Clinical benefits and feasibility of transcutaneous auricular vagus nerve stimulation in treatment of drug resistant epilepsy; a multicenter prospective study

Authors:

Anne Sabers[a], (alphabetic) Sophia Aumüller-Wagner[b], Lars Rune Christensen[b], Oliver Henning[c], Konstantin Kostov[c], Morten Lossius[c], Marian Majoie[d], Lene Nielsen[b], Kristl Vonck[e], Louis Wagner[d].

[a:] The Epilepsy Clinic, Rigshospitalet, University Hospital, Inge Lehmanns Vej 7, DK-2100, Copenhagen, Denmark

[b:] IT University of Copenhagen, Ruud Langgaards Vej 7, DK-2300, Copenhagen, Denmark

[c:] The National Center for Epilepsy, Rikshospitalet, University Hospital, Sandvika, Norway

[d:] Academic Center for Epileptology Kempenhaeghe and Maastricht University Medical Center, Heeze and Maastricht, The Netherlands

[e:] 4Brain, Department of Neurology, Ghent University Hospital

Abstract

Background

Transcutaneous auricular vagus nerve stimulation (ta-VNS) is a new non-invasive technique developed as treatment option for drug resistant epilepsy. A few studies have been carried out showing that the efficacy and tolerability of ta-VNS is comparable with traditional implanted VNS but the feasibility of the therapy has been poorly described. This study aimed to explore potential clinical benefits of ta-VNS and to evaluate adaptation, compliance, as well as the usability of the device from a service design perspective.

Methods

A prospective, multicenter, clinical, investigator-initiated trial was conducted using the NEMOS® ta-VNS device. After eight weeks baseline, all subjects started ta-VNS with individually adjusted currents for four hours per day for six-months (first endpoint) followed by optional 12 months follow-up (second endpoint). The primary outcome was six months retention rate of ta-VNS therapy. Secondary outcomes included the user retention rate at 12 months follow-up, compliance, changes in scores of psychometric measures. For the study of feasibility, a service design questionnaire on medical devices used in the home was developed.

Results

In total 37 subjects had been included in the study after 45 months where the study was prematurely terminated due to recruitment problems and due to a high drop-out rate. Twenty-two subjects (59 %) completed the first six months of the study and in total six subjects (16 %) completed the following 12 months follow-up. The reasons for discontinuation were a mixture of medical and practical issues of which the majority were related to a combination of both. Those, who managed to continue to use ta-VNS throughout the study, gave generally higher scores for the device usability and compatibility with lifestyle. The study turned out to be inadequately powered to reach any conclusion in terms of the clinical benefits of ta-VNS but present an example of difficulties that are encountered in conducting high-quality studies with digital devices.

Conclusion

The feasibility of ta-VNS therapy showed to be relatively modest which is most likely due to practical usability issues and lifestyle fits. The results of this study stress the importance of generating data based on patients experiences at an early stage during the development phase and when designing clinical trials on medical devices that depend on patient's active participation and motivation.

1. Introduction

Vagus nerve stimulation (VNS) has been used for pharmaco-resistant epilepsy for more than 25 years and the clinical efficacy and safety have been documented in several controlled studies (Ben-Menachem et al., 1994; Privitera et al., 2002). VNS is generally well tolerated and often associated with improvement in mood and quality of life (Klinkenberg et al., 2012; Ryvlin et al., 2014). In the traditional form, VNS consists of an implantable device and an electrode that is wrapped around the cervical vagus nerve trunk (Beekwilder and Beems, 2010; Vonck et al., 2001). Limitations of VNS include the involvement of neurosurgical procedures in relation to the implantation of the device and the fact that it is unpredictable which patients will benefit from the treatment (Elliott et al., 2011). Traditional VNS is therefore a treatment option that still presents barriers and is generally only offered to a minority of patients. For that reason, external non-invasive stimulation paradigms are of interest and may be attractive and a much cheaper alternative option for some patients.

Recently new types of technical devices that can stimulate the vagus nerve branch in the skin of the outer ear have been developed (transcutaneous auricular VNS (ta-VNS)), (He et al., 2013; Stefan et al., 2012). The stimulation is applied to the part of the concha corresponding to the sensory area of the vagus nerve. Experimental studies demonstrate that electrical stimulation in this zone projects to the brain and activates cortical networks comparable to that of the implanted VNS (Kraus et al., 2013; Yakunina et al., 2017). The potential advantages of ta-VNS compared to traditional VNS are several. If there is no positive effect, the therapy can be stopped and removed easily, there are no implanted electrodes that may complicate Magnetic Resonance techniques, and there are no risks of infection and nerve damage. In addition, ta-VNS could potentially be a tool to predict the effect of VNS before implantation.

However, the evidence for the effectiveness of ta-VNS is not fully explored. Previous studies are relatively small and often too underpowered to obtain statistically significant results (Barbella et al., 2018; He et al., 2013; Schupf and Ottman, 1994; Stefan et al., 2012) and most studies have explored the effect of ta-VNS for relatively few months (Barbella et al., 2018; Bauer et al., 2016; Stefan et al., 2012) which may be too short to gain effect of neurostimulation (Elliott et al., 2011).

In general, designing a double-blind randomized controlled clinical trial of the effect a medical device is challenging due to the difficulty to construct a sham device that may work as a legitimate placebo. From a clinical perspective, sham procedures can often easily be unmasked by the patients and physicians in particular for CE-marked devices where product descriptions can be found and unraveled on the internet. Active control stimulation procedures are also often associated with high placebo effects (Bauer et al., 2016). In addition, it cannot be excluded that the sham stimulation may be therapeutic in some degree (Bauer et al., 2016; He et al., 2013; Kraus et al., 2013; Shu et al., 2005).

Facing these challenges, and in lieu of a double-blind randomized trial, we aimed to construct a clinical trial which could provide the best possible indirect evidence of the efficacy of ta-VNS by evaluating the clinical benefits and usability of the device. We hypothesized, that if the subjects continued ta-VNS they most likely had experienced clinical benefits. If the subjects discontinued ta-VNS, there could be several causes due to a combination of lack of effect, adverse events, difficulty in functional handling of the device, or incompatibility with the patient's lifestyle. In addition, realizing that the treatment response will highly depend on the patients' active motivation and compliance, we also aimed to explore the usability of the device from a service design perspective by testing the adaption of ta-VNS in different patient populations.

2. Material and methods

2.1. Study Population

Subjects were recruited consecutively from the Epilepsy Clinics at Rigshospitalet, Copenhagen (DK), National Center for Epilepsy, Sandvika (NO), The University Hospital Ghent (BE), and Kempenhaeghe, Heeze (NL).

Inclusion criteria: Subjects above 17 years of age, suffering from drug resistant epilepsy (focal or generalized epilepsy) and with at least two seizures per month and not more than 28 days between seizures. Subjects should be willing to receive a stable dose of antiseizure medication (ASM) during the baseline period and six months study period (rescue medication accepted), and to use the device for four hours per day.

Exclusion criteria: Subjects with a current diagnosis of progressive neurodegenerative-, neoplastic-, or cardiac arrhythmic disease, a history of psychogenic non-epileptic seizures (PNES), any form of implanted electric stimulator (VNS, deep brain stimulation or cardiac

pacemaker).

The study protocol was approved by the responsible Ethical Committees of all participating centres before subject enrolment and applicable with local laws and regulations.

It was pragmatically planned to include 100 subjects, which was equal to the number of the NEMOS® devices that was provided from the company Cerbomed GmbH (see paragraph 2.5.)

Information on epilepsy duration, seizure types, ASM treatment and monthly seizure frequency in the previous three months was collected at the baseline visit.

2.2. Study Design

The study was an investigator initiated, international, multicenter, prospective clinical trial that consisted of 8 weeks baseline phase, a 6-month phase with fixed ASM and antidepressant drugs and a subsequent 12 months follow-up phase open for changes in the medications, Fig.1.

We used a pragmatic study design to provide the best available indirect evidence for the effectiveness of ta-VNS by evaluating the user retention rate of NEMOS® after 6 months and subsequent after 12 months at follow-up.

During the baseline period and at each study visits (V1 - V7), the seizure frequency and adverse effects were monitored by the registration of seizures in the subject's seizure diary and notes. Psychometric measures were recorded at each visit (V1-V7). In case of adverse events, technical or practical problems the subjects were offered a subacute consultation by the study nurse.

2.3. Psychometric measures

The following questionnaires were used at each study visits (V1 - V7).

Quality of Life in Epilepsy (QOLIE-31-P); to assess health-dependent quality of life. (Cramer et al., 1998).

Pittsburgh Sleep Quality Index (PSQI); to assess subjective sleep quality (Buysse et al., 1989).

Beck Depression Inventory Scale (BDI); to measure items relating to symptoms of depression (Bech et al., 2015).

Service Design Questionnaire on Medical Devices Used in the Home (SDQ1): To determine if lifestyle and usability issues. The subjects were contacted by telephone at 2, 4, 8, 12, 16 and 20 weeks after inclusion (T1-T7) to access potential usability complications related to the use of the device as well as the fit of the device and therapy with the lifestyle of the subject. Calls were conducted according to the questionnaire on usability and service design issues (SDQ1), which

was specifically designed for this study and developed by the authors to generate data on the subject's experience of using the device, including usability issues and lifestyle compatibility issues.

Questions on device usability comprised of eight questions and included overall satisfaction with how easy it is to use this device (SDQ1-1) and the ear-plugs (SDQ1-2), and if interaction with the device is pleasant (SDQ1-5). Question SDQ1-4 marks potential side effects. SDQ1-3 inquired if contact spray was used.

Questions on lifestyle issues included a statement on overall satisfaction with how easy it is for the subject to find the time to use the device (SDQ1-6), whether the subject uses the device at home, at work, when they exercise or other (SDQ1-7), as well as when they use the device (SDQ1-8). The purpose of these questions was to determine the usability of the device in the everyday lifestyle, and in what parts of their daily lives they find time to use it four hours every day.

Question (SDQ1-9) was an open-ended question on how the device could be improved. As this is a design-oriented question meant to inform the designers of the device on how to improve it, it is not part of the clinical study of the device per se. However, advice on improvements of the interface design and other concerns may indicate lifestyle and/or usability issues as experienced by the subjects and are important information to enrich the data analysis of the trial.

2.4. The Medical Device

The CE certificated ta-VNS device NEMOS® (Cerbomed GmbH, Erlangen, Germany) was used. This device includes an external pulse generator and a cutaneous contact electrode developed to be placed manually at the cymba concha in the auricular tract of the left ear, Fig 2. The electrode is connected to rechargeable a pulse generator via a connector cable. The device stimulates standardly with 25 Hz stimulation frequency, 250 μsec. pulse width and 30 sec on/30 sec off time whereas the current output is individually adjusted to tolerance (from 0.5 mA- 5 mA).

The subjects were instructed in the use of the device to titrate the current output until a mild tingling sensation in the earlobe was felt and to try to increase dosage but staying at a level causing no painful sensation. The planned stimulation time was 4 hours daily. Subjects using ta-VNS at least 3 hours (≥ 75% stimulation time) were regarded as compliant. Daily stimulation time and intensity was automatically recorded by the device.

2.5. Study outcomes

Primary objectives were to evaluate beneficial effects and gain insight into factors influencing the practical feasibility of the device.

Primary outcome was 6 months (first endpoint, V4) user retention rate of ta-VNS therapy.

If the subjects aimed to continue into the follow up phase after V4, the therapy was regarded as beneficial.

Secondary outcomes included the user retention rate at 12 months follow-up (second endpoint, V7), compliance with the treatment (defined as a daily ta-VNS stimulation ≥ 75% of the recommended 4-hour daily), and changes in scores of QOLIE-31-p, Pittsburgh Sleep Quality Scale and BDI from V2 to first endpoint at V4. The feasibility was assessed by recording the SDQ1.

Safety was assessed in all patient contacts (visits and telephone contacts).

3. Results

Due to the fact that the recruitment of subjects was more difficult than expected and because of a rapid and high number of drop-outs (only 59 % reached the first endpoint) the study was prematurely terminated after 45 months (December 2016 - September 2019).

Forty-four subjects were initially screened of which three appeared not to have enough seizures to fulfill inclusion criteria at V 2, one subject was excluded after baseline due to severe hypertension, one subject appeared to have PNES, and two subjects decided to withdraw (without reason given) after baseline before start of ta-VNS at V2.

3.1. Subject characteristics

Thirty-seven subjects (DK=11; NO=12; BE=4; NL=10), all Caucasians, were included in the study from July 2016 - August 2019. The last patient terminated the study in December 2020. Demographics and epilepsy characteristics are presented in table 1.

Of the 37 subjects, 22 completed V4 (59%) and most of these (n=14) were willing to continue into the open phase follow-up. In total six subjects (16%) completed the following 12 months follow-up phase until V7.

3.2. Treatment characteristics

The mean daily stimulation intensities from V3 - V7 are listed in table 2. There was a tendency

toward gradually increasing the intensity in the first phase of the study and the stimulation intensity at the highest tolerated level was stabilized in the follow-up phase with an average stimulation of mean 3.1 mA at V7.

Compliance was relative stable in the first phase of the study with 82 % and 81 % full compliance / compliance with ta-VNS (≥ 3h stimulation per day) at V3 and V4, table 2. In the follow up phase only 50 % of subjects were compliant until the last visit where 67 % reported at least 3h use of ta-VNS per day.

3.3. Drop-out characteristics

Drop-outs before the first endpoint at V4 (n=15) were due to: only medical reasons in 4 cases (adverse events n=2, change of ASM n=1, sudden unexpected death n=1), combined medical and usability / lifestyle reasons in 7 cases (side effects n=4, no effect or increased seizure frequency n=3), and solely due to usability problems (n=3). In one case no reasons were given.

Drop-outs between first and second endpoint at V4 to V7 (n=8) were due to medical reasons n=6 (side effects n=2, no effect or increased seizure frequency n=2, VNS implant was decided n=1, periods without use of ta-VNS /protocol violation n=1). In two cases no reasons were given.

3.4. Adverse events

Subjects were instructed to titrate the current until a mild tingling sensation in the earlobe was felt and to reduce the current if they experienced any unpleasant or painful sensation. Excluding painful sensation in the ear, a total of six subjects reported one or more adverse reactions: headache, dizziness, tinnitus, itching, burning sensation in the ear and arms and irritation of the skin. One subject got a superficial wound in the ear at the stimulation site.

One subject died (between V3 and V4). The death occurred postictally and was regarded as sudden unexpected death in epilepsy unrelated to the ta-VNS therapy. The subject had focal epilepsy with focal and bilateral tonic-clonic seizures. At the last visit (V3) she had reported unchanged seizure frequency with in average four focal seizures per month. The current output of the ta-VNS at time of the death was 0.7 mA with 100 % stimulation time, 4 hours per day.

No other serious adverse events occurred.

3.5. Seizure frequency

Results from the seizure diaries showed four weeks after initiation of ta-VNS (V3) that 92 % of subjects (n=31) described unchanged seizure frequency or less than 50 % reduction. Two

subjects (5%) had experienced more than 50 % seizure reduction and one subject (3%) had worse seizure frequency. From V4 - V7, 90 % - 50 % reported unchanged or less than 50 % seizure reduction and up to 50 % reported increased seizure frequency at V7 (n=6). No subjects experienced ≥ 50 % seizure reduction, table 3. None of the subjects obtained complete seizure control at any time point.

3.6. Psychometrics

Results from QOLIE-31 showed the total mean score was generally unchanged throughout the study, table 4. For the subgroup of subjects (n=6) who completed the follow-up at V7 the total mean QOLIE-31 score was 63 (SD 10) when they started the study whereas subjects who terminated the use of ta-VNS before the first endpoint at V4 (n=16) had a total mean QOLIE-31 score on 56 (SD 15).

The mean total score of BDI at time of initiating ta-VNS therapy was 12 (SD 12) (cut of score > 14). The mean total BDI scores were fairly unchanged throughout the study except for the subgroup who terminated follow-up (n=6) with the total mean BDI score of 8 (SD 11). However, this group had also BDI of 8 (SD 13) when they started the study. The initial mean BDI score for the subgroup of subjects who terminated the use of ta-VNS before the first endpoint at V4 (n=16) was 11 (SD 11), table 4.

PSQI was 1,0 (SD 0.8) at baseline and 0.7 (SD 0.8) at V3, 0.9 (SD 0.8) at V4, 1.2 (SD 0.5) at V5, 1.5 (SD 0.5) at V6 and 1,3 (SD 0,5) at the end of follow up, indicating an unchanged or slightly worse sleep quality though the study.

3.7. Usability assessed by Service Design Questionnaire on Medical Devices Used in the Home (SDQ1)

The overall satisfaction with usability of the device and the ear-plugs, if it was physically comfortable to use the device (no skin irritation and/or pains), to what extend the device was pleasant to use and the ability to find time to use the device 4 hours every day, were evaluated at the telephone calls T1 - T7, are listed in table 5. The SDQ3 rating of the use of contact fluid was not evaluated.

An overall of 75 % of all study subjects suggested improvements for the NEMOS® device. One of the number one suggestion was to make the device wireless to carry around like a headset and increasing battery capacity to make it easier to move around with the device. Making the

interface simpler as well as connecting it to an app to make patient-doctor consultation easier and ease use of the device data was increasingly suggested as the study carried on. Some subjects also suggested automatic stimulation to ease incorporating the device into their everyday lives. Among all subjects, there was no significant change in the satisfaction with the usability of the device during the study (T1-T7). Of the 15 subjects who dropped out before the first endpoint, three reported that a low usability and lifestyle fit was the main reason of discontinuing and seven indicated clear usability and lifestyle fit issues were not acceptable.

The satisfaction with interacting with ta-VNS was generally lower in the group of early drop-out compared to those who completed follow up and the discrepancy was obvious already from the beginning of the study, table 5. However, the satisfaction with the use of the device in the group who completed follow up decreased with time. The same tendency was seen for the satisfaction with using the device for four hours per day.

4. Discussion

This study did not meet the target and was prematurely terminated due to challenges regarding the recruitments of subjects that were considerably higher than anticipated, combined with a high drop-out rate. However, the work is an example of the difficulties that are encountered in conducting high-quality studies with digital medical devices that depends on the subject's active motivation and participation. Therefore, albeit negative results, we find it valuable to present and discuss these limitations and challenges. Focusing on the practical long-term feasibility of ta-VNS used in a real patient population has to our knowledge not been done before as the incorporation of usability and lifestyle issues typically are not included in traditional clinical trials.

As the study turned out to be inadequately powered to detect any statistically significant results or conclusions for the effect of ta-VNS therapy on seizure frequency or psychometric outcomes, we have focused on evaluating the practical usability and lifestyle issues.

We have therefore explored the reasons for dropping out early in the study (before six months, already before effect of VNS could be expected) and compared the personal characteristics of these subjects with those who managed to complete the study at follow-up.

We found that 59 % of subjects (n=22) continued ta-VNS until the first endpoint after 6 months but only 39 % of all subjects (n=14) aimed to continue the second phase. Only 16 % of all subjects (n=6) used ta-VNS for 18 months and completed the follow-up.

4.1. Characteristics for early drop-out

At the first endpoint 41% of all subjects (n=15/37) had dropped out. The reasons for discontinuation were a mixture of medical and practical issues of which the majority were related to a combination of both, table 3. Only three subjects discontinued ta-VNS solely because of usability or lifestyle problems but two thirds of the early drop-outs subjects faced severe challenges regarding the usability and lifestyle fit and most of these indicated specific improvement potentials for the device. The main reported issues were difficulty to find the time to use the device for four hours every day and electrode connection issues (especially the ear-electrode was very hard to keep in place if the subject was just moderately active). In fact, they had to more or less sit still for four hours every day to cope with the treatment, creating a lot of frustration.

4.2. Characteristics for those who completed the follow up

Those, who managed to continue to use ta-VNS throughout the study (n=6), gave higher scores for the device usability and lifestyle fit already at the first telephone visit, table 5. When comparing this group with the subjects that drop-out early, they generally seemed to have less problems handing the device and found it easy to use the device for four hours every day, at least in the beginning. Five of the six subjects who completed the study were females, but no other demographic variables of these subjects (mean 36.8 years, range 21 - 51 years) were different from the rest of the cohort. Although the BDI scores showed a trend toward lower scores in the group who completed the follow-up, neither quality of life scores nor depression scores differed significantly from the subjects with early drop-out ($p=0.5$ and $p=0.2$, respectively).

4.3. Limitations

This study has several limitations and turned out to be inadequately powered to reach any conclusion in terms of the clinical benefits of the device. Even in the few subjects who managed to continue into long term extension of the study, we were not able to demonstrate any positive effect on seizure frequency, table 3. However, the number of subjects were very low and the study was not designed to measure the effectiveness of ta-VNS which would require a much

larger cohort and a controlled study design with a longer follow-up.

The value gained from the experiences of the trial adds to the understanding of the complexity in setting up a high-quality study on a novel medical device categorized as a self-care technique which highly depends on the subject's active participation and motivation (Nunes, 2015; Shah, 2009). For future studies that include these technologies, our study illustrates the need for controlled trials a at very early stage because the devices are CE marked and therefore already up for use in clinical practice before proving efficacy. It also raises a new view on these designs and suggests that the interpretation of such studies would benefit from generating data from a service design perspective in different patient populations and emphasizes that in cases where a device under trial is expected to interfere with the everyday life for prolonged periods of time, it is strongly advisable to generate preclinical data on lifestyle fits based on the subject's experiences to avoid development of a device that is unlikely to be used on the long run.

5. Conclusions

This proof-of-concept study demonstrates that the feasibility of this novel ta-VNS technique is relatively modest and that the limitations most likely are related to the practical usability of the device. As a self-care technology, ta-VNS depends heavily on the patient's active participation and motivation to create any positive medical effects. While the study could not conclude whether ta-VNS had significant clinical benefits, it showed that those who found it more user-friendly and easier to integrate into their lifestyles, were more likely to continue using it. The Service Design Questionnaire developed for this study revealed that most subjects experienced usability or lifestyle fit issues of the device, which highlights the importance of early collection of data on usability and lifestyle factors for future studies.

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