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A retrospective study of transcutaneous vagus nerve stimulation for poststroke epilepsy

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Abstract

Background: This study assessed the effect transcutaneous vagus nerve stimulation (TVNS) for poststroke epilepsy (PSE).

Methods: Fifty-two patients with PSE were included in this study. Twenty-seven patients received TVNS, 30 minutes each session, once daily, twice weekly for a total of 4 weeks; and were assigned to the treatment group. Twenty-five patients were at waiting list and were assigned to the control group. The primary outcome included weekly seizure frequency. The secondary outcomes consisted of each seizure episode, and quality of life, measured by the Quality of Life in Epilepsy Inventory-31 (QOLIE-31), as well as the adverse events. All outcomes were measured before and after 4-week treatment.

Results: After treatment, TVNS failed to show better outcomes in weekly seizure frequency (treatment group, $P = .12$; control group, $P = .56$), seizure episode (treatment group, $P = .65$; control group, $P = .92$), and QOLIE-31 (treatment group, $P = .73$; control group, $P = .84$) compared with these before the treatment. Furthermore, TVNS also did not elaborate the promising effect in seizure frequency ($P = .81$), seizure episode ($P = .75$), and QOLIE-31 ($P = .33$), compared with these in the control group. In addition, minor and acceptable adverse events were recorded in this study.

Conclusion: The results of this study showed that TVNS may be not effective for Chinese patients PSE after 4-week treatment.

Abbreviations: AED = antiepileptic drug, AEs = adverse events, PSE = poststroke epilepsy, QOLIE-31 = Quality of Life in Epilepsy Inventory-31, TVNS = transcutaneous vagus nerve stimulation.

Keywords: effect, epilepsy, poststroke, transcutaneous vagus nerve stimulation

1. Introduction

Epilepsy is one of the most common chronic neurological disorders, and affects more than 50 million people worldwide.[1–3] It has been reported that its prevalence was 6 to 8 per 1000 people, and its incidence was 26 to 40 per 100,000 people each year.[4] The other study has also reported that about 10% people will suffer from at least 1 seizure in their lifetime.[5] Of those, one third people will develop to epilepsy.[5,6]

Many factors can cause epilepsy. However, stroke is one of the most common reasons for epilepsy in the elderly.[7,8] It is reported that 11.5% of patients with poststroke had a high risk of developing poststroke epilepsy (PSE) by 5 years, according to the Oxfordshire community stroke project.[9]

Regarding the treatment, antiepileptic drug (AED) therapy is reported to be effective in preventing recurrence and treatment in patients with epilepsy.[10–12] However, if patients take long-term medications, serious adverse events (AEs) also accompanied with them.[13,14] Additionally, a minority of patients can be cured by the invasive resective epilepsy surgery. Thus, it is very important and necessary to find out an alternative therapy with few AEs to treat such disorder.

Invasive transcutaneous vagus nerve stimulation (TVNS) is a potential intriguing candidate.[11–14] It has been reported that TVNS has been used to treat patients with epilepsy, and have achieved a promising effectiveness.[15–17] However, no studies provide published data to support the TVNS therapy for treating PSE. In this study, we firstly evaluated the potential effects of TVNS therapy for the treatment in patients with PSE.

2. Methods and design

2.1. Design

This study was approved by the Ethical Committee of First Affiliated Hospital of Jiamusi University. It was conducted between January 2016 and May 2017 at First Affiliated Hospital of Jiamusi University. All patients provided written informed consent. Fifty-two patients with PSE were included in this study. They were equally divided into a treatment group, underwent TVNS therapy, and a control group, at waiting list. The outcomes were measured before and after treatment. The patients and investigators were not blinded because of the retrospective study. However, the analyst and outcome assessors were masked to the design of this study.

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G-fS and H-yW contributed equally to this study.

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Table 1

Characteristics of included patients at baseline.

Characteristics	Treatment group (n = 27)	Control group (n = 25)	*P* value
Mean age, y	54.8 ± 13.6	52.6 ± 14.3	.57
Gender, n, %			
Male	17 (63.0)	16 (64.0)	.94
Female	10 (37.0)	9 (36.0)	.94
Epilepsy duration, mo	8.6 ± 3.1	8.3 ± 3.4	.74
Stroke duration, mo	15.4 ± 4.9	16.1 ± 5.2	.62
Weight, kg	62.9 ± 11.3	63.2 ± 11.7	.93
Epilepsy types, n, %			
Systemic attack	4 (14.8)	6 (24.0)	.40
Partial attack	16 (59.3)	13 (52.0)	.60
Atypical attack	7 (25.9)	6 (24.0)	.87
Previous antiepileptic drugs used, n, %			
Carbamazepine	4 (14.9)	5 (20.0)	.62
Gabapentin	5 (18.5)	4 (16.0)	.81
Topiramate	11(40.7)	9 (36.0)	.73
Phenytoin	3 (11.1)	2 (8.0)	.70
Lorazepam	4 (14.8)	5 (20.0)	.62

Data are present as mean ± standard deviation or number (%).

2.2. Patients

This study included 52 eligible patients with epilepsy aged from 22 to 73 years old. All patients were reported to experience more than 2 epilepsy attacks during the past 3 months with 2 episodes at least 24 hours intervals before the recruitment. Additionally, all patients underwent at least 1 antiepileptic drug before the study. The exclusion criteria applied to subjects who had brain tumors, abnormal functions of liver and kidney, history of drug or alcohol addiction, drug allergy history, history of epilepsy, status epilepticus, or epilepsy surgeries before the stroke, gestational or lactating women, and received TVNS therapy 1 month before the treatment.

2.3. Treatment

Twenty-seven patients in the treatment group received TVNS therapy at bilateral auricular concha by using TVNS device NEMOSR (cerbomed GmbH, Erlangen, Germany). It has 2 electrode clips, which placed at the ear vagus nerve. Each patient received TVNS, 30 minutes each session, 1 session daily, twice weekly for a total of 4 weeks. Twenty five patients in the control group were at waiting list during the treatment period.

2.4. Outcomes

The primary outcome was weekly seizure frequency. The secondary outcomes included seizure episode, and quality of life, measured by the Quality of Life in Epilepsy Inventory-31 (QOLIE-31).[18] Additionally, AEs were also recorded duration the treatment period. All primary and secondary outcomes were measured and assessed before and after 4 weeks treatment.

2.5. Statistical analysis

All data were analyzed by a professional statistician using SPSS Statistics 17.0 (IBM Corp, Armonk, NY). Student *t* test was performed to analyze the continuous outcome data. Pearson χ^2 or Fisher exact tests were applied to analyze the categorical outcome data. Statistical significance was defined as $P < .05$.

3. Results

The characteristics of all 52 included patients are listed in Table 1. No significant differences were found regarding age, gender, epilepsy duration, stroke duration, weight, epilepsy types, and previous antiepileptic drugs used between 2 groups.

After treatment, patients in both groups did not show better outcomes in weekly seizure frequency (treatment group, $P = .12$; control group, $P = .56$; Table 2), seizure episode (treatment group, $P = .65$; control group, $P = .92$; Table 3), and QOLIE-31 (treatment group, $P = .73$; control group, $P = .84$; Table 4), when compared with these outcomes before the treatment.

After treatment, patients in the treatment group also did not exert better effect in seizure frequency ($P = .81$; Table 2), seizure episode ($P = .75$; Table 3), and QOLIE-31 ($P = .33$; Table 4), when compared with patients in the control group.

Table 2

Comparison of weekly seizure frequency.

Outcomes	Treatment group		Control group	
	Before treatment (n = 27)	After treatment (n = 27)	Before treatment (n = 25)	After treatment (n = 25)
Weekly seizure frequency, times/wk	2.4 ± 0.6	2.1 ± 0.8	2.2 ± 0.5	2.1 ± 0.7
Difference (range)$_{\text{within group}}$	—	−0.3 (−0.5,−0.1)		−0.1 (0.2,−0.1)
P value $_{\text{within group}}$	—	.12		.56
Difference (range)$_{\text{between groups}}$				−0.2 (−0.3,−0.1)
P value $_{\text{between groups}}$				.81

Data are present as mean ± standard deviation.

Table 3

Comparison of each seizure episode (min).

Outcomes	Treatment group		Control group	
	Before treatment (n = 27)	After treatment (n = 27)	Before treatment (n = 25)	After treatment (n = 25)
Each seizure episode, min	13.8 ± 3.9	13.3 ± 4.1	13.5 ± 3.6	13.4 ± 3.8
Difference (range)$_{\text{within group}}$	—	−0.5 (−0.8,−0.2)		−0.2 (−0.3, −0.1)
P value $_{\text{within group}}$	—	.65		.92
Difference (range)$_{\text{between groups}}$				−0.3 (−0.5, −0.1)
P value $_{\text{between groups}}$				.75

Data are present as mean ± standard deviation.

Table 4

Comparison of quality of life, measured by QOLIE-31.

Outcomes	Treatment group		Control group	
	Before treatment (n = 27)	After treatment (n = 27)	Before treatment (n = 25)	After treatment (n = 25)
QOLIE-31	50.6 ± 8.4	51.4 ± 8.7	52.6 ± 9.1	52.1 ± 8.9
Difference (range)$_{within\ group}$	—	0.8 (0.3–1.2)		−0.5 (−0.8, −0.1)
P value $_{within\ group}$	—	.73		.84
Difference (range)$_{between\ groups}$				1.2 (0.6–1.7)
P value $_{between\ groups}$				.33

Data are present as mean ± standard deviation.
QOLIE-31 = Quality of Life in Epilepsy Inventory-31.

AEs related to the treatment are shown in Table 5. All AEs are mild and acceptable. No severe AEs occurred during the treatment period, and no death related to the treatment was recorded.

4. Discussion

To our best knowledge, this study first explored the effect of TVNS for PSE among Chinese stroke population. We applied TVNS therapy for treating PSE patients for a total of 4 weeks. Unfortunately, we did not find promising improvement in all outcome measurements.

Previous related study has reported to use TVNS just for treating epilepsy patients, but not the PSE subjects. It designed as a randomized controlled trial with TVNS treatment for a total of 20 weeks. It utilized both 1 Hz and 25 Hz TVNS stimulations for treating epilepsy patients.[17] The results found that TVNS had a high treatment adherence and was well tolerated.[17] In our study, we only applied 4 weeks and used 1 Hz TVNS stimulation.

The results this study did not show better outcomes neither in the reduction of weekly seizure frequency, and seizure episode, nor in the improvement of quality of life, measured by QOLIE-31 among Chinese PSE population. Such results presented may be due to the short treatment duration, and small number of sample size included in this study.

This study has following limitations: the treatment duration is relative short with only 4 weeks, which may affect the effect assessment of TVNS for PSE patients; the dose of this study may insufficient when compared with the previous study;[17] the sample size in this study is also quite small; this study is a retrospective study, which may increase the risk of patient cases selection. Thus, further studies should avoid the above limitations to further investigate the effect of TVNS for the treatment in patients with PSE.

Table 5

Adverse events between 2 groups.

Adverse events	Treatment group (n = 27)	Control group (n = 25)	*P* value
Headache	3 (11.1)	1 (4.0)	.36
Nausea	2 (7.4)	0 (0)	.31
Vomiting	1 (3.7)	0 (0)	.52
Ear pain	3 (11.1)	1 (4.0)	.32
Dizziness	2 (7.4)	1 (4.0)	.60
Vertigo	1 (3.7)	0 (0)	.52
Fatigue	2 (7.4)	1 (4.0)	.60

Data are present as number (%).

5. Conclusion

The results of this study showed that TVNS may be not efficacious for the PSE after 4 weeks treatment.

Author contributions

Conceptualization: Guang-fu Song, Hao-yan Wang, Cheng-ji Wu, Xin Li, Fu-yi Yang.
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References

[1] Brodie MJ, Shorvon SD, Canger R, et al. Commission on European Affairs: appropriate standards of epilepsy care across Europe. ILEA. Epilepsia 1997;38:1245–50.
[2] Usui N. Current topics in epilepsy surgery. Neurol Med Chir (Tokyo) 2016;56:228–35.
[3] Sauro KM, Wiebe S, Dunkley C, et al. The current state of epilepsy guidelines: a systematic review. Epilepsia 2016;57:13–23.
[4] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993;34:453–68.
[5] Hesdorffer DC, Logroscino G, Benn EK, et al. Estimating risk for developing epilepsy. A population based study in Rochester, Minnesota. Neurology 2011;76:23–7.
[6] Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. N Engl J Med 2010;363:2522–9.
[7] Luhdorf K, Jensen LK, Plesner AM. Etiology of seizures in the elderly. Epilepsia 1986;27:458–63.
[8] Olsen TS. Post-stroke epilepsy. Curr Arthroscler Rep 2001;3:340–4.
[9] Burn J, Dennis M, Bamford J, et al. Epileptic seizures after a first stroke: the Oxfordshire community stroke project. BMJ 1997;315:1582–7.
[10] Sada N, Lee S, Katsu T, et al. Epilepsy treatment. Targeting LDH enzymes with a stiripentol analog to treat epilepsy. Science 2015;347:1362–7.
[11] Sadowski K, Kotulska-Jóźwiak K, Jóźwiak S. Role of mTOR inhibitors in epilepsy treatment. Pharmacol Rep 2015;67:636–46.

[12] Lindhout D. Epilepsy treatment: precision medicine at a crossroads. Lancet Neurol 2015;14:1148–9.
[13] Matsuo M, Fuji A, Matsuzaka T, et al. Effectiveness and safety of long-term levetiracetam treatment in patients with refractory epilepsy. No To Hattatsu 2015;47:272–8.
[14] Wallander KM, Ohman I, Dahlin M. Zonisamide: pharmacokinetics, efficacy, and adverse events in children with epilepsy. Neuropediatrics 2014;45:362–70.
[15] Klinkenberg S, van den Borne CJ, Aalbers MW, et al. The effects of vagus nerve stimulation on tryptophan metabolites in children with intractable epilepsy. Epilepsy Behav 2014;37:133–8.
[16] Aihua L, Lu S, Liping L, et al. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. Epilepsy Behav 2014;39:105–10.
[17] Bauer S, Baier H, Baumgartner C, et al. Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial (cMPsE02). Brain Stimul 2016;9:356–63.
[18] Vickrey B, Perrine K, Hays R, et al. Scoring manual for the Quality of life in epilepsy Inventory-31 (QOLIE-31). Santa Monica, CA: Rand, 1993. Available at: https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/qolie/qolie31_scoring.pdf (accessed January 25, 2016).