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Non-Invasive Neuromodulation for Drug-Resistant Epilepsy in Children: A Randomized Controlled Trial of Transcranial Magnetic Stimulation (TMS) versus Vagus Nerve Stimulation (VNS) in Jakarta, Indonesia

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A B S T R A C T

Introduction: Drug-resistant epilepsy (DRE) significantly impacts the quality of life in children. While vagus nerve stimulation (VNS) is an established treatment, repetitive transcranial magnetic stimulation (rTMS) offers a non-invasive alternative. This study aimed to compare the efficacy and safety of rTMS versus VNS in a pediatric DRE population in Jakarta, Indonesia. **Methods:** This was a single-center, randomized, controlled, open-label trial conducted at Private Hospital, Jakarta. Children aged 5-18 years with DRE, defined as failure to achieve seizure freedom despite adequate trials of two appropriate antiepileptic drugs (AEDs), were randomly assigned (1:1) to receive either rTMS or VNS. The primary outcome was the percentage reduction in seizure frequency at 6 months post-intervention compared to baseline. Secondary outcomes included responder rate (≥50% seizure reduction), quality of life (QoL) using the PedsQL, cognitive function (using standardized neuropsychological tests), and adverse events. **Results:** A total of 60 children were randomized (30 rTMS, 30 VNS). At 6 months, the mean percentage reduction in seizure frequency was significantly greater in the rTMS group (48.5%, SD 15.2%) compared to the VNS group (35.2%, SD 12.8%) ($p = 0.001$). Responder rates were 63.3% for rTMS and 46.7% for VNS ($p = 0.17$). PedsQL scores showed a significant improvement in the rTMS group compared to baseline in the psychosocial health summary score ($p = 0.005$), but not the VNS group ($p=0.1$). No significant differences were observed in cognitive function between the groups. Adverse events were generally mild and transient in both groups, though VNS was associated with more voice alteration and coughing. **Conclusion:** rTMS demonstrated superior efficacy in reducing seizure frequency compared to VNS in this Indonesian pediatric DRE population. While VNS is an established method, rTMS may present a non-invasive and potentially more effective therapeutic alternative. Further, larger, multicenter studies are warranted to confirm these findings and explore long-term outcomes.

1. Introduction

Epilepsy, a chronic neurological disorder characterized by recurrent seizures, poses a significant health challenge worldwide, affecting individuals of all ages, including children. In the pediatric population, epilepsy is particularly prevalent, with an estimated incidence of 0.5-1%, making it one of the most common neurological disorders in this age group. The impact of epilepsy on children extends far beyond the seizures themselves, often leading to cognitive impairment, behavioral problems, psychosocial difficulties, and a reduced quality of life.

While the majority of children with epilepsy achieve seizure control with antiepileptic drugs (AEDs), approximately 20-30% of these children have drug-resistant epilepsy (DRE). DRE is defined as the failure to achieve sustained seizure freedom despite adequate trials of two tolerated and appropriately chosen AED schedules, whether as monotherapies or in combination. The consequences of DRE are profound, as uncontrolled seizures can lead to increased risk of injury, cognitive decline, behavioral problems, and social isolation, significantly impacting the child's overall development and well-being.[1-3]

The challenges posed by DRE underscore the urgent need for alternative treatment options that can effectively manage seizures and improve the quality of life for these children. While AEDs remain the cornerstone of epilepsy treatment, their effectiveness is limited in children with DRE. Therefore, exploring and evaluating alternative therapies, particularly those that are non-invasive and have minimal side effects, is crucial. Neuromodulation, a therapeutic approach that involves altering nerve activity through targeted delivery of a stimulus, has emerged as a promising avenue for treating DRE. Two widely recognized neuromodulation techniques, vagus nerve stimulation (VNS) and repetitive transcranial magnetic stimulation (rTMS), have shown potential in reducing seizure frequency and improving quality of life in individuals with DRE.[4,5]

VNS, an FDA-approved adjunctive therapy for DRE in both adults and children, involves the implantation of a device that delivers intermittent electrical stimulation to the left vagus nerve. This stimulation modulates neuronal activity in various brain regions, leading to a reduction in seizure frequency and severity. Numerous studies have demonstrated the efficacy and safety of VNS in DRE, with significant improvements in seizure control, quality of life, and cognitive function. rTMS, a non-invasive neuromodulation technique, uses magnetic pulses to induce electrical currents in the brain, thereby modulating cortical excitability. The effects of rTMS depend on the frequency of stimulation, with low-frequency rTMS (≤1 Hz) generally decreasing cortical excitability and high-frequency rTMS (>1 Hz) increasing it. rTMS has gained attention as a potential treatment for DRE, with several studies demonstrating its ability to reduce seizure frequency in both adults and children. The non-invasive nature of rTMS, coupled with its minimal side effects and potential for targeted cortical stimulation, makes it an attractive alternative to VNS.[6-8]

While both VNS and rTMS have shown promise in treating DRE, direct comparisons between the two therapies, particularly in the pediatric population, are limited. Most of the existing research has been conducted in Western countries, and there is a paucity of data from Southeast Asia, including Indonesia. Indonesia, with its large pediatric population and a significant burden of epilepsy, faces unique challenges in managing DRE due to limited resources and access to specialized care. Therefore, exploring effective and accessible treatment options for DRE in this setting is crucial.[9,10] This randomized controlled trial (RCT) aimed to compare the efficacy and safety of rTMS versus VNS in a pediatric DRE population in Jakarta, Indonesia.

2. Methods

This research employed a single-center, randomized, controlled, open-label trial design. The study was conducted at a single site, the Pediatric Neurology Division of a Private Hospital in Jakarta, Indonesia. This design allows for a focused investigation of the interventions within a specific population and clinical setting, ensuring consistency in patient characteristics, treatment protocols, and data collection procedures. However, it is important to acknowledge that the single-center nature of the study may limit the generalizability of the findings to other populations and clinical settings. The open-label nature of the trial, where both participants and treating clinicians were aware of the treatment assignment, is another methodological consideration. While open-label designs have limitations with respect to blinding and potential bias, they are often necessary in clinical trials involving interventions that are difficult or impossible to mask, such as rTMS and VNS. To mitigate potential bias, outcome assessors, including neurologists responsible for seizure

frequency assessment and neuropsychological testing, were blinded to treatment allocation.

The study included children aged 5-18 years with a confirmed diagnosis of drug-resistant epilepsy (DRE). DRE was defined according to the International League Against Epilepsy (ILAE) criteria, which require the failure to achieve sustained seizure freedom after adequate trials of two tolerated and appropriately chosen antiepileptic drug (AED) schedules, whether as monotherapies or in combination. In addition to age and DRE diagnosis, eligible participants were required to have a seizure frequency of at least four seizures per month during a 3-month baseline observation period. This criterion ensured that participants had a sufficient seizure burden to allow for meaningful assessment of treatment effects. Furthermore, participants were required to have been on a stable AED regimen for at least 4 weeks prior to enrollment to minimize the confounding effects of medication changes during the study period. The ability to comply with study procedures, including attending rTMS sessions or undergoing VNS implantation and follow-up visits, was also an essential inclusion criterion. This ensured that participants could fully participate in the study and that data collection would be complete and reliable. Several exclusion criteria were applied to ensure the safety of participants and the integrity of the study results. Children with progressive neurological disorders were excluded, as these conditions could confound the assessment of treatment effects on seizure frequency and cognitive function. The presence of a cardiac pacemaker or other implanted electronic devices was a contraindication for both rTMS and VNS, as these devices could be affected by the interventions. Similarly, a history of significant head trauma with loss of consciousness within the past 6 months was an exclusion criterion, as it could influence seizure patterns and confound the assessment of treatment effects. Previous treatment with rTMS or VNS was also an exclusion criterion, as prior exposure to these interventions could alter the response to treatment in the study. Pregnancy or breastfeeding was excluded due to the potential risks of the interventions to the developing fetus or infant. Significant psychiatric comorbidity that could interfere with study participation, such as severe depression or anxiety, was also an exclusion criterion. Finally, metal implants in the head were a contraindication for rTMS due to the potential for these implants to heat up or move during stimulation.

Participants meeting the inclusion and exclusion criteria were randomly assigned to receive either rTMS or VNS using a computer-generated randomization sequence. The randomization process was stratified by age (5-11 years and 12-18 years) and seizure type (focal vs. generalized) to ensure balance between the treatment groups with respect to these potentially confounding factors. Allocation concealment, a critical component of randomized controlled trials, was ensured by using sequentially numbered, opaque, sealed envelopes. This prevented researchers and participants from knowing the treatment assignment in advance, minimizing the risk of selection bias. As mentioned earlier, blinding of participants and treating clinicians was not possible due to the nature of the interventions. However, outcome assessors, including neurologists responsible for seizure frequency assessment and neuropsychological testing, were blinded to treatment allocation to minimize potential bias in outcome assessment.

The rTMS intervention was delivered using a Magstim Rapid2 stimulator with a figure-of-eight coil. The figure-of-eight coil design allows for relatively focal stimulation of cortical regions, minimizing the spread of the magnetic field to surrounding areas. The stimulation target was the epileptogenic zone, the area of the brain where seizures originate. Determining the precise location of the epileptogenic zone can be challenging and often relies on a combination of seizure semiology, electroencephalography (EEG) findings, and neuroimaging (MRI). In cases where the epileptogenic zone could not be clearly localized, the vertex (Cz), a central location on the scalp, was targeted. The rTMS protocol consisted of 1 Hz stimulation, which is considered low-frequency rTMS and is generally thought to decrease cortical excitability. The intensity of stimulation was set at 90% of the resting motor threshold (RMT), which is the minimum intensity required to elicit a motor response in a target muscle. RMT was determined using single-

pulse TMS over the motor cortex, a standard procedure for assessing cortical excitability. Each rTMS session consisted of 1200 pulses delivered over a period of approximately 20 minutes. Participants received one session per day, 5 days per week, for 4 weeks, for a total of 20 sessions. This intensive protocol was designed to induce long-term depression (LTD) of cortical excitability, potentially leading to a sustained reduction in seizure frequency. The VNS intervention involved the implantation of a VNS Therapy System device. The implantation procedure was performed by a qualified neurosurgeon according to standard surgical procedures, ensuring the safety and efficacy of the device placement. The VNS device was programmed by a trained neurologist according to a standardized protocol. The initial settings were as follows: output current of 0.25 mA, frequency of 30 Hz, pulse width of 500 μs, on-time of 30 seconds, and off-time of 5 minutes. These settings were chosen based on established clinical practice guidelines and previous research on VNS in epilepsy. The output current was gradually increased by 0.25 mA every 2 weeks, as tolerated, up to a maximum of 3.5 mA, or until optimal seizure control was achieved. This titration process allowed for individual adjustment of the stimulation parameters to maximize therapeutic benefit while minimizing side effects.

The primary outcome of the study was the percentage reduction in seizure frequency at 6 months post-intervention compared to baseline. Seizure frequency was recorded by parents/caregivers in a seizure diary, a widely used method for monitoring seizure activity in epilepsy clinical trials. The use of seizure diaries provides a reliable and objective measure of seizure frequency, allowing for comparison between treatment groups and assessment of treatment effects over time. In addition to the primary outcome, several secondary outcomes were assessed to provide a comprehensive evaluation of the interventions. The responder rate, defined as a ≥50% reduction in seizure frequency at 6 months compared to baseline, was a key secondary outcome. This measure provides a clinically meaningful indicator of treatment response, as a 50% or greater reduction in seizure frequency is often associated with significant improvements in quality of life. Quality of life (QoL) was assessed using the Indonesian version of the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales. The PedsQL is a well-validated and widely used instrument for measuring health-related quality of life in children and adolescents. It assesses various domains of QoL, including physical, emotional, social, and school functioning, providing a comprehensive picture of the child's overall well-being. Cognitive function was assessed using a battery of standardized neuropsychological tests, including the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV), the Trail Making Test (Parts A and B), and the Rey Auditory Verbal Learning Test (RAVLT). These tests assess various aspects of cognitive function, including general intellectual ability, attention, executive function, and verbal memory, providing a comprehensive evaluation of cognitive abilities in the study participants. Adverse events were monitored throughout the study and recorded using a standardized adverse event reporting form. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, a widely used standardized classification system for adverse events in clinical trials. This systematic monitoring and reporting of adverse events allowed for a thorough assessment of the safety of both interventions.

The sample size for this study was calculated based on previous studies comparing rTMS and VNS in DRE. Assuming a mean percentage reduction in seizure frequency of 40% for rTMS and 30% for VNS, with a standard deviation of 20% for both groups, a sample size of 27 patients per group was required to detect a non-inferiority margin of 10% with 80% power and a one-sided alpha of 0.05. To account for a potential 10% dropout rate, the study aimed to recruit a total of 60 participants (30 per group).

Data analysis was performed using SPSS version 25. Continuous variables were presented as means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on the distribution. Categorical variables were presented as frequencies and percentages. The primary outcome, the difference in the percentage reduction in seizure

frequency between the two groups, was analyzed using an independent t-test. A non-inferiority analysis was also performed using a one-sided 95% confidence interval (CI) for the difference in means. If the lower bound of the CI was greater than -10%, rTMS was considered non-inferior to VNS. Secondary outcomes were analyzed using appropriate statistical tests. Responder rates were compared using the chi-square test or Fisher's exact test, as appropriate. PedsQL scores and neuropsychological test scores were compared between groups using independent t-tests or Mann-Whitney U tests, as appropriate. Changes from baseline within each group were analyzed using paired t-tests or Wilcoxon signed-rank tests. Adverse events were summarized descriptively. A p-value of <0.05 was considered statistically significant for all analyses.

3. Results and Discussion

Table 1 presents the baseline characteristics of the 60 participants enrolled in the study, divided into two groups: those receiving repetitive transcranial magnetic stimulation (rTMS) (n=30) and those receiving vagus nerve stimulation (VNS) (n=30). The average age of participants in both groups was similar, with the rTMS group having a mean age of 11.2 years (standard deviation [SD] of 3.5 years) and the VNS group having a mean age of 10.8 years (SD of 3.2 years). The p-value of 0.68 indicates that there was no statistically significant difference in age between the two groups. The distribution of males and females was comparable between the two groups. 60% of the rTMS group were male, compared to 53.3% in the VNS group. This difference was not statistically significant (p=0.61). The types of seizures experienced by the participants were also similar across both groups. The majority of participants in both groups had focal (40% in rTMS, 46.7% in VNS) or focal to bilateral tonic-clonic seizures (50% in rTMS, 43.3% in VNS). A small percentage in each group had generalized seizures (10% in both). The overall distribution of seizure types was not significantly different between the groups (p=0.72). The average duration of epilepsy was approximately 4.8 years (SD 2.1 years) for the rTMS group and 4.5 years (SD 1.9 years) for the VNS group. This difference was not statistically significant (p=0.55). The average number of seizures per month at the start of the study was also similar between the groups, with 8.2 seizures (SD 2.5) in the rTMS group and 7.9 seizures (SD 2.3) in the VNS group (p=0.60). Participants in both groups were taking a similar number of antiepileptic drugs (AEDs) at the start of the study, with an average of 2.3 AEDs (SD 0.5) in the rTMS group and 2.4 AEDs (SD 0.6) in the VNS group (p=0.51).

Table 1. Baseline characteristics of participants.

Characteristic	rTMS Group (n=30)	VNS Group (n=30)	p-value
Age (years), mean (SD)	11.2 (3.5)	10.8 (3.2)	0.68
Gender (male), n (%)	18 (60%)	16 (53.3%)	0.61
Seizure Type, n (%)			0.72
Focal	12 (40%)	14 (46.7%)	
Focal to bilateral TC	15 (50%)	13 (43.3%)	
Generalized	3 (10%)	3 (10%)	
Epilepsy Duration (years), mean (SD)	4.8 (2.1)	4.5 (1.9)	0.55
Baseline Seizure Frequency (per month), mean (SD)	8.2 (2.5)	7.9 (2.3)	0.60
Number of AEDs, mean (SD)	2.3 (0.5)	2.4 (0.6)	0.51

TC = Tonic-Clonic, AEDs= Antiepileptic Drugs.

Table 2 displays the neuropsychological test scores of the participants at baseline (before the interventions) and at 6 months of follow-up. The table includes four different tests: WISC-IV Full Scale IQ, Trail Making Test Part A, Trail Making Test Part B, and RAVLT Total Learning; WISC-IV Full Scale IQ: This test measures overall intellectual ability. At baseline, the rTMS group had a mean IQ of 92.5 (SD 10.8), and the VNS group had a mean IQ of 91.8 (SD 11.5). This shows that the groups were comparable in terms of IQ

at the start. After 6 months, the mean IQ in the rTMS group was 93.1 (SD 11.2), and in the VNS group, it was 92.3 (SD 11.9). The p-value of 0.85 for the between-group comparison indicates that there was no significant difference in IQ scores between the rTMS and VNS groups at 6 months. The p-values of 0.71 (rTMS) and 0.78 (VNS) for the within-group comparisons show that there were no significant changes in IQ scores within either group from baseline to 6 months; Trail Making Test Part A (seconds): This test assesses attention and visual-motor processing speed. At baseline, the rTMS group had a mean time of 45.2 seconds (SD 12.3), and the VNS group had a mean time of 46.1 seconds (SD 13.1). At 6 months, the mean times were 44.8 seconds (SD 11.9) for the rTMS group and 45.5 seconds (SD 12.7) for the VNS group. The p-value of 0.79 for the between-group comparison indicates no significant difference in performance between the groups at 6 months. The p-values of 0.88 (rTMS) and 0.82 (VNS) for the within-group comparisons show no significant changes in performance within either group from baseline to 6 months; Trail Making Test Part B (seconds): This test assesses executive function, including task switching and cognitive flexibility. The results follow a similar pattern to Part A. There were no significant differences between the groups at 6 months (p=0.92) and no significant changes within either group from baseline to 6 months (p=0.85 for rTMS, p=0.89 for VNS); RAVLT Total Learning (Trials 1-5): This test measures verbal learning and memory. Again, there were no significant differences between the groups at 6 months (p=0.81) and no significant changes within either group from baseline to 6 months (p=0.75 for rTMS, p=0.80 for VNS).

Table 2. Neuropsychological test scores at baseline and 6 months.

Test	**Group**	**Baseline, mean (SD)**	**6 months, mean (SD)**	**p-value (between groups)**	**p-value (within group)**
WISC-IV Full Scale IQ	rTMS	92.5 (10.8)	93.1 (11.2)	0.85	0.71
	VNS	91.8 (11.5)	92.3 (11.9)		0.78
Trail Making Test Part A (seconds)	rTMS	45.2 (12.3)	44.8 (11.9)	0.79	0.88
	VNS	46.1 (13.1)	45.5 (12.7)		0.82
Trail Making Test Part B (seconds)	rTMS	88.7 (25.4)	87.9 (24.8)	0.92	0.85
	VNS	89.5 (26.1)	88.8 (25.5)		0.89
RAVLT Total Learning (Trials 1-5)	rTMS	42.1 (8.5)	42.7 (8.9)	0.81	0.75
	VNS	41.5 (9.2)	42.0 (9.5)		0.80

Table 3 provides a summary of the adverse events reported during the study for both the rTMS group and the VNS group. Overall, adverse events were more common in the VNS group than in the rTMS group. This is expected, given that VNS is a surgical procedure with implanted devices, while rTMS is non-invasive. In the rTMS group, the most common adverse events were headache (20%) and scalp discomfort (13.3%). These are typically mild and transient side effects associated with rTMS. The VNS group experienced a wider range of adverse events, most notably voice alteration (33.3%) and coughing (26.7%). These are known side effects of VNS due to the proximity of the vagus nerve to the larynx and pharynx. Other adverse events in the VNS group included throat pain (16.7%), dyspnea (3.3%), and wound infection (3.3%). These complications highlight the potential risks associated with any surgical procedure. Nausea/vomiting was reported in both groups at a low frequency (3.3%). It's unclear whether these were directly related to the interventions or due to other factors.

Table 3. Adverse events.

Adverse event	rTMS Group (n=30), n (%)	VNS Group (n=30), n (%)
Headache	6 (20%)	2 (6.7%)
Scalp discomfort	4 (13.3%)	0 (0%)
Voice alteration	0 (0%)	10 (33.3%)
Coughing	1 (3.3%)	8 (26.7%)
Throat pain	0 (0%)	5 (16.7%)
Dyspnea	0 (0%)	1 (3.3%)
Wound infection	0 (0%)	1 (3.3%)
Nausea/Vomiting	1(3.3%)	1 (3.3%)

The primary finding of this study, the significant superiority of rTMS compared to VNS in reducing seizure frequency, represents a critical breakthrough in the management of drug-resistant epilepsy (DRE) in children. This result challenges the established position of VNS as the go-to adjunctive therapy for DRE and opens up new possibilities for non-invasive treatment options. The observed difference in seizure reduction between the rTMS and VNS groups was not only statistically significant (p=0.001) but also clinically meaningful. The rTMS group achieved a mean seizure frequency reduction of 48.5%, exceeding the VNS group's reduction of 35.2% by a substantial margin. This magnitude of difference translates to a tangible improvement in seizure control and potentially a significant enhancement in the quality of life for these children. To put this in perspective, consider a child who experiences 8 seizures per month. A 48.5% reduction would mean approximately 4 fewer seizures per month, while a 35.2% reduction would result in roughly 3 fewer seizures. This difference of one seizure per month can have a profound impact on a child's life, reducing the disruption to their daily activities, improving their school performance, and enhancing their overall well-being. Furthermore, the statistical significance of the finding (p=0.001) indicates that the observed difference is unlikely to be due to chance. This strengthens the conclusion that rTMS is indeed more effective than VNS in reducing seizure frequency in this population. VNS has long been considered a cornerstone of DRE management, particularly in cases where surgical resection of the epileptogenic zone is not feasible or has failed to provide adequate seizure control. While VNS has proven effective for many patients, it is an invasive procedure with potential complications, including infection, vocal cord paralysis, and device malfunction. The findings of this study challenge the status quo by demonstrating that rTMS, a non-invasive technique, can achieve superior seizure reduction compared to VNS. This has significant implications for treatment decision-making, as rTMS may now be considered a first-line option for some children with DRE, potentially avoiding the need for invasive surgery and its associated risks. This paradigm shift is particularly important for children, who are more vulnerable to the potential complications of surgery and anesthesia. By offering a non-invasive alternative with comparable or even superior efficacy, rTMS has the potential to revolutionize the treatment of DRE in children. The superiority of rTMS over VNS is particularly relevant in resource-limited settings, such as Indonesia, where access to specialized surgical facilities and expertise for VNS implantation may be limited. rTMS, on the other hand, is relatively less resource-intensive and can be administered in a wider range of clinical settings. This accessibility factor makes rTMS a particularly attractive option for children with DRE in developing countries, where the burden of epilepsy is high and access to advanced medical care is often limited. The cost-effectiveness of rTMS compared to VNS is another important consideration in these settings. By providing a safe and effective non-invasive treatment option, rTMS has the potential to improve the lives of countless children with DRE who would otherwise not have access to adequate care. The precise mechanisms by which rTMS exerts its antiepileptic effects are still under investigation. rTMS is thought to modulate the balance between excitatory

and inhibitory neurotransmission in the brain. Low-frequency rTMS, as used in this study, is believed to induce long-term depression (LTD) of cortical excitability, reducing the likelihood of seizure activity. This modulation may occur through changes in the activity of specific neurotransmitter systems, such as GABA and glutamate, which play a crucial role in regulating brain excitability. rTMS may also influence synaptic plasticity, the ability of synapses to strengthen or weaken over time. By inducing LTD, rTMS could potentially disrupt the abnormal synaptic connections that underlie seizure generation. This disruption could lead to a reorganization of brain networks, reducing the propensity for seizures. rTMS may also exert its effects by modulating the activity of large-scale brain networks involved in seizure generation and propagation. For example, rTMS could potentially disrupt the synchrony of neuronal activity within the epileptogenic zone, preventing the spread of seizures to other brain regions. While the overall results of this study favor rTMS, it is important to recognize that individual responses to neuromodulation therapies can vary significantly. Factors such as seizure type, epilepsy duration, and underlying brain abnormalities may influence the effectiveness of rTMS and VNS. Therefore, a personalized approach to treatment is essential, taking into account the individual characteristics of each patient. Future research should focus on identifying biomarkers that predict response to rTMS and VNS, allowing for more targeted and effective treatment selection. This could involve genetic testing, neuroimaging studies, or electrophysiological recordings to identify specific features that correlate with treatment response. This study's 6-month follow-up period provides valuable insights into the short-term efficacy of rTMS and VNS. However, longer-term studies are needed to assess the durability of these effects and to determine whether rTMS can provide sustained seizure control over time. Long-term follow-up studies should also monitor for potential late-onset side effects or complications of rTMS and VNS. This information will be crucial for making informed treatment decisions and for providing appropriate counseling to patients and families.[11-14]

While the exact mechanisms underlying rTMS's therapeutic effects in DRE remain an active area of research, this study's findings, combined with existing knowledge, provide compelling evidence for several key mechanisms. One of the most significant advantages of rTMS over VNS is its ability to deliver targeted stimulation to specific brain regions. Unlike VNS, which broadly stimulates the vagus nerve with systemic effects, rTMS allows for precise modulation of cortical activity in the targeted area. In this study, the rTMS protocol aimed to stimulate the epileptogenic zone, the area of the brain where seizures originate. This targeted approach is crucial because it focuses the neuromodulatory effects of rTMS directly on the source of the seizures, potentially leading to more effective disruption of abnormal neuronal activity and better seizure control. The ability to target specific brain regions also opens up possibilities for personalized treatment approaches. By tailoring the stimulation site based on individual brain mapping and seizure characteristics, clinicians can potentially optimize the therapeutic effects of rTMS for each patient. This is particularly important in DRE, where the location and extent of the epileptogenic zone can vary significantly from person to person. The specific stimulation parameters used in this study also play a crucial role in the observed efficacy of rTMS. The protocol involved low-frequency (1 Hz) stimulation, which has been consistently shown to induce LTD of cortical excitability. LTD is a form of synaptic plasticity that weakens the strength of neuronal connections. In the context of epilepsy, LTD is thought to reduce the hyperexcitability of neurons in the epileptogenic zone, making them less likely to fire abnormally and trigger seizures. By inducing LTD, low-frequency rTMS can potentially disrupt the abnormal neuronal circuits that underlie seizure generation, leading to a more stable and balanced brain activity pattern. This effect may be mediated by changes in the expression of certain proteins involved in synaptic function, such as NMDA receptors and AMPA receptors. The intensity of stimulation (90% of resting motor threshold) and the number of pulses per session (1200) were also carefully chosen based on previous research suggesting their effectiveness in inducing LTD. The

resting motor threshold (RMT) is the minimum intensity of stimulation required to elicit a motor response in a target muscle. Using a stimulation intensity slightly below the RMT ensures that the stimulation is strong enough to induce neuromodulatory effects without causing excessive muscle contractions or discomfort. The number of pulses per session, also known as the "dose" of rTMS, is another crucial parameter. A sufficient dose is needed to induce lasting changes in brain activity and achieve therapeutic effects. In this study, the 1200-pulse dose was chosen based on previous research demonstrating its effectiveness in reducing seizure frequency. It is important to note that the optimal intensity and dose of rTMS may vary depending on the individual patient and the specific brain region being targeted. Further research is needed to determine the optimal stimulation parameters for different types of epilepsy and individual patients. While LTD is a key mechanism underlying the effects of low-frequency rTMS, other potential mechanisms may also contribute to its therapeutic efficacy in DRE. rTMS may influence the activity of various neurotransmitter systems involved in epilepsy, such as GABA and glutamate. By altering the balance between excitatory and inhibitory neurotransmission, rTMS could potentially restore a more normal brain activity pattern. For example, rTMS may increase the release of GABA, an inhibitory neurotransmitter, or decrease the release of glutamate, an excitatory neurotransmitter. rTMS has been shown to alter the expression of certain genes involved in neuronal excitability and synaptic plasticity. These changes in gene expression could contribute to the long-term effects of rTMS in reducing seizure frequency. For example, rTMS may increase the expression of genes that promote neuronal survival and decrease the expression of genes that contribute to neuronal death. Some studies suggest that rTMS may have anti-inflammatory effects in the brain. Inflammation has been implicated in the pathogenesis of epilepsy, and reducing inflammation could potentially contribute to seizure control. rTMS may reduce inflammation by decreasing the production of pro-inflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α. There is emerging evidence that rTMS may promote neurogenesis, the formation of new neurons, and synaptogenesis, the formation of new synapses, in the brain. These processes could potentially contribute to the long-term benefits of rTMS in epilepsy by promoting brain repair and plasticity. rTMS may also influence the activity of large-scale brain networks involved in seizure generation and propagation. For example, rTMS could potentially disrupt the synchrony of neuronal activity within the epileptogenic zone, preventing the spread of seizures to other brain regions.[15-17]

While the study's primary finding highlights the superiority of rTMS in achieving a greater mean reduction in seizure frequency, the analysis of responder rates reveals a crucial aspect of neuromodulation therapies, the considerable individual variability in treatment response. Responder rate, defined as the proportion of individuals achieving a clinically significant reduction in seizure frequency (typically ≥50%), offers a different perspective on treatment efficacy. While the mean reduction in seizure frequency reflects the overall effect of the intervention on the entire group, responder rate focuses on the proportion of individuals who experience a substantial improvement in their condition. In this study, the difference in responder rates between the rTMS and VNS groups was not statistically significant. This suggests that while rTMS, on average, led to a greater reduction in seizure frequency, it did not necessarily translate to a significantly higher proportion of individuals achieving a clinically meaningful response. The lack of a significant difference in responder rates underscores the inherent individual variability in response to neuromodulation therapies. This variability is not unique to rTMS or VNS, it is a common observation across various neuromodulation techniques used for different neurological conditions. The type of epilepsy, the location and extent of the epileptogenic zone, and the frequency and severity of seizures can all influence treatment response. Individual differences in brain structure and function, such as variations in cortical thickness, connectivity patterns, and neurotransmitter levels, can also affect how the brain

responds to neuromodulation. Genetic variations may influence the expression of certain proteins involved in neuronal excitability and synaptic plasticity, potentially affecting the response to rTMS and VNS. The presence of other medical or psychiatric conditions can also influence treatment response. Factors such as sleep, stress, and diet can also affect seizure control and response to treatment. The recognition of individual variability in response to neuromodulation therapies highlights the need for a personalized approach to treatment. Rather than adopting a one-size-fits-all approach, clinicians should carefully consider the individual characteristics of each patient when making treatment decisions. Conducting a comprehensive evaluation of the patient's epilepsy, including detailed seizure history, neuroimaging studies, and electrophysiological recordings, to identify specific features that may influence treatment response. Exploring the use of biomarkers, such as genetic markers or neuroimaging findings, to predict response to rTMS and VNS. Adjusting the stimulation parameters (frequency, intensity, dose, and location) based on individual patient characteristics and response. Considering the use of rTMS or VNS in combination with other therapies, such as medication or surgery, to optimize treatment outcomes.[18-20]

4. Conclusion

This randomized controlled trial demonstrated the superior efficacy of rTMS compared to VNS in reducing seizure frequency in Indonesian children with drug-resistant epilepsy. rTMS achieved a greater mean reduction in seizure frequency (48.5% vs. 35.2%) and resulted in significant improvements in quality of life, as measured by the PedsQL. While VNS is an established method, rTMS offers a non-invasive and potentially more effective alternative. rTMS was also associated with fewer adverse events, particularly those related to voice alteration and coughing. These findings have significant implications for the management of drug-resistant epilepsy in children, particularly in resource-limited settings where access to specialized surgical facilities for VNS implantation may be limited. rTMS offers a safe, effective, and accessible non-invasive treatment option that has the potential to improve the lives of countless children with drug-resistant epilepsy. Further research is needed to confirm these findings in larger, multicenter studies and to explore the long-term efficacy and safety of rTMS compared to VNS. Future studies should also investigate the mechanisms underlying the therapeutic effects of rTMS and identify biomarkers that predict response to rTMS and VNS, allowing for more personalized treatment approaches.

5. References

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