans routinely obtained as part of presurgical workups (eg, scans used to localize intracranial electrodes; positron emission tomography). Given the smaller head size and potentially thinner scalp, it is more critical to optimize the positioning of the device to best fit the contour of the skull thus minimizing the risk of skin breakdown in young children (usually parietal area). The postoperative CT and skull X-rays in our 3-yr-old patient (Figure 2) demonstrate that the RNS device can be placed appropriately along the contour of the skull in a young patient. Slightly larger craniectomy could be considered for the device to accommodate a growing skull. Long-term follow-up of these patients who had RNS implantation at a very young age will be particularly important to evaluate the use of the RNS system in the pediatric population.

With the establishment of open-loop deep brain stimulation targeting the anterior nucleus of the thalamus,[12] as well as closed-loop RNS, the role of neuromodulation in treatment of epilepsy has been expanding. However, their FDA-approved indication is limited to adult patients. Given the diversity and complexity of pediatric epilepsy, neuromodulation will likely play a significant role in this population. Therefore, it is important to further investigate the effectiveness and safety of these devices and establish the roles of these options in pediatric epilepsy in a randomized multicenter study. The current study represents an important first step towards the investigation of neuromodulation in the pediatric population.

Limitations

The limitations of this current study include those typical of a retrospective observational study (ie, no randomization, no control arm, no blinded evaluation, no systematic prospective documentation of seizure events). The follow-up duration was also limited in some patients, likely underestimating the effectiveness of RNS therapy in those patients.

Generalizability

This study involved a diverse and heterogenous group of pediatric epilepsy patients who underwent workups at the participating pediatric centers with different approaches and strategies. The study therefore reflects the growing real-world experience with pediatric RNS use.

CONCLUSION

This retrospective multicenter study suggests that the use of RNS (NeuroPace) in the pediatric population is safe and feasible with more than half the patients in this series achieving ≥50% reduction of disabling seizures. The preliminary data suggest efficacy compatible with the adult RNS experience. A future long-term prospective study on pediatric RNS use will be critical to further assess the efficacy and safety of RNS use in children and to examine issues unique to children, such as skull immaturity/growth and more surgeries for battery replacement over longer life expectancies.

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The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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