Vagal nerve stimulation is effective in pre-school children with intractable epilepsy: A report of two cases

Zhao Yang
National Engineering Laboratory for Neuromodulation, School of Aerospace Engineering, Tsinghua University, Beijing 100084, China

Ciliu Zhang
Department of Pediatrics, Xiangya Hospital of Central South University, Changsha 410008, Hunan, China; Hunan Intellectual and Developmental Disabilities Research Center of Children, Changsha 410008, Hunan, China

Zhiyan Wang
National Engineering Laboratory for Neuromodulation, School of Aerospace Engineering, Tsinghua University, Beijing 100084, China

Tungyang Cheng
National Engineering Laboratory for Neuromodulation, School of Aerospace Engineering, Tsinghua University, Beijing 100084, China

Xiaoya Qin
National Engineering Laboratory for Neuromodulation, School of Aerospace Engineering, Tsinghua University, Beijing 100084, China; Precision Medicine and Healthcare Research Center, Tsinghua-Berkeley Shenzhen Institute, Tsinghua University, Shenzhen 518071, China

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Zhao Yang1, Ciliu Zhang2,3, Zhiyan Wang1, Tungyang Cheng1, Xiaoya Qin1,4, Jin Deng1, Xi Fang1, Hongwei Hao1, Jing Peng2,3, Fei Yin2,3, Luming Li1,4,5

1 National Engineering Laboratory for Neuromodulation, School of Aerospace Engineering, Tsinghua University, Beijing 100084, China
2 Department of Pediatrics, Xiangya Hospital of Central South University, Changsha 410008, Hunan, China
3 Hunan Intellectual and Developmental Disabilities Research Center of Children, Changsha 410008, Hunan, China
4 Precision Medicine and Healthcare Research Center, Tsinghua-Kohei Shenzhen Institute, Tsinghua University, Shenzhen 518071, China
5 Center of Epilepsy, Beijing Institute for Brain Disorders, Beijing 100069, China

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KEYWORDS
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ABSTRACT
There is lack of prospective evidence regarding vagal nerve stimulator (VNS) in younger children with intractable epilepsy. Here, we report the outcomes of using VNS in two pre-school patients for pediatric intractable epilepsy (VNS-PIE) study. Medical treatment was ineffective in both the patients, and they underwent VNS implantation. Seizure frequency, score on the Gesell scale, and heart rate variability (HRV) were assessed following VNS therapy. After 6 months VNS treatment, the seizure frequency in the two patients decreased by 50% from that at baseline, based on the records in their epileptic diary. Video electroencephalography (EEG) examinations showed that abnormal fast waves diminished in the background in Patient 1, and captured seizure frequency in Patient 2 remarkably decreased. The adaptability, language, and individual and social interaction on their Gesell scales increased slightly, suggesting that VNS had a positive effect on the development of these two children. Moreover, the changes in the different HRV indices indicated improved cardiac autonomic function. In conclusion, these two cases indicated that VNS may not only be a superior therapy for pre-school children with intractable epilepsy, but also may exert a positive effect on their mental development and cardiac autonomic function.

1 Introduction
Vagal nerve stimulator (VNS) has been used as an adjunction therapy in the clinical setting for pre-school children with intractable epilepsy [1]; however, preliminary studies have given limited attention to the outcomes in pre-school age range. Over 300,000 children worldwide are estimated...
to have intractable epilepsy, demonstrating age-related disease progress and seizure expression [2]. Thus, the age for VNS implantation might be an important factor that affects the effectiveness of the therapy [3]. Recently, the US Food and Drug Administration (FDA) approved VNS for use in patients aged > 4 years who exhibit partial-onset seizures and drug-resistant epilepsy based on retrospective non-inferiority analysis [4]. However, whether early VNS implanting would improve the condition in pre-school patients is unclear [5].

Intractable epilepsy is associated with impairment in cognition, social maturation, behavior, academic achievement, language, psychopathology and healthy quality of life [6–10]. Early and better seizure control may improve the cognitive outcome and quality of life in children, as demonstrated in several retrospective studies that have studied the effect of epilepsy surgery [11, 12]. Moreover, VNS is suggested to exert a non-negative impact on cognition and behavior [13, 14]. Few studies have focused on the mental development of pre-school children with intractable epilepsy. Thus, the Gesell development scale was chosen to assess the cognitive and behavior function of pre-school subjects in this report [15].

Heart rate variability (HRV) is considered as an accurate marker of the sympathovagal balance of the cardiac autonomic nerve system (CANS) [16]. In general, a higher HRV reflects better conditioned adaptability of the CANS, while a lower HRV indicates deficient and abnormal control of the CANS. Hirfanoglu et al. reported that the use of a VNS enables substantial improvement in the HRV indicators via increased parasympathetic effects in short-term therapy in children aged > 6 years [17]. However, to our knowledge, no studies have assessed the effect of VNS use on the HRV index in preschool children.

The aim of these two cases was to assess the efficacy of VNS in pre-school children with intractable epilepsy.

2 Methods

2.1 Subject

Patient 1:

The first case (named as ZZB) was that of a male who was born with no significant perinatal complications. Fever-induced initial seizure was observed when the patient was 1 year and 3 months of age (Oct 31, 2013). He underwent an initial evaluation at the Xiangya Hospital and valproic acid taking was initiated. Despite this medication, he continued to experience recurrent clustered seizures after a 1-month of seizure-free period; the clustered seizures were often induced by fever. Then he failed to monomedicine, including: topiramate (max dose: 6.8 mg/kg), nitrazepam (max dose: 0.25 mg/kg), oxcarbazepine (max dose: 40 mg/kg), and clobazam (max dose: 0.73 mg/kg). He was taking valproic acid, topiramate, clobazam, and a ketogenic diet at baseline in VNS pediatric intractable epilepsy (VNS-PIE). He was noted to have global developmental delay, was non-verbal with the exception of “mama” and “baba”, and was able to walk with assistance. Video electroencephalography (EEG) monitoring (24 h) reports revealed spike, slow spike, and fast waves in the left posterior and bilateral temporal regions during sleep, with background 6-7-Hz activity at the bilateral occipital region. One type of epileptiform activity, focal to bilateral tonic-clonic seizures was captured, showing as bilateral temporal region dominant with generalized mid-high amplitude and sharp waves. He was noted to have frequent thermosensitive seizures. The gene panel and magnetic resonance imaging (MRI) of epilepsy showed negative results.
Patient 2: The second case (name as TYH) was a female who was born without any significant perinatal complications. She was noted to have intermittent fever, recurrent convulsions, and coma at the age of 1 year and 7 months, with diagnostic considerations for viral encephalitis. After disease onset, she was confused and had disturbed consciousness; she exhibited right limb involuntary activities and declined muscle strength. Rehabilitation treatment helped her to recover her consciousness, ability to speak, and capacity to perform physical activity. At almost 2 years of age, she began to experience ictal events of extension spasms that usually appeared in clusters. Seizures could not be controlled by taking adreno-cortico-tropic hormone, ketogenic diet, or 6 single medicines, including nitrazepam (max dose: 0.28 mg/kg), valproic acid (max dose: 22.8 mg/kg), lamotrigine (max dose: 0.4 mg/kg), topiramate (max dose: 1.8 mg/kg), sabril (max dose: 100.0 mg/kg), and levetiracetam (max dose: 70.0 mg/kg). She took valproic acid and topiramate at baseline in VNS-PIE. Video EEG monitoring (24 h) revealed some 1.5-3.5-Hz fast wave activity, under the background of 6-7-Hz activity in the bilateral occipital region. Several different epileptiform activities were captured, including epileptic spasms, ankylosis spasm, and ankylosis spasm with focal seizures. Ictal activity included generalized mid-high amplitude spike and wave activity at 0.8-1.5 Hz or generalized fast wave at 15-25 Hz that lasted for 2-4 s. MRI testing demonstrated malacias that occurred in the bilateral parietal lobe, the right occipital lobe and the right thalami.

2.2 VNS-PIE

The time line of the VNS-PIE study is presented in Fig. 1, and the study protocol has been published [18]. For Patient 1 and Patient 2, at the time of referral for VNS evaluation, their parents signed informed consent and reported about 6 and 40 seizures daily, respectively. The same medications were continued. The patients became more alert and attentive after VNS implantation and recorded the obvious seizure. Patient 1 underwent VNS implantation (G112, PINS Medical, Beijing, China) at 3 years and 4 months of age. After randomization, he received recommended electric stimulation during the double-blind period. The VNS electric pulse generator was turned on with initial settings at a current amplitude of 0.5 mA, frequency of 30 Hz, pulse width of 500 μs, signal on time of 30 s, and signal off time of 5 min. Rapid adjustments were made at intervals of about 1 week until the stimulation reached 1.5 mA. Personal optimization of his VNS parameters setting was conducted during the open-label period and the final current amplitude was 1.5 mA at the end of the trial. Patient 2 underwent VNS (G112, PINS Medical, Beijing, China) implantation at 5 years of age with turning-off of the settings initially during the double-blind stage. Her VNS settings were increased and optimized during the open-label stage with a final current amplitude of 1.5 mA, frequency of 30 Hz, pulse width of 500 μs, signal on time of 30 s and signal off time of 5 min. The Gesell scale was assessed by a professional doctor at baseline, 12th week (W12), W18, and W24 follow-ups (Fig. 1). A 12-lead, 24-hour ambulatory ECG recording device (MIC-12H-3S, JincoMed, Beijing) was used for the two patients to record 24-hour consecutive ECG at baseline, W6, W12, W18, and W24 follow-ups.

The ECG data were sampled digitally at a rate of 500 sps per channel and analyzed using Kubios HRV software (version 2.2, University of Eastern Finland). All R-wave peaks were first marked automatically. Thereafter, a visual check was performed for every R-wave mark. Inaccurate
recordings owing to artifacts and ectopic beats in the interval between two R wave peaks (RR) of ECG were excluded before analysis. At least 21 of the 24-hour ECG recording had to be suitable for analysis and be included as per the issued guidance [19]. The HRV was measured using the following three analytical methods: (1) time domain; (2) frequency domain; and (3) non-linear domain. For frequency and non-linear domains, detrending preprocess for RR intervals was conducted to decrease the ultra-low frequency noise. The explanation of HRV has been provided in a previous paper [20].

3 Results

Although there was a difference in the frequency and severity of seizures at baseline between the two patients, there was considerable reduction in these two parameters of the patients after the electrical stimulation (Fig. 2). For Patient 1, the baseline seizure frequency was 180 times per month, and it decreased to 7, 35, 17, and 19 times per month at W6, W12, W18, and W24 follow-up respectively. The percentage change in the overall seizure frequency from that at baseline was −96.1%, −80.6%, −90.6%, and −89.4%, respectively. For Patient 2, the baseline seizure frequency was 1200 times per month, and it changed to 1280, 1131, 1021, and 591 times per month at W6, W12, W18, and W24 follow-up respectively. The percentage change in the overall seizure frequency from baseline was 6.7%, −5.8%, −15.0%, and −50.8%, respectively. At the end of the double-blind period, seizure frequency in Patient 1 achieved over 50% reduction from baseline (Responder50), while that in Patient 2 did not. At the end of the open-label period, both Patient 1 and Patient 2 were Responder50s.
According to the EEG reports at the end of the open-label period, fewer abnormal slow spike and fast waves were detected in the background in Patient 1, while no remarkable change was found in the ictal and interictal period. Patient 2 had a significant diminishment in the number of captured seizures during the EEG recording, from >100 at baseline to 13 times at the end of the open-label period; this result coincided with the suppression of seizure frequency recorded in the diary.

In Fig. 3. At the end of the open-label period, the development quotient (DQ) of adaptability, gross motor skills, fine motor skills, language, and individual and social interaction in Patient 1 improved by 2.1, 4.4, 3.5, 11.9, and 7.9 compared to that at baseline, respectively; the improvement in the DQ of five functional regions was shown at nearly any follow-up after VNS therapy. However, there was no consistent increase trend with longer stimulation duration. At the end of the open-label period, the DQ of adaptability, language, and individual and social interaction in Patient 2 improved by 3.2, 5.3, and 6.8 from that baseline, while the DQ of gross motor skills and fine motor skills decreased by 1.3, 0.7, respectively, from that at baseline. When receiving electrical stimulation of VNS at W12, Patient 2 showed slight improvement in adaptability, fine motor skills, and language at W18 and/or W24.

With respect to the HRV index in the time and non-linear domain, for both patients, the standard deviation of RR interval, root mean square of successive difference (RMSSD), Poincare_standard deviation 1 (Poincare_SD1) and Poincare_standard deviation 1 (Poincare_SD2) showed overall improvement at each follow-up after VNS implantation and electrical stimulation. There was large variability in the total_power at different time points; therefore, normalized frequency band power was used to demonstrate the characters in the frequency domain. However, for Patient 1, the LF_power_nu (low frequency power normalization), the HF_power_nu (high frequency power normalization) and LF/HF seems no obvious change during the trial. Contradictory findings were observed for Patient 2. HF_power_nu improved after VNS therapy, while LF_power_nu decreased, causing LF/HF to change from 1.2 to 0.6. Overall, these results indicate that VNS might benefit the function of the CANS.

4 Discussion

Here, we report the case of two pre-school children with intractable epilepsy who benefited from VNS therapy in their seizure frequency control, behavior, cognitive development, and cardiac autonomic function. The improvement in seizure control and behavior, patience tolerance,
that frequency and RR, discussions VNS potential epilepsy difference; extended patients formal receives report Table

<table>
<thead>
<tr>
<th>Follow-ups</th>
<th>Baseline</th>
<th>W6</th>
<th>W12</th>
<th>W18</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean RR (ms)</td>
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<td>545.1</td>
<td>569.6</td>
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<td>521.1</td>
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<td>STD RR (ms)</td>
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<td>23.0</td>
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<tr>
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<td>30.8</td>
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<td>32.5</td>
<td>30.1</td>
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<td>HF_power_nu</td>
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<td>67.3</td>
<td>69.7</td>
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<tr>
<td>LF/HF</td>
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<td>0.5</td>
<td>0.4</td>
<td>0.8</td>
<td>0.5</td>
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<tr>
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<td>527.2</td>
<td>812.4</td>
<td>404.3</td>
<td>386.3</td>
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<td>17.5</td>
<td>21.8</td>
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<td>15.6</td>
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<tr>
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<td>26.0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>640.3</td>
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<td>36.1</td>
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<td>1.6</td>
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<td>1.7</td>
<td>1.7</td>
<td>1.8</td>
<td>1.7</td>
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</table>

RR, the interval between two R peaks; STDRR, standard deviation of RR interval; RMSSD, root mean square of successive difference; LF_power_nu, low frequency power normalization; HF_power_nu, high frequency power normalization; LF/HF, high frequency power normalization; Poincare_SD1, Poincare standard deviation 1; Poincare_SD2, Poincare standard deviation 2.

and parental satisfaction has led to optimism that the application of the VNS system can be extended to younger children. Although the formal use of this technology for pediatric patients depends on whether the manufacturer receives FDA approval, we believe that this report can be used as a reference in informal discussions with healthcare providers, parents, and insurance companies with respect to potential open-period applications.

Compared to the decision irreversibility of epilepsy surgery in younger childhood [11], VNS implantation is less risky in children and is reversible as well as adjustable. It can optimize the parameters over time based on adverse-event tolerance and characterization of seizures. However, VNS implantation was performed for fewer patients aged 3–6 years and was the focus of our research. Few early studies have assessed the efficacy of VNS implantation in pre-school children, with large variability in outcomes, and a lack of high-level evidence studies [5, 21–25]. Although doctors and researchers now believe that the efficacy in children is comparable to that in adults, the acceptance of doctors and parents remains low, and fewer cases are
available for study. The response of refractory epilepsy to continuous VNS treatment may also improve over time. Patient 1 began to receive electrical stimulation treatment about 2 weeks after implantation, and Patient 2 received electrical stimulation at about 14 weeks after implantation. Patient 1 received longer electrical stimulation, and achieved more reduction in the seizure frequency. This was consistent with the view that the efficacy of continuous VNS treatment for refractory epilepsy may also improve over time [3, 5]. Video EEG monitoring reports also help demonstrate more normal signals of the brain and fewer seizures following VNS therapy. However, it may not capture any seizure during monitoring for patients with few seizures, such as Patient 1. An epileptic diary and EEG report could together help confirm the change in seizure frequency.

For preschool children, frequent epilepsy seizures have long-term adverse effects on the immature plastic brain system development and may be irreversible [2]. Although the two children were very young, the results of the Gesell scale at baseline showed that the two children were already in an extremely backward state. After VNS therapy, the five functional regions of Patient 1 were upgraded, especially in terms of language. The adaptability, language, and individual and social interaction in Patient 2 also improved. Owing to the short duration of VNS treatment and possible individual differences, the improvement in the motor function region in Patient 2 warrants further observation. Knorr et al. found that patients who have undergone VNS implantation at the age of ≤ 2 years showed a strong association with better developmental, cognitive outcome, and quality of life [26]. From this perspective, the earlier implantation of children appears to have exerted a more positive developmental impact.

In addition to seizure frequency and Gesell scale that are observable indicators, HRV is an accepted indicator that can assess cardiac autonomic function. In both patients, VNS could improve some of the HRV indicators in the time domain and non-linear domains, mainly characterizing the improvement in vagal tension. As we know, the HF_power_nu in the frequency domain was positively correlated with the RMSSD in the time domain, and the two index characterize the vagal tension. In this report, although the HF_power_nu and RMSSD in Patient 2 improved after VNS treatment which was consistent with previous opinion, the HF_power_nu in Patient 1 was similar to the change of results in time domain indicators. This may be due to case specificity or short treatment duration.

It is noteworthy that both patients experienced fever-induced seizures, suggesting that VNS was more effective in intractable epilepsy with seizure of fever. Moreover, during the whole trial period, neither patient reached the optimal stimulation parameters, and the adjustment of the parameters and the stable curative effect are still to be observed for a long time.

The limitations of our study are the small sample size and short VNS treatment duration. Thus, long-term follow-ups with more samples are needed to evaluate the efficacy of VNS for younger children with intractable epilepsy. Complex type of seizure and epilepsy, anti-epilepsy drugs and various behaviors may be the mixed factors that cannot be controlled in this clinical study, further random controlled trial will be needed.

5 Conclusion

The report proved that VNS therapy achieved more improvement in pre-school children with refractory epilepsy and had a positive effect on the mental development and cardiac autonomic function.
Conflict of interests

All contributing authors report no conflict of interests in this work.

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References


Zhao Yang. B.D., Ph.D. candidate. She is interested in neuromodulation and physiological signal analysis concerned to pediatric and adult epilepsy. She has 7 publications in recent 5 years. E-mail: z-yang14@mails.tsinghua.edu.cn

Ciliu Zhang. Ph.D., attending physician, specializes in children neurological disorders including neuromuscular disease, epilepsy, neuroimmune diseases, and dyskinesia. E-mail: zhangciliu@163.com

Zhiyan Wang. Ph.D. Wang is interested in the efficacy and mechanism of neuromodulation therapy for new indications. She has 6 publications in recent 5 years. E-mail: wzyann@126.com
Tungyang Cheng, B.D., Ph.D. candidate. His research interest focuses on neuromodulation and physiological signal analysis. E-mail: zhengdy19@mails.tsinghua.edu.cn

Xiaoya Qin, M.D., Ph.D. candidate. Her research interest focuses on neuromodulation and physiological signal analysis. E-mail: qinxiaoya47@163.com

Jin Deng, M.D. His research interest focuses on neuromodulation and physiological signal analysis. E-mail: dengj16@mails.tsinghua.edu.cn

Xi Fang, B.D., M.D. candidate. She is interested in image processing and vagal nerve stimulation. E-mail: 875766401@qq.com

Hongwei Hao, Ph.D, professor. He is interested in the neuromodulation technologies for neurological disorders. He has more than 15 publications in recent 5 years. E-mail: haohw@tsinghua.edu.cn
Jing Peng, Ph.D., professor. She is the director of pediatric department, Xiangya Hospital and the director of Xiangya Neurodevelopmental Disabilities Research Center of Children. She is interested in children neurological disorders. She won the First Prize of 2016 National Science and Technology Progress Award, and had more than 20 publications in recent 5 years. E-mail: pengjing4346@163.com

Fei Yin, Ph.D., professor in pediatric department, Xiangya Hospital, the director of Hunan Intellectual and Developmental Disabilities Research Center of Children, China. He is interested in children neurological disorders. He has more than 20 publications in recent 5 years. E-mail: yf2323@hotmail.com

Luming Li, Ph.D., professor. He is currently the dean of the School of Aerospace Engineering, the director of the Institute of Human-Machine and the National Engineering Laboratory for Neuromodulation, a PI of the IDG/McGovern Institute for Brain Research, and the vice president of the Chinese Neuromodulation Society. His current research interests include implantable technology and neuromodulation. He has authored or coauthored more than 190 academic papers, and holds more than 130 patents. E-mail: lilm@mail.tsinghua.edu.cn