Short-Term Follow-Up for Patients with Refractory Epilepsy Receiving T-VNS Compared to Those with a VNS-Implanted Device, an Electroencephalography-Based Study

Abstract

Refractory epilepsy defined as persistent seizure occurrence despite triple anti-epileptic drugs treatment with maximum dose. accounting for 30-40% of all epileptic patient. Vagus nerve stimulation (whether implanted or transcutaneously performed) is advanced treatment option for these patients, both procedures show rewarding and promising outcome in reducing seizure frequency and duration. Electroencephalogram is a non-invasive procedure used to measure electrical brain activity and demonstrating epileptic discharges if present.

This study aims to assess the short-term efficacy of Transcutaneous Vagus Nerve Stimulation in comparison to Invasive Vagus Nerve Stimulation in reducing epileptic discharges using Long Term Video Electroencephalography.

This is a prospective, comparative study that included 30 patients clinically diagnosed with refractory epilepsy. The study sample was divided into two groups; Group 1; includes 15 patients receiving Transcutaneous Vagal Nerve Stimulation, and Group 2, includes 15 patients receiving Implanted Vagal Nerve Stimulation. Participants in Group 1 and Group 2 were matched on age, gender, residency, occupation, educational level and clinical criteria.

Patients belong to both groups were assessed with Long Term Video Electroencephalography at baseline visit and 3 months after the intervention.

The results showed that all patients within both groups had abnormal Electroencephalography findings before the intervention. The second Electroencephalography test, 3 months after the intervention, normalized in 3 patients (20.0%) within Group 1 and 11 patients (73.3%) within Group 2. The difference was statistically significant ($p = 0.023$).

This study concluded that the short-term effect of Implanted Vagal Nerve stimulation was the best for the reduction of epileptic discharges recorded in patients with refractory epilepsy.

Keywords: Electroencephalography (EEG), Invasive Vagus Nerve Stimulation (i-VNS), Transcutaneous Vagus Nerve Stimulation (t-VNS).

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Introduction

Epilepsy is defined by international league against epilepsy as a chronic neurological condition in which a patient suffers from repeated seizures resulting in psychological, physical, and economical sequalae. On the other hand, Refractory epilepsy is defined as persistent seizure occurrence despite triple anti-epileptic treatment with maximum dose. Refractory epilepsy represents a serious clinical issue in neuromedicine that require in addition to poly-drug treatment, a neuromodulation procedure to control seizures when multiple drug therapy is not sufficient (Singh et al., 2020; Menachema et al., 2023).

In late 20th century Invasive Vagus Nerve Stimulation (i-VNS) was developed and when regarded as treatment option for refractory epilepsy shows rewarding results in controlling seizure (Helmers et al., 2012; Li et al., 2020). Many large cohort studies and meta-analysis illustrate high response rate in decreasing seizure frequency up to 50% in about 45-65% of epileptic patients and reported increase in effectiveness (reduce seizure occurrence) as time passes (Toffa et al., 2020 Shan et al., 2022; Chen et al., 2025 and Lee et al., 2025).

The i-VNS is a neuromodulation procedure based on implantation of the device under the left clavicle connected to coil rounded over cervical branch of vagus nerve that ends in nucleus tactus solitarius that projecting to multiple cortical areas (Zhang et al., 2024). Clinically, the i-VNS is recommended for refractory epilepsy and depression, and recently implicated for headache, heart failure gastro-intestinal disease and asthma. Furthermore, the application of i-VNS is updated for rehabilitation of upper limbs, especially after cerebrovascular accidents (Yuan & Silberstein, 2016; Zhang et al., 2024). Still, there were a lot of serious complications of i-VNS, primarily related to the implantation surgery such as infection at site of surgery, asystole during surgery, vocal cord paresis and bradycardia. Other complications were related to the stimulation mechanism, like pharyngitis, change in voice tone and intensity, cough and headache. Such side effects usually can be overcomed by readjustment of the stimulation and, in severe cases, instrument deactivation (Ben-Menachem et al., 2015).

Nevertheless, the complications associated with the implementation surgery necessitated the development of less risky neuromodulation approach with minimum side effect; Transcutaneous Vagus Nerve Stimulation (t-VNS) (Barbella et al., 2018). Although many short term studies had approved the efficacy of the t-VNS in seizure reduction, still its efficacy is less than that of i-VNS. However, the side effects that may accompany the t-VNS is much lower (Ben-Menachem et al., 2015; Costa et al., 2023). Numerous clinical researches, trials and studies supported by meta-analysis had proved t-VNS safety with minimal side effects like skin irritation at site of stimulation, headache and slight ear pain. That is why, no withdrawal for t-VNS has been recorded (Kim et al., 2022). The t-VNS is recommended for different clinical conditions like; drug-resistant epilepsy, depression, migraine, chronic pain and others (Hilz, 2022 and Gerges et al., 2024). Its mechanism of action depends on stimulation of auricular branch then transferring electrical impulses through afferent divisions of vagus nerve that end in nucleus tractus solitrius and locus ceruleus then projecting to cortical areas that influencing mood, cognition and autonomic system (Poppa et al., 2021).

The electroencephalography (EEG) represent a fundemental diagnostic procedure used to assessing brain activity and recording abnormal epileptic discharges, if present, and to follow the patient with epilepsy (Ajeena and Al-Muhanna, 2016; Ajeena et al., 2022). The EEG study done for patients after intervention showed undefended fact that i-VNS ameliorate synchronization of abnormal cortical activity in responders (Sangaré et al., 2020 and Lanzone et al., 2022). However, many studies postulated that t-VNS modify the pattern of epileptic discharges in EEG recording, modulating epileptic activity with reduction in seizure frequency and duration (Sarma et al., 2023).

The Long Term Video Electreoencephalographic Monitoring (LTVEM) is a special diagnostic procedure that recording brain activity in synchronization with video recording for extended period usually more than 24 hours. It is a pioneer in evaluation of patients with suspected seizure or seizure like events especially when routine EEG shows normal record (Shih et al., 2018 and Tatum et al., 2021). It aid to increase the accuracy of the diagnosis by relating the clinical manifestation with brain activity recorded by EEG and enable accurate discrimination between epileptic and non-epileptic events, classification of seizure a long with seizure onset localization (Mann et al.,2021 and Aslan et al., 2022).

Aim of the study

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This study aims to assess the short-term efficacy of Transcutaneous Vagus Nerve Stimulation in comparison to Invasive Vagus Nerve Stimulation in reducing epileptic discharges using Long Term Video Electroencephalography Monitoring.

Material and methods

A randomized controlled trial (RCT) was not practicable owing to the intrinsic variations in the interventional modalities (non-invasive vs. surgical) and patient predilections; thus, a prospective comparative cohort design was implemented that was done in Al-Imam Al-Sadiq teaching hospital (a tertiary care neurology center) from January 2025 through September 2025. The study was carried out in line with the ethical requirements of the responsible committee on human experimentation of the ethical considerations of the Declaration of Helsinki (revised 2000) by the World Medical Association. Ethical approval of the study protocol was provided by the Local Health Directorate Ethics Committee, Babylon, Iraq (24056 at 26/12/2024). All individual adult participants who were part of the study received written informed consent after the nature, purpose, and procedures of the research were fully stated. To ensure confidentiality of the participants, all data were gathered and interpreted with anonymous codes; no personal details, including names, initial or hospital identification numbers, are brought out in the current manuscript.

A total of 40 patients were assessed for eligibility, of whom 30 patients, aged above 18 years, with refractory epilepsy were included in this study. They have no history of previous neurological insult (e.g. cerebrovascular accident) or history of head trauma. As well, if patients with psychiatric illnesses, other implanted devices (like pacemakers), or specific epilepsy types/syndromes were excluded.

The study sample was divided into two groups: Group 1; includes 15 patients receiving t-VNS, and Group 2, which includes 15 patients receiving i-VNS. The group assignment was conducted on a joint clinical decision by the treating neurologist and the patient with the factors being taken into consideration: the ability to tolerate surgery, surgical eligibility, and personal choice, (flow chart).

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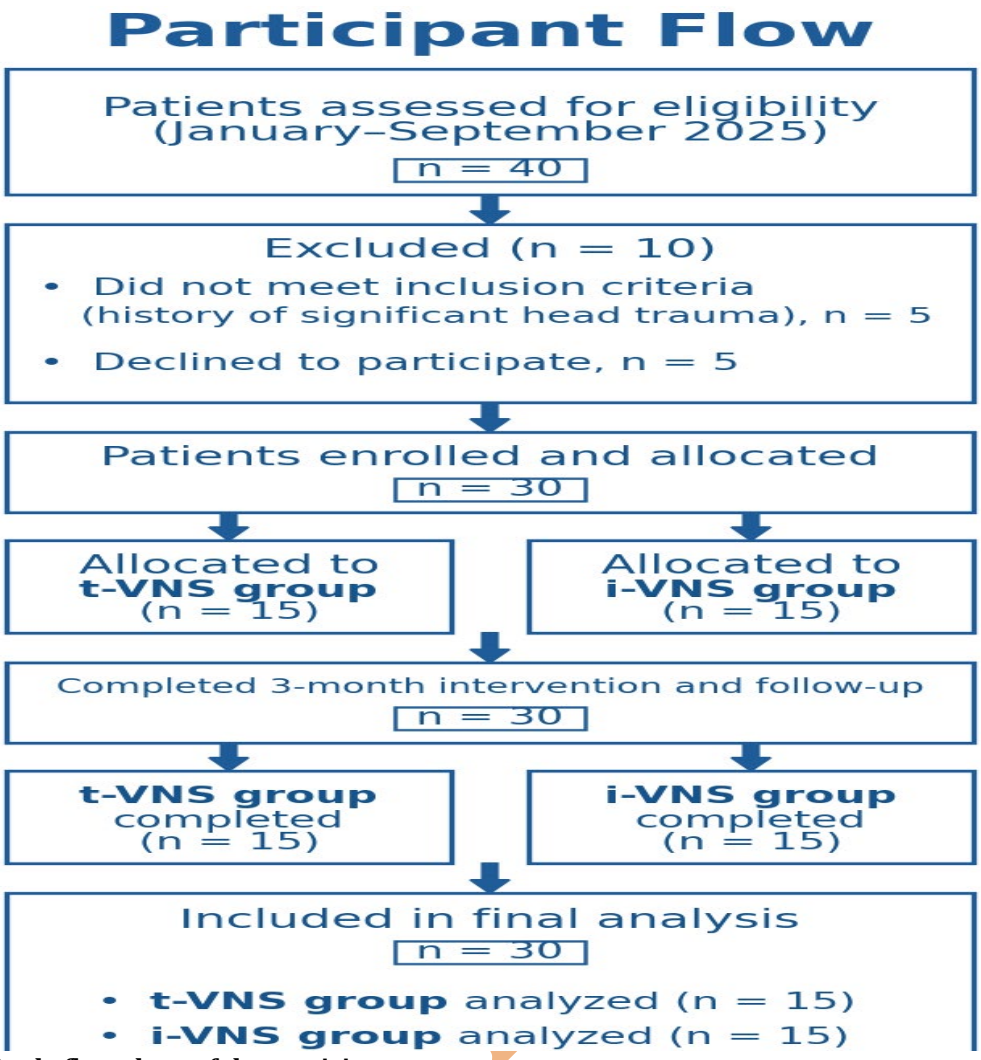

Study flow chart of the participants

For each patient within Group 1, the t-VNS (VNS Therapy® System, LivaNova PLC, London, UK) was introduced for 3 months according to established protocols, with 2 sessions per day, each lasting for 30 minutes, separated by one hour, 5 days a week. The stimulation specification was as follows: a continuous biphasic waveform that was asymmetrically balanced with a 200 µs wave width, 5 Hz wave density. The intensity was adjusted to the strongest sensation the individual can tolerate without pain, typically 4–6 mA.

For Group 2, the stimulation parameters were set according to the related clinical guidelines (standard initial settings: output current 0.25 mA, frequency 30 Hz, pulse width 500 µs, signal ON time 30 sec, OFF time 5 min).

The LTVEM was done for each one of the participants twice; the first was before the intervention and the second was 3 months after. The technique adopts the standardized scalp electrodes using the 24-channel system (Nihon Kohden EEG-1200 system) with periods of eyes open/closed, photic stimulation, hyperventilation, and sleep, if possible.

For statistical analysis, the Statistical Package for Social Sciences (SPSS) version 28 software (SPSS Inc., Chicago, IL, USA) for Windows 11 was used for the statistical analysis of data that was obtained as a Microsoft excel format sheet. Continuous variables, including age and age at seizure onset, were presented as mean ± standard deviation (SD), and categorical variables, including gender, residency, occupation, and education, were summarized as counts and percentages. In between-group comparisons for continuous variables were performed using independent t-tests, while for categorical variables given the small sample size chi-square test was not applicable and were compared using Fisher's exact test, Within-group comparisons of seizure frequency were

conducted using the Wilcoxon signed-rank test due to non-normal distribution and small sample size. Between-group comparisons of seizure reduction were performed using the Mann–Whitney U test. A p-value of <0.05 was considered statistically significant.

Result

Table 1 shows the demographic data (basic participant characteristics) of the participants.

Table 1: Basal demographic data of the study participants

Variable	t-VNS (n=15)	i-VNS (n=15)	P value
Age group (years)			
<20	3 (20.0%)	2 (13.3%)	*0.784*
20–29	6 (40.0%)	7 (46.7%)	
30–39	4 (26.7%)	3 (20.0%)	
≥40	2 (13.3%)	3 (20.0%)	
Mean ± SD	28.3 ± 8.1	29.1 ± 10.8	
Gender			
Male	8 (53.3%)	7 (46.7%)	*0.715*
Female	7 (46.7%)	8 (53.3%)	
Residency			
Urban	10 (66.7%)	9 (60.0%)	*0.702*
Rural	5 (33.3%)	6 (40.0%)	
Occupation			
Housewife	5 (33.3%)	4 (26.7%)	*0.786*
Employee	4 (26.7%)	5 (33.3%)	
Free job	3 (20.0%)	2 (13.3%)	
Retired	2 (13.3%)	2 (13.3%)	
Student	1 (6.7%)	2 (13.3%)	
Education			
Illiterate	2 (13.3%)	1 (6.7%)	*0.468*
Primary school	5 (33.3%)	6 (40.0%)	
Secondary school	3 (20.0%)	3 (20.0%)	
College	5 (33.3%)	5 (33.3%)	
Age at seizure onset (years)			
Mean ± SD	9.8 ± 5.9	8.1 ± 5.2	*0.087*

Table 2: Seizure Outcomes and Effect Size Analysis

Measure	t-VNS (n=15)	i-VNS (n=15)	Between-Group p-value	Effect Size (95% CI)
Baseline seizures/week, mean (range)	28.9 (5–95)	5.2 (1–8)	—	—
Post-VNS seizures/week, mean (range)	9.4 (2–36)	0.9 (0–2)	—	—
Raw reduction (seizures/week), mean	19.5	4.3	***0.038***	Hedges' g = 1.36 (0.04–2.68)
% reduction, median (IQR)	68.1% (52–95)	82.5% (74–98)	*0.17*	—
ANCOVA: Adjusted post-VNS seizures (mean ± SE)	8.5 ± 2.0	1.2 ± 2.0	***0.044***	Partial η^2 = 0.43
EEG normalization post-VNS, n (%)	3 (20.0%)	11 (73.3%)	***0.023***	RD = 0.53 (0.18–0.83)

Abbreviations: VNS = Vagus Nerve Stimulation; IQR = Interquartile Range; SE = Standard Error; RD = Risk Difference.

Table 3: Spearman's Rank Correlation (ρ) Between Clinical Variables

Variable 1	Variable 2	Spearman's ρ	p-value	Interpretation
Age	**Seizure reduction (%)**	−0.15	*0.68*	Very weak negative relationship.
Age at seizure onset	**Seizure reduction (%)**	−0.41	*0.16*	Moderate negative trend, not significant.
Baseline seizure frequency	**Seizure reduction (%)**	**−0.69**	***0.024***	**Strong negative correlation.**
Baseline seizure frequency	**Post-VNS seizure frequency**	**0.92**	***<0.001***	**Very strong positive correlation.**
Age	**EEG improvement**	0.12	*0.71*	Negligible relationship.
Age at seizure onset	**EEG improvement**	−0.32	*0.29*	Weak negative relationship.

Abbreviations: VNS = Vagus Nerve Stimulation; EEG improvement = conversion from abnormal to normal EEG after VNS.

Notes:

- Seizure reduction (%) calculated as: [(Pre – Post) / Pre] × 100.
- EEG improvement coded as: 0 = No change (abnormal → abnormal), 1 = Improved (abnormal → normal).
- **Bold** indicates statistical significance ($p < 0.05$).

Table 4: Seizure Frequency, Duration, and Percent Change After VNS

Measure	t-VNS (n=15)	i-VNS (n=15)	p-value
Before VNS – Seizures/week, mean (range)	28.9 (5–95)	5.2 (1–8)	—
After VNS – Seizures/week, mean (range)	9.4 (2–36)	0.9 (0–2)	—
Absolute reduction, mean	19.5	4.3	*0.038*
Percent reduction – median (IQR)	68.1% (52.0–95.0%)	82.5% (74.0–98.0%)	*0.17*
Seizure duration after VNS – n (%) reduced	13 (86.7%)	14 (93.3%)	0.540

Abbreviations: VNS = Vagus Nerve Stimulation; IQR = Interquartile Range.

Discussion

The demographic distribution of the participants (Table 1) showed no significant difference when considering both groups. This is very important so we can disregard the effect of age, gender, residency, occupation, education and age at seizure onset as being the cause for the findings of this study as some researches blame the sex, age of the patient and the age at onset of seizure to affect the response to VNS (Gianlorenço et al, 2024, Wessel et al, 2024 and Urian et al, 2025).

Although the age of participants was insignificantly different in both groups of this study, it is noticed that the youngest patients showed better gained results. This possibly due to the normal physiologic and structural changes with aging and because younger patients usually are more committed to treatment sessions and they tolerate the t-VNS sessions better also they hope to get rid of seizure and completely cure from epilepsy. This finding comes in parallel with the findings of Trifilio et al, 2023 and Gianlorenço et al, 2024, considering that some other studies disagree (Gurbani et al, 2016 and Wessel et al, 2024).

As there were no much reported studies focusing on possible impact of the education, occupation and residency on patients outcome, we preferred to select the patients of nearly similar demographic characteristics to avoid their possible impact.

Results represented in table number 2 postulated that both VNS modalities reduce seizure frequency, i-VNS is significantly more effective in achieving EEG normalization and superior seizure control after adjusting for baseline severity, with large effect sizes supporting clinical relevance. After VNS, mean weekly seizures decreased in both groups indicating that no matter what type of VNS used, seizure frequency is effectively reduced post intervention. Similarly, the duration of the seizure decreases in both groups post-intervention. These results were consistent with the findings

of Hajtovic et al., 2022; Agus et al., 2025; Alwazna et al., 2025; Chen et al., 2025; Gong et al., 2025; Marti et al., 2025 and Muniyandi et al., 2025. However, Bauer et al., 2016 and Makkawi et al., 2025 reported no strong or consistent evidence that t-VNS reduce seizure frequency. And that could be attributed to different t-VNS regimen used (regarding stimulation parameters) and other confounders such as personal variation, type of seizure (whether generalized or focal) or epilepsy syndromes.

The i-VNS is significantly more effective in achieving EEG normalization (Table 2). Although the t-VNS group had a larger absolute reduction in seizures, the i-VNS group achieved near-complete seizure control from a lower baseline and that supported by other studies (Wu et al., 2020; Lampros et al.,2021; Panebianco et al., 2022; Makkawi et al., 2025; Moro et al., 2025. All these studies document that more than 50% reduction of seizure occurs with i-VNS while t-VNS shows less effect.

Table (3) shows that there is a strong negative correlation between Baseline Seizure Frequency versus percent of Seizure Reduction, meaning patients with higher baseline seizure counts showed a smaller percentage reduction after VNS. This highlights that absolute reduction may be misleading without considering baseline severity. by simple meanings if patient number one had only 4 seizure per months after treatment with VNS show absolute reduction up to 50% and still had 2 seizure per month, on the other side patient number two who had about 40 seizure per month and with 50 % reduction after VNS treatment still having 20 seizure per month, patient number two will be in more burden and more clinically disabled than patient number one, despite that both of them showed exactly same reduction percent. That supported by Jain et al., 2021;Chen et al., 2025; Niazi et al., 2025, all of them considering baseline severity is a predictor of response not just percent of reduction and not in agreement with Li et al., 2020 who consider seizure percentage reduction is major factor in prediction for improvement. That could be related to multifactorial corporation to predict the improvement or response to treatment like seizure severity, underling clinical condition of patient (if he already had cognitive or clinical disability before starting treatment with VNS), duration and shift in seizure time scale (whether daily or weekly). Additionally, an extremely strong positive correlation indicates that pre-treatment seizure burden is a major predictor of post-treatment burden, regardless of VNS type. And that agreed with Touma et al., 2022; Haneef & Skrehot (2023); Gouveia et al. (2024) and Samanta et al., (2025), on the other hand not in parallel with Panebianco et al., (2022) and Kostov et al., (2025) whom postulated other factors as predictor for post-tretament burden like stimulation parameters setting, duration of treatment and that could be due to short duration for follow up in our study and usage of one setting of parameters that limit the effect of treatment time and stimulation parameters. There were no significant correlations were found, suggesting that in this small sample, patient age and age at epilepsy onset did not strongly influence short-term EEG or seizure frequency outcomes , since Chen et al., 2021 who document that early age at seizure onset markedly control long-term seizure control but age effect on EEG abnormality at baseline assessment not do so Naganur et al., 2025 Pirgit & Beniczky (2024). postulated modest age effect on predicting seizure occurrence and EEG abnormality. That could be due to age & age at epilepsy onset are long term comorbidity determinant rather than short term follow up.

The baseline weekly seizure frequency was higher in the t-VNS group than in the i-VNS group (Table 4). After 3 months of VNS, seizure frequency decreased in both groups. The absolute reduction was greater in the t-VNS group (mean reduction 19.5 vs. 4.3 seizures/week, $p = 0.038$). However, when expressed as median percent reduction from baseline—which accounts for differences in baseline severity—the t-VNS group achieved 68.1% compared to 82.5% in the i-VNS group. Seizure duration was reduced in the majority of patients in both groups (86.7% in the t-VNS group and 93.3% in the i-VNS group).

Also table number (4) showed that After VNS, mean weekly seizures decreased in both groups indicating that no matter what type of VNS used, seizure frequency is effectively reduced post-intervention. Similarly, the duration of the seizure decreases in both groups post-intervention. These results were consistent with the findings of Agus et al., 2025; Alwazna et al., 2025; Chen et al., 2025; Gong et al., 2025; Marti et al., 2025; Muniyandi et al., 2025 and, Hajtovic et al., 2022. However, Bauer et al., 2016 and Makkawi et al.,2025 reported no strong or consistent evidence that t-VNS reduce seizure frequency.

Conclusion:

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In a patient with refractory epilepsy, a short course of stimulation by an implantable Vagus nerve device shows more effectiveness with EEG clearance than when the stimulation is given per transcutaneous route.

Limitations

Notwithstanding the promising outcomes, some important limitations must be acknowledged. First, the sample size (n=30) is too small to provide much statistical power in the analysis and generalize the conclusions; the study might have been underpowered to pick up more subtle and thus significant differences between the two interventions. Second, the non-randomized, comparative design presents the possibility of selection and allocation bias. Although the match of the groups was made with the basis of the main demographics, the allocation to t-VNS or i-VNS occurred due to a common clinical choice that could have been biased with the unmeasured confounding elements, including disease severity at the baseline, the kind of epilepsy syndrome, and patient comorbidities. Third, three months of short-term follow-up does not adequately measure the long-term effectiveness, tolerance, and possible habituation of each of the VNS modality. Lastly, the researchers did not blind either the subjects or outcome assessors; although objective EEG normalization was one of the main outcomes, the awareness of the treatment allocation might have contributed to bias in clinical and patient reporting.

Authors contribution

Sura contributed to the conception and design of the study, acquisition and analysis of data, definition of intellectual content, literature search, and drafted the initial manuscript. **Ihsan** contributed to the design, supported data acquisition, definition of intellectual content, literature search, critically revised the manuscript for important intellectual content, and supervised the project. Both authors read and approved the final manuscript for publication.

Conflicts of Interest/Competing Interests

The authors disclose any conflicts of interest they may have with the publication of this manuscript or with any institution or product mentioned herein. This includes conflicts related to products that compete with those referenced in the study. The authors reported no potential conflicts of interest.

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