Chapter 10
Stimulation Therapy for Epilepsy

CQ 10-1

Is vagus nerve stimulation therapy effective for drug-resistant epilepsy?

Summary

Vagus nerve stimulation (VNS) is one of the non-pharmacological, accommodative therapies for epilepsy, in which an implantable electrical stimulator activates the left cervical vagal nerve intermittently to reduce or attenuate drug-resistant epileptic seizures. This method is covered by medical insurance, but implementation of the treatment requires certification.

Comment

Vagus nerve stimulation (VNS) is used as an adjunctive accommodative treatment for patients with drug-resistant epileptic seizure, who are not indicated for epileptic surgery with craniotomy, or who do not respond adequately to the surgical treatment.

The first evidence for the efficacy of VNS was based on two randomized controlled trials (RCTs) conducted in the United States in the 1990s[1, 2]. In RCTs of therapies that require surgical treatment and implantation procedure, we usually have difficulties in including an appropriate control group. However, in these two RCTs, efficacy was compared with a sham stimulation (low level stimulation) control group. In the sham stimulation group, an implantation procedure was performed in the same manner as in the treatment group, but the stimulation intensity was so low that it almost had no effect (active control group) even though the patients feel something (**Table 1**). In patients aged 12 years or above with drug-resistant partial seizures, the mean seizure reduction rate 3 months after surgery was 25–28% in the high-level stimulation group and 6–15% in the low-level stimulation group (see Systematic Review Digest on page 162). Furthermore, as a more clinically oriented comparative study, an RCT was conducted to compare best medical therapy (BMT) alone with a combination of BMT and VNS (BMT + VNS), and significantly greater improvement of health-related QOL was achieved by a combination of VNS and BMT[3].

Although the effectiveness of VNS increases on long-term continued administration[4, 5], RCT for long-term treatment is difficult to establish because of the ethical issue, and only a limited number of patients can be recruited. The study by Ryvlin et al.[3] was initially planned for a two-year follow-up period, but the study was terminated prematurely due to difficulties in patient recruitment. We should take this limitation into consideration when evaluating the outcome assessment in systematic review. Regarding the long-term effect, many reports have indicated that seizure reduction rate by VNS for 2 years is approximately 50%, and the responder rate (seizure reduction ≥ 50%) is mostly reported to be approximately 50%.

In addition to RCT, many investigations such as registry research and case series have demonstrated the seizure reduction effect of VNS[5, 6], and the VNS has been established as an accommodative treatment for drug-resistant epilepsy. This treatment has been covered by medical insurance from 2010 in Japan, although it was delayed as compared with other countries.

Some studies have reported the effectiveness of VNS in children or for generalized seizures[7, 8]. In Japan, there are no restrictions regarding seizure type and age for the use of VNS. However, since RCT has not been performed, indications have to be decided cautiously when used in children or for generalized seizures. Adverse effects associated with VNS include cough, hoarseness, throat discomfort, and swallowing disturbance, but the occurrence rate decreases during continuation of VNS[2, 3].

In addition to the accommodative effects on epileptic seizures, VNS was reported to be efficacious against concomitant symptoms such as cognitive dysfunction and affective disorder seen in patients with epilepsy[9-11]. However, it should be noted that the primary end point of those studies was the effect of VNS on epileptic seizures, and the effect on concomitant symptoms was not the main objective.

References

1) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology. 1995; 45(2): 224-230.
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3) Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia. 2014; 55(6): 893-900.
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9) Clark KB, Naritoku DK, Smith DC, et al. Enhanced recognition memory following vagus nerve stimulation in human subjects. Nat Neurosci. 1999; 2(1): 94-98.
10) Elger G, Hoppe C, Falkai P, et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res. 2000; 42(2-3): 203-210.
11) Harden CL, Pulver MC, Ravdin LD, et al. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav. 2000; 1(2): 93-99.

Table 1. Stimulation conditions used in RCTs of VNS.

	High-level stimulation		Low-level stimulation	
	Reference 1995	Reference 1998	Reference 1995	Reference 1998
Current (milliamperes)*	0.25–3.0	1.3**	0.25–2.75	1.2**
Frequency (Hz)	20–50	30	1 or 2	1
Pulse width (microseconds)	500	500	130	130
ON time (seconds)	30–90	30	30	30
OFF time (minutes)	5–10	5	60–180	180
Magnet mode	used	used	not used	used***

*: At high-level stimulation, current was set at the highest tolerable level for each patient. At low-level stimulation, current was set at the lowest level that could be sensed by the patient.
**: Mean value of final current
***: Current at magnet mode was set at 0.
(Data excerpted from: A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology. 1995; 45(2): 224-230. / Handforth A,, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology. 1998; 51(1): 48-55.

CQ 10-3

Is intracranial electrical stimulation therapy with implanted electrodes effective for epilepsy?

Summary

Shot-term (1–3 months) efficacy of stimulation of the anterior nucleus of thalamus and responsive stimulation of the seizure onset zone has been shown for partial seizures. Although a limited number of reports have also indicated the long-term efficacy of these methods and the effectiveness of other intracranial stimulation methods (hippocampus, paracentral thalamic nucleus, and cerebellum), evidence is not sufficient and further verification is required.

Comment

Many patients do not achieve freedom from seizure even with appropriate drug therapies and surgical treatments. In recent years, intracranial electrical stimulation therapy with implanted electrodes has attracted attention as a treatment for these patients. However, as of December 2017, intracranial electrical stimulation therapy with implanted electrodes has not been approved in Japan.

Stimulation of the anterior nucleus of thalamus is performed by stimulating bilateral anterior nuclei of the thalamus intermittently using an implanted stimulator. For partial seizures in adults, the median seizure reduction rate is 40% after three months of treatment[1]. The effect may last for 5 years[2]. Adverse events include subjective depressive symptoms and memory impairment.

Responsive stimulation of the seizure onset zone is performed by implanting deep or subdural electrodes at 1–2 epileptogenic zones, which automatically detect seizure onset and initiate stimulation. For partial seizures in adults, the mean seizure reduction rate is 38% after 3 months of treatment[3]. The effect may last for 5 years[4]. Adverse events include intracranial hemorrhage and wound infection.

Multiple institutes have reported the efficacy of hippocampal stimulation for temporal lobe epilepsy, but the number of cases is limited[5-9].

■ References

1) Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010; 51(5): 899-908.
2) Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015; 84(10): 1017-1025.
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7) McLachlan RS, Pigott S, Tellez-Zenteno JF, et al. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia. 2010; 51(2): 304-307.
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9) Cukiert A, Cukiert CM, Burattini JA, et al. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. Seizure. 2014; 23(1): 6-9.

■ Search formula and secondary reference sources

PubMed search: December 11, 2014
epilepsy AND treatment AND brain stimulation AND clinical trial = 184
Sprengers M, Vonck K, Carrette E, et al. Deep brain and cortical stimulation for epilepsy (Review). The Cochrane Library 2014, Issue 6.

CQ 10-1

Should vagus nerve stimulation therapy be added to drug therapies for drug-resistant temporal lobe epilepsy?

Recommendation

We suggest to add vagus nerve stimulation to drug therapies (GRADE 2D) (weak recommendation, very low level of evidence).

- **Supplementary note: In principle, vagus nerve stimulation is considered for patients with no indication for curative surgery. Implantation of the vagus nerve stimulation device involves surgery under general anesthesia in an experienced hospital. After implantation, the patients need to be followed in the hospital where the operation was performed or other facilities by experts with experience in stimulator control.**

1. Background, priority of the problem

In patients with drug-resistant epilepsy in whom seizures are not controlled even after trials of two appropriate antiepileptic drugs, further addition of drugs has only limited effect. Vagus nerve stimulation added to antiepileptic drug therapy is expected to provide additive effect of seizure frequency reduction. Because vagus nerve stimulation is less invasive and has lower seizure control effect as compared with brain surgery with craniotomy, it may be selected as a treatment option in patients with no indication for curative neurosurgery.

2. Comment

Evidence summary

Only one randomized controlled trial (RCT) examined the effectiveness of vagus nerve stimulation adjunct to best medical practice (BMP) (intervention group) versus BMP alone (control group) for drug-resistant epilepsy[1]. We therefore considered also to use observational studies. However, because the outcomes of those studies, such as reduced seizure frequency and mood change, are susceptible to placebo effect, we determined to use the single RCT.

Regarding efficacy, the relative risk for 50% seizure frequency reduction was 1.34 (95% confidence interval 0.59−3.04), and NNT (number needed to treat: indicating the number of persons needed to treat to achieve the outcome for one person) was 25. As for mood changes, there were no significant differences between the intervention group and control group in the scores for several scales: QOLIE-89 (89-item Quality of Life in Epilepsy Inventory), CES-D (Center for Epidemiologic studies Depression scale), and NDDI-E (Neurological Disorders Depression Inventory in Epilepsy scale). Regarding mood changes, the only scale showing a statistically significant difference was the 7-point evaluation scale CGI-I (Clinical Global Impression of Impression Important Scale), but the difference was only 0.5 (95% confidence interval 0.99−0.01), showing a small effect. For serious adverse events, vocal cord paralysis and brief respiratory arrest occurred only in the intervention group, but were transient with no sequelae. There was no significant difference in the adverse event of dysphonia between the intervention group and the control group.

It should be noted that the selected RCT was prematurely terminated by the sponsor due to a low recruitment rate, because many study candidates did not accept randomization of the treatment. Therefore, the study may be underpowered for detection of the outcome.

3. Panel meeting

3-1. What is the overall quality of evidence across outcomes?

In the study reviewed, the risk of bias was high overall, which was judged as serious for all the outcomes, and was downgraded by one rank. The inconsistency of results was not downgraded because of only one study used. The indirectness was judged as not serious and without any problems. As for imprecision, the confidence intervals in many analyses crossed the clinical decision threshold, and it was hence downgraded by one or two ranks. As for publishing bias, there was only one study, and therefore was not downgraded. Consequently, the level of evidence for the outcomes was as follows: “very low” for seizure frequency ≤ 50%, serious adverse events, and dysphonia; and “low” for the other outcomes. The overall level of evidence was “very low”.

3-2. What is the balance between benefits and harms?

Since there was only one RCT, the certainty of the effect estimate was low, and it was difficult to consider the balance between benefits and harms.

3-3. What about patients' values and preferences?

The importance of outcomes has great inter-individual differences, and it should be diverse. It should be noted that some patients place importance on the reduction of seizure frequency, while others regard the risk of adverse effects to be more important.

3-4. What is the balance between net benefit and cost or resources?

The electrode implantation for VNS surgery is conducted under general anesthesia. Vagus nerve stimulation is covered by medical insurance, and the medical insurance fee scale for implantation is 24,350 points, and that for exchange is 4,800 points (as of January 11, 2018). The reoperation should be done once every few years for replacement of the power generator because of degradation of the condenser. Considering the effectiveness for refractory epilepsy and the above-mentioned factors, the cost was judged to be moderate.

3-5. Recommendation grading

During the discussions at the panel meeting, considering the moderate burden and cost, and the few alternative treatment options available, the panelists concluded that it was reasonable to use this treatment method despite a certain amount of harm, burden and cost. The unanimous decision was "to propose implementing vagus nerve stimulation for drug-resistant epilepsy". As an additional consideration, the patients' families at the panel meeting expressed the following opinion: "We desire to overcome social constraints. If there is any method to solve this, please include it as one of the options."

4. Descriptions in other related guidelines

In Japan, the "Practice guideline of vagus nerve stimulation therapy for epilepsy"[2] was published by the Japan Epilepsy Society in 2012, which states that "VNS has accommodative effect on drug-resistant epileptic seizures [recommendation grade A]". Also, the American Academy of Neurology released a guideline update entitled "Vagus nerve stimulation for the treatment of epilepsy" in 2013. This guideline update describes the possibilities of the effectiveness of vagus nerve stimulation appearing several years after VNS operation, the effectiveness in children [rate of > 50% seizure reduction: 55% (95% confidence interval 50−59%)], and an increased risk of infection in children compared to adults [odds ratio 3.4 (95% confidence interval 1.0−11.2)].

According to the guidelines in Japan and overseas and the recommendation from the ILEA, the indication for vagus nerve stimulation is, in principle, patients who have no indication for curative neurosurgery[2-4].

5. Treatment monitoring and evaluation

Vagus nerve stimulation treatment requires adjustment of the stimulation conditions, management of complications, and solving equipment troubles. Epilepsy specialists or doctors trained by the specialists should perform monitoring and evaluation after the operation based on expert knowledge.

6. Possibility of future research

The RCT reviewed for this CQ had high risk of bias. Therefore, it is desirable to have more RCTs with better quality. In addition, further research focusing on how to identify good responders and the effects on status epilepticus is needed in the future.

7. RCT reports reviewed for this CQ

Ryvlin 2014[1]

8. List of appendices (to be shown later)

Appendix CQ10-1-01. Flow diagram and search formula for references
Appendix CQ10-1-02. Risk of bias summary
Appendix CQ10-1-03. Risk of bias graph
Appendix CQ10-1-04. Forest plot
Appendix CQ10-1-05. Summary of findings (SoF) table
Appendix CQ10-1-06. Evidence-to-decision table

■ References

1) Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia. 2014; 55(6): 893-900.
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CQ 10-2

When conducting vagus nerve stimulation for drug-resistant epilepsy, which intensity of stimulation (high or low) should we use?

Recommendation

When conducting vagus nerve stimulation (VNS) for drug-resistant epilepsy, we suggest to use high intensity stimulation rather than low intensity stimulation (GRADE 1C) (strong recommendation, low level of evidence).

- **Supplementary note: Adjustment of stimulation conditions should be conducted in the hospital where the electrode implantation was performed or in a hospital/institution where VNS specialist is present.**

1. Background, priority of this issue

The efficacy of vagus nerve stimulation is known to depend on the stimulation conditions. The intensity of stimulation should be adjusted while monitoring its therapeutic effect and adverse effects. Therefore, it is necessary to clarify whether high intensity stimulation or low intensity stimulation is superior when conducting VNS.

In addition, as mentioned in CQ 10-1 "Should vagus nerve stimulation therapy be added to drug therapies for drug-resistant temporal lobe epilepsy?", we have difficulty in performing comparison between real VNS and sham VNS (with no stimulation). Therefore, there is an increase in randomized controlled trials (RCTs) using low intensity stimulation as sham stimulation (placebo stimulation or pseudo-stimulation) to compare with high intensity stimulation.

There is one Cochrane Review[1] on a similar clinical question. This review shows that high intensity stimulation has superior therapeutic effect, while treatment withdrawal is rare both when using high and low intensity stimulation.

2. Comment

Evidence summary

There were 4 RCTs that examined the efficacy of vagus nerve stimulation therapy for drug-resistant epilepsy[2–5].

For efficacy, the relative risk for seizure frequency ≤ 50% was 1.74 (95% confidence interval 1.14–2.65) and NNT (number needed to treat: indicating the number of persons needed to treat to achieve the outcome for one person) was 10. For adverse events, low level stimulation was significantly superior in dysphonia and hoarseness (relative risk 2.06, 95% confidence interval 1.34–3.17) and dyspnea (relative risk 2.43, 95% confidence interval 1.29–4.57). Treatment withdrawal, cough, and pain did not differ significantly between high level and low level stimulations.

3. Panel meeting

3-1. What is the quality of evidence about the overall outcomes?

In all the studies collected, the risk of bias was low overall, and the level was not downgraded for all the outcomes. For inconsistency of the results, I_2 was 32% for only dysphonia / hoarseness. Since the effect estimate differed between studies, heterogeneity was considered high. Inconsistency was thus considered serious and was downgraded one rank. There was no problem with indirectness, and was judged not serious. As for imprecision, the confidence intervals in many analyses crossed the clinical decision thresholds, and hence was downgraded by one or two ranks. Regarding publication bias, there were only four studies, and therefore was not downgraded. Consequently, the level of evidence for the outcomes was as follows: "moderate" for seizure frequency ≤ 50%, cough, and dyspnea; "low" for treatment withdrawal, dysphonia / hoarseness, and pain. The overall level of evidence was "low".

3-2. What is the balance between benefits and harms?

High level stimulation was superior to low level stimulation for the outcome of seizure frequency ≤ 50%. Among the adverse events, dysphonia/hoarseness and dyspnea showed lower rates in low level stimulation, but since there was no significant difference in treatment withdrawal between two groups, there must be few adverse events serious enough to cause treatment withdrawal. According to expert opinion, many adverse events are reversible and can be controlled by adjusting the stimulation current intensity. Taken together, we decided that high level stimulation is probably superior in terms of the balance between benefits and harms.

3-3. What about patients' values and preferences?

We concluded that there is probably no significant uncertainty and variability in patient's values and preferences because high level stimulation is more effective than low level stimulation, and although adverse events are more prevalent in high level stimulation, they are reversible and can be controlled by adjusting the stimulation current.

3-4. What is the balance between net benefit and cost or resources?

Adjustment of stimulation intensity can be done by placing the programming wand over the subcutaneously implanted generator; thus resources and costs are negligible. However, reoperation is needed every few years to replace the generator when the battery runs out of power. Battery consumption is higher for high level stimulation than for low level stimulation. Based on these, it was decided that high level stimulation costs moderately more as compared to low level stimulation.

3-5. Recommendation grading

In the discussions at the panel meeting, high level stimulation was considered superior in efficacy, and adverse effects were acceptable because most of them were presumably at a level that would not cause treatment withdrawal. As for burden and cost, high level stimulation was expected to consume more battery power, requiring more frequent generator exchange. Based on the above arguments, despite considerable adverse events that did not cause treatment withdrawal as well as the increased burden and cost, we finally unanimously recommended using high level stimulation, considering the highly anticipated seizure control effect.

4. Descriptions in other related guidelines

In Japan, the "Guideline on implementation of vagus nerve stimulation therapy for epilepsy"[6] was published by the Japan Epilepsy Society in 2012, which states that "In principle, initiate VNS two weeks after implantation. Start with low stimulation intensity and then gradually increase the intensity while monitoring the adverse effects [recommendation grade C]".

In 2013, the American Academy of Neurology released a guideline update entitled "Vagus nerve stimulation for the treatment of epilepsy"[7]. There is no recommendation for high level or low level stimulation in that guideline. However, it states that whether stimulation at a higher frequency is more likely to reduce seizures than usual stimulation remains unknown.

5. Treatment monitoring and evaluation

For adjusting stimulation intensity, we need a system which is capable of managing complications and coping with equipment troubles.

6. Future research issues

Further research on the optimal intensity of stimulation is needed. In addition, other than stimulus intensity, there is no RCT on supplementary techniques such as magnet stimulation, which will be a future research subject. It is also desirable to elucidate the mechanisms underlying the subgroup with high response and develop evaluation methods to identify these subjects.

7. RCT reports reviewed for this CQ

Michael 1993[2], VNS study Group 1995[3], Handforth 1998[4], Klinkenberg 2012[5]

8. List of appendices (to be shown later)

Appendix CQ10-2-01. Flow diagram and search formula for references
Appendix CQ10-2-02. Risk of bias summary
Appendix CQ10-2-03. Risk of bias graph
Appendix CQ10-2-04. Forest plot
Appendix CQ10-2-05. Summary of findings (SoF) table
Appendix CQ10-2-06. Evidence-to-decision table

■ References

1) Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev. 2015; (4): CD002896.
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