Promising effect of vagal stimulation in Danish patients with epilepsy

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ABSTRACT

INTRODUCTION: Nervus vagus stimulation (VNS) is an option for additional surgical treatment for epilepsy. The aims of this study were to evaluate the effect of VNS on seizure frequency and to investigate patient satisfaction of and quality of life effects of VNS treatment.

MATERIAL AND METHODS: We investigated 94 patients treated with VNS for intractable epilepsy in Denmark. The patients were operated in the 1996-2006 period. We performed a retrospective survey based on questionnaires which were adjusted to the following subgroups of patients: competent adults, children and mentally retarded adults.

RESULTS: 46% of the patients reported a reduction in seizure frequency and 38% of adults reported a positive effect on quality of life with a benefit on long-term treatment. Around 20% also reported a positive effect on quality of life measures like coping, mood, self-confidence and social abilities. In the children's group, 21% reported a positive effect on quality of everyday life for the child and the family, 52-55% reported no change and 10% a negative effect. The patients had mild side effects, except for one case of vocal cord paralysis.

CONCLUSION: VNS is a palliative add-on antiepileptic treatment in selected patients with medically intractable epilepsy. The effect may increase with long-term treatment. However, the impact on quality of life is modest. We found that side effects from VNS treatment were relatively mild. Future studies are needed.

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Patients selected for nervus vagus stimulation (VNS) are those suffering from medically intractable epilepsy. Intractable epilepsy is defined as the failure of at least two different antiepileptic medications, which leaves the patient without seizure relief, and where neither conventional epilepsy surgery nor a ketogenic diet is an option. Approximately 33,000 Danish patients suffer from epilepsy [1]. It is estimated that a third of these still have seizures despite treatment with antiepileptic medication. VNS is one option in additional surgical treatment for epilepsy which has been used since 1989, and several studies have shown the beneficial effect of VNS treatment [2].

VNS is an add-on treatment used primarily to reduce the frequency of seizures and secondarily to reduce the quantity of concomitant antiepileptic medications. It is unclear which patients with epilepsy gain more benefit from this treatment option. The objectives of this study were to evaluate the effect of VNS on seizure frequency and to investigate patients' satisfaction with VNS treatment.

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MATERIAL AND METHODS

Study design

The study was an investigator-initiated retrospective questionnaire survey of patients operated with VNS implantation during a ten-year period.

Patients

The study consisted of 94 medically intractable epilepsy patients treated with VNS in the Department of Neurosurgery, Rigshospitalet, Copenhagen, during the period from April 1996 through October 2006. There were 50 adults (median age 34 yrs, range 18-64 yrs) and 44 children (median age 12 yrs, range 3-17 yrs). For all 44 children and one adult aged 18 yrs (registered as a child by his father), the forms were answered by their parents.

Operation procedure

The operations were performed by the same surgeon using the method described by Reid [3]. Briefly, the VNS consists of an adjustable unit with a battery, which is implanted subcutaneously below the left clavicle. The battery is connected to three electrodes, which are placed around the left vagus nerve.

Post-operative procedure

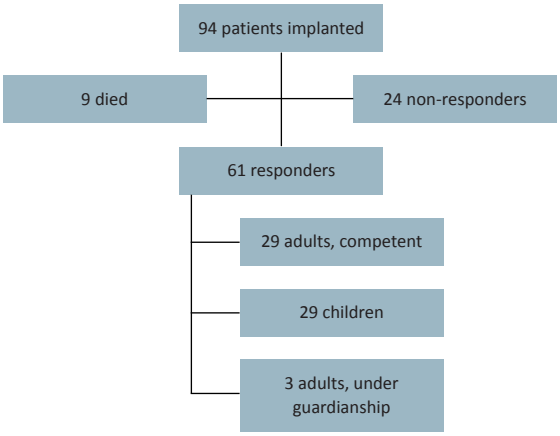
Post-operatively, voltage, duration of stimulation, duration of pauses between stimulations and frequency of stimulation cycles of the VNS are adjusted during clinical visits. Check of the VNS is performed at clinical visits by a specially trained nurse in collaboration with a paediatrician or a neurologist. The duration of observation of the study was from the date of operation until follow-up on 1 January 2008.

Questionnaire

We used a quality-of-life questionnaire modified according to Camfield et al [4] (with permission) particularly for the children's group, as there was no standardized

FIGURE 1

Consort diagram of patients enrolled in the study.



model which could clarify our issues of interest. The questions included the following:

1) The experienced change in the number of seizures per month
2) Change in quality of life in general and with regard to specific measures
3) Whether the VNS was in use, turned off, or removed
4) Any alteration of seizure pattern
5) Side effects.

As the groups of patients were inhomogeneous, we designed three versions of the questionnaires: one for competent adults, one for children and one for mentally retarded adults under guardianship.

As questionnaires for the children were often evaluated by peers, the questionnaire was arranged differently as all quality-of-life measures were first asked with reference to the situation before the implant and then the same questions were repeated, but now making reference to the situation after the implant. In the adult group, questions were asked about changes in quality-of-life measures after the operation.

The questionnaires were forwarded in December 2007. When no response was received, three attempts were made to obtain answers by telephone.

Ethics

The study was approved by the Regional Danish Committee on Biomedical Research Ethics. We obtained oral and written consent from participants.

Statistical analyses

Data are presented as median and range. The χ^2-test was used to compare categorical variables. Continuous variables between two groups were analyzed by Student's t-test using Microsoft Office Excel 2007. A p-value < 0.05 was considered statistically significant.

Trial registration: not relevant.

RESULTS

As shown in **Figure 1**, 61 patients answered the questionnaire, 48 by mail and 13 by telephone interview. In 31 cases, parents or guardians answered on behalf of children and mentally retarded patients.

It was reported that the patients received treatment in the form of one to five types of antiepileptic drugs. Two patients took no medication. One patient was on the Atkins diet (low-carbohydrate diet).

The effect of the VNS on frequency of seizures is presented in **Table 1**. Approx. 46% of the responders experienced a seizure reduction, 51% reported no change in seizure frequency or did not know, and two children were reported as having suffered an increase in the frequency of seizures. There was no significant difference with regard to seizure reduction between children and adults (χ^2: $p > 0.05$).

One patient reported a reduction in seizure frequency possibly due to reduction in mental stress following retirement. Another patient had the VNS removed due to mental side effects and experienced an increase in the frequency of seizures. In a mentally retarded patient, it was noted that the patient was more aggressive in periods of up-regulation. One patient became completely seizure-free. Two patients reported being free from generalized seizures; in one of these patients the VNS was subsequently turned off.

Patients were asked whether their stimulator was turned on or not. A total of 49 patients had the stimulator turned on; 11 had the stimulator turned off or removed and two did not report. There was no significant difference between adults and children (χ^2: $p > 0.05$).

Comparison of patients in long-term stimulation versus short-term stimulation showed a trend towards a difference in favour of patients receiving long-term treatment with respect to reported seizure reduction.

The mean follow-up period was 58 months (range 14-144 months). Competent adults who benefitted from the treatment regarding seizure frequency had a mean observation period of 64 months (19-139 months) versus 54 months (15-139 months) for those with no effect. The corresponding figures for children with a reported effect was 70 months (14-133 months) versus 45 months (15-117 months) for those who had no benefit. There was no significant difference between adults with and without effect (t-test; $p = 0.46$). However, there was trend towards a difference between children with and

without effect (t-test; p = 0.07) and for children and adults with and without effect (t-test; p = 0.06).

The questions concerning quality of life are shown in **Table 2** for adults and in **Table 3** for children. A total of 38 adults reported a positive effect on quality of life in general; no effect was reported by 41%, and 3% reported a negative effect. Questions on quality of life in more specific matters such as the ability to handle new situations, the ability to interact socially, self confidence and mood were answered positively in 21-24%, no improvement was reported in 48-59% and a negative effect in 3-17%.

Eight patients were presently employed, 20 were unemployed and one did not reply.

For quality of life in children, it was determined that 14% had experienced a positive impact of the VNS on their quality of life in general, 59% found no effect and 10% observed a negative effect. Peers answered positively on the specific quality-of-life questions about impact on everyday life for the patient and the family, social abilities and relations to siblings in 14-21% of patients, no effect in 38-59% and negatively in 3-10%. No effect was found on the children's self confidence or planned education.

The effect on seizure and quality of life measures in retarded adults was not included as only three peers answered the questionnaire, and the data were therefore inconclusive.

Ten patients had side effects of the treatment or the operation. Side effects were noted as follows: behavioural changes (n = 2), infection (n = 1), hoarseness (stimulation dependent) (n = 1), dyspnoea on exertion (stimulation dependent) (n = 1), paralysis of vocal cords (n = 1), cosmetic complaints (very obvious stimulator in a lean patient (n = 1). In addition, lost ability to sing, difficulties to swallow and to speak were reported.

Red, wide or itchy scars were reported by 24 (44%) patients.

DISCUSSION

This study presents the first data on the effect of VNS in Denmark, and the data are generally in accordance with those of studies presented from other countries [2, 5, 6]. Thus, a 46% seizure reduction was reported in both children and adults in this study. However, it was not possible to quantify the seizure reduction in detail due to the study design. An indirect, subjective measure of effect may be that 82% of the patients still had their stimulator turned on.

One Cochrane review [7] has concluded that "VNS appears to be an effective treatment" in medically refractory, focal epilepsy. The effect was measured by a seizure frequency reduction by 50% or more in patients older than 12 yrs, where patient groups consisted of a group receiving higher stimulation (in terms of more frequent cycles and a higher amplitude) compared with a patient group receiving a "baseline" stimulation. There was no control group not receiving stimulation or not undergoing operation.

A number of studies have suggested a cumulative effect of VNS on seizure reduction with long-term follow up [2, 6, 8]. Our study showed a similar effect, in that adults who benefitted from VNS had a long duration of treatment effect at 64 months albeit this was not statistically different from that at 54 months in patients without effect. The same applies to the difference in treatment effect in the children group as positive effect was reported at mean treatment period of 70 months versus 45 months mean with children without reported effect of the VNS.

Seizures may cease spontaneously, but complete termination of seizures has been reported owing to VNS [2, 9].

Two patients reported termination of seizures and termination of secondary generalized seizures, respectively, after implantation. In one of these patients, the stimulator was subsequently turned off, and the cause

TABLE 1

The reported effect on seizure frequency by nervus vagus stimulation. The values are n (%).

	Adults	Children	Retarded	All
Seizure reduction	15 (52)	11 (38)	1	27
No change or do not know	13 (45)	15 (52)	2	30
Seizure increase	0	2 (7)	0	2
No reply	1 (3)	1 (3)	0	2

TABLE 2

Effect of nervus vagus stimulation (VNS) on quality of life in adults. The values are n (%).

	Positive effect	No change	Negative effect	Do not know	No reply
Do you feel that VNS has affected your life in general?	11 (38)	12 (41)	1 (3)	1 (3)	4 (14)
Do you feel that new situations and problems are easier to handle or harder to handle than before?	7 (24)	14 (48)	1 (3)	5 (17)	2 (7)
Have you been more open and social towards others?	6 (21)	16 (55)	2 (7)	3 (10)	2 (7)
Has it affected your self-confidence?	6 (21)	17 (59)	1 (3)	1 (3)	4 (14)
Has it affected your mood?	6 (21)	16 (55)	1 (3)	3 (10)	3 (10)

TABLE 3

Effect of nervus vagus stimulation (VNS) on quality of life in children. The values are n (%).

	Positive effect	No change	Negative effect	Do not know	No reply
How much does the epilepsy affect the child's general health as compared to before the implant?	4 (14)	17 (59)	3 (10)	1 (3)	4 (14)
How much does the epilepsy affect the child's everyday life as compared to before?	6 (21)	15 (62)	3 (10)	1 (3)	4 (14)
How much does the epilepsy affect the family's everyday life?	6 (21)	16 (55)	3 (10)	2 (7)	3 (10)
How much does the epilepsy influence the child's social life, accept from others and number of activities?	4 (14)	17 (59)	1 (3)	2 (7)	5 (17)
Did the epilepsy influence relations to siblings and did VNS change this?[a]	6 (21)	11 (38)	3 (10)	5 (17)	4 (14)

a) In case of no siblings registered as "Do not know".

for seizure termination is thus less likely to be an effect of the VNS.

An adequate response rate is necessary for achieving reliable and clinically meaningful information. Our 65% response rate required contact by telephone in addition to the posted questionnaires (response rate 56%). This approach, which yielded a satisfactory response rate, is therefore advisable in similar investigations.

How a person considers his or her quality of life is said to reflect a gap between hopes and expectations on one hand and practical circumstances of life on the other [10, 11]. Our patients had different life conditions and the three versions of questionnaire applied were therefore designed to take due account of this.

Thirty-eight of the adults reported that VNS had a positive effect on their quality of life. In general, they were less worried about psychological, physical and/or social matters. In agreement with our findings, in a double-blinded study using the QOLIE-31 (Quality in life in epilepsy-31), Dodrill & Morris [12] found a modest positive effect on quality of life in a 12-16 week period.

In the present survey, 21-24% of the patients reported a change for the better with regard to the ability to cope with personal problems, self confidence, mood and coping in a social context. The majority of patients, however, reported that their mood was unchanged, which is in line with the results of Chavel [13], who found no significant effect on depressive measures in patients with VNS.

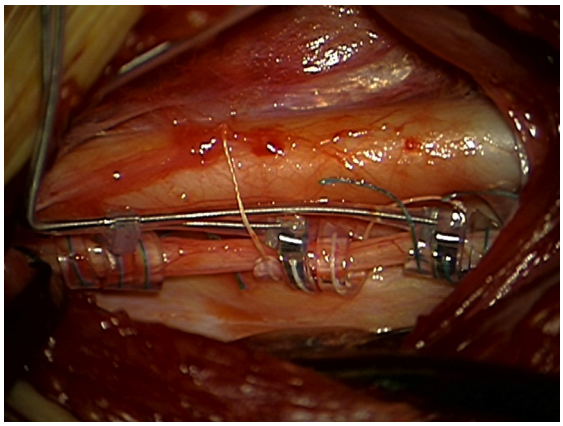
A positive effect on children's quality of life has been found using a visual analogue scale score [5, 14]. However, in our study a small share of respondents reported a positive effect on general health. Also, 14-21% reported a positive effect on the every-day life of the child and the family and an increased ability to cope in a social context. Thus, quality of life in children treated with VNS in our survey has not shown convincing results, albeit our patient group is small. Questions regarding the children's self confidence and planned education were irrelevant to the group.

Less than half of the adult patients reported having a job. Our study does not allow conclusions as to whether VNS treatment had made any difference in this respect.

Ten patients reported mild, known side effects, and 24 reported discomfort of the operation scar, which was an issue specifically asked for. The modest reporting of side effects may be due to the long follow-up period, as patients may either have become accustomed to their side effects or these may have subsided with time. Another explanation could be that the stimulator was turned off or removed.

Salinsky [15] claimed that all patients were mildly hoarse to begin with, a characteristic which is stimulation-dependent and fades with time. One of our patients reported this. Cough, throat pain and dyspnoea on exertion are stimulation-dependent side effects, which were reported by one patient. Reversible vocal cord paralysis was observed in two out of 198 patients in the E05 study recorded by Privitera et al [7], which is in accordance with our results (n = 1).

One patient reported that the VNS had influenced her ability to sing, which may be due to hoarseness or vocal cord paralysis. One patient had a post-operative infection. Twenty one percent of the adults and 69% of the children were unsatisfied with the operation scar on



The left vagus nerve with the tree helix shaped electrodes in place and above the common carotid artery. Reproduced with permission of *Bo Jespersen.*

the chest. Thus, an alternative operative approach may be explored.

This study design was retrospective and applied on a patient population in which the first patient received the operation 12 yrs before the study was performed. The patients' life situation will almost certainly have changed in the interval, influencing evaluation of the vagus stimulator. Evaluation must therefore be made with caution as evaluation will not reflect VNS alone but also changed life circumstances. The greatest challenge in the interpretation of results is the lack of seizure frequency before the VNS was inserted, which conflicts with an objective measure of effect on epileptic seizures. Therefore future studies are needed.

A prospective study could provide us with useful information that would help us to optimize treatment and direct it towards the group of patients who would benefit the most. The following questions are outstanding: Is there a differential effect on various types of seizures and syndromes? What characterizes patients experiencing a complete termination of seizures owing to VNS and, what are the cost-benefit effects from reduced medical costs and reduced adverse effects of anti-epileptic drugs owing to add-on treatment with VNS?

These questions will be addressed in a prospective, national, multicenter database survey that we are currently planning.

CONCLUSION

VNS is a palliative add-on antiepileptic treatment for use in selected patients. The results of our study are in agreement with others and suggest that effects seem to increase with long-term treatment. Another conclusion might be that the patients who choose to keep the stimulator for the longest time are positively biased towards the treatment.

Our results are modest, but the stimulator has only been applied to those patients who were intractable, so future studies are needed where objective measures are applied.

The impact on quality of life was modest in the adult group and insignificant in the children's group. Furthermore, we found that side effects of the VNS stimulator were relatively mild.

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