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The Importance of Stimulation Cycle in Vagus Nerve Stimulation for Drug-Resistant Epilepsies- Our Experience and Literature Review

Nicola Montano*, Filomena Fuggetta, Fabio Papacci, Rina Di Bonaventura, Mario Meglio and Gabriella Colicchio

Institute of Neurosurgery, Catholic University School of Medicine of Rome, Italy

***Corresponding author:** *Nicola Montano, Institute of Neurosurgery, Catholic University, Largo Agostino Gemelli, 800168 Rome, Italy, Tel: +39 0630154120,+39 0630154358; Fax: +39 063051343; E-mail: nicolamontanomd@yahoo.it*

Abstract

The impact of stimulation cycle on the outcome of patients submitted to vagal nerve stimulation (VNS) has been only marginally investigated in the literature. Nonetheless this is an important factor in term of tolerability of side effects, duration of generator and costs of therapy. Here the role of this parameter was evaluated on 21 patients who underwent to VNS implant at our Institution from January 1994 to February 2011 and responded to VNS (they reported a stable decrease of seizure number at least of 50%). We studied 3 stimulation cycles: slow (30''on-5'off), intermediate (30''on-3'off), fast (7''on-20''off). Each cycle was 1 year in duration. The stimulation cycle was recorded at the latest available follow-up (FU) for each patient (mean FU was 80.42 ± 54.01 months). Our protocol was to start with the slow cycle, to switch to the fast cycle and then to the intermediate one. The mean seizure frequencies before VNS and at latest FU were 26.08 ± 29.73 and 7.54 ± 10.22, respectively ($p<0.0001$; Wilcoxon Signed Rank Test). At latest FU, 11 cases (52.38%) were using the slow cycle and 8 (38.09%) the intermediate one. Among patient with a FU longer than 3 years (n=16), 15 of them (93.75%) were using slow or intermediate cycles. When considering the subgroup of patients with a 75% of reduction of number of crisis (n=12) nobody was using the fast cycle. Our results indicate that in patients responding to VNS the slow and intermediate cycles maintain the benefit of stimulation. If there is no response with these two cycles the probability of become a responder with the fast cycle is low.

Keywords

Vagus nerve stimulation, Epilepsy, Stimulation cycle

Introduction

Vagus nerve stimulation (VNS) is an adjunctive treatment for drug-resistant epileptic patients excluded from ablative surgery. The results reported in the literature are highly variable due to a widening of indications in the last years [1-4], the lack of defined prognostic factors [5] and the absence of full understanding of mechanism of action [6,7]. Recently we published on this topic and showed that the lesional etiology and an implant age less than 18 years were associated with an higher probability to be a responder after VNS [8]. Nevertheless the role of patient's stimulation cycle was not investigated in that analysis. Moreover this data is only marginally reported in the literature [2,9-11] and not investigated in a recent meta-analysis analyzing the results of this therapy in drug resistant epilepsies [5]. Recently an evidence-based guideline update on VNS failed to find recommendation for this topic [12]. Here we investigated how stimulation cycle affects the efficacy of VNS. We also reviewed the pertinent literature.

Table 1: Clinical records and stimulation parameters of 21 "responders" to vagal nerve stimulation.

Patients (No)	21
Sex (M/F)	14/7
Mean age of onset of epilepsy (years)	9.22 ± 10.02 (range: 1-54)
Mean pre-implant epilepsy duration (years)	21.71 ± 11.07 (range: 3-42)
Mean age at implant (years)	31.42 ± 14.7 (range: 10-62)
Etiology	
cortical malformations	2
ischemia	8
tumor	2
infection	1
tuberous sclerosis	3
non lesional	5
Stimulation frequency (Hz)	30
Pulse width (μsec)	500
Stimulation cycles	
slow	30 sec on / 5 min off,
intermediate	30 sec on / 3 min off
fast	7 sec on / 20 min off
Mean follow-up (months)	80.42 ± 54.01

Methods

We retrospectively reviewed the clinical records and stimulation parameters of 21 patients (14 M and 7 F) (Table 1) submitted to VNS implant at the Functional and Spinal Neurosurgery of the Catholic University from January 1994 to February 2011. To minimize the impact of other possible confounding factors we included in this analysis only the patients who responded to VNS (we identify patients as "responders" when the decrease of seizure number was at least 50%). Pre-implant evaluation, surgical procedure and post-implant

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Table 2: Literature review of studies comparing stimulation cycles in vagus nerve stimulation for drug-resistant epilepsies.

Author/year	Cases (No)	Responders (No)	Stimulationcycleused	Frequency	Mean follow-up (months)	Conclusions
Scherrmann J et al. 2001 [2]	95	38	7 sec on/30 sec off 30 sec on/5 min off	20 Hz 30 Hz	15.8 ± 10.3	Better outcome in patients with stimulation-on period of 30 sec
DeGiorgio CM et al. 2001 [3]	154	NR	12-66 sec off/7-60 sec on 1.8 min off/7-60 sec on 3 min off/7-60 sec on 5 min off/7-60 sec on	30 Hz	12	Patients with 30 sec on and 5 min off continue to respond or improve in their response over 1 year period. Some patients may benefit from reductions in off time (increases duty cycle)
Labar D et al. 2004 [1]	269	153	≥ 3 min off (standard cycle) ≤ 1.8 min off(rapid cycle)	NR	12	No differences between standard or rapid cycle
DeGiorgio C et al. 2005 [4]	61	18	7 seconds on/18 seconds off 30 seconds on/30 seconds off 30 seconds on/3 minutes off	20-30 Hz	3	In the first 3 months of therapy, initial setting of 30 seconds on/3 minutes off is well tolerated, and produce the most 75% responders

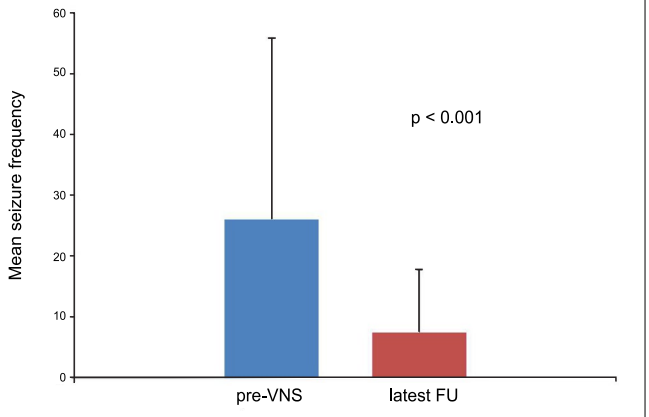

Figure 1: Wilcoxon Signed Rank Test.

evaluation have previously been reported [13]. Mean follow-up (FU) was 80.42 ± 54.01 months. The stimulation frequency was 30 Hz and the pulse width 500 μsec. Stimulation cycles used were the following: slow (30"on-5'off), intermediate (30"on-3'off), fast (7"on-20"off). Each cycle was 1 year in duration. Our protocol was to start with the slow cycle, to switch to the fast cycle and then to the intermediate one. Ethical approval of this protocol was previously obtained by the institutional review board [13]. We recorded the stimulation cycle at the latest available FU for each patient.

Results

The mean age of onset of epilepsy was 9.22 ± 10.02 years (range: 1-54 years) and the mean pre-implant epilepsy duration was 21.71 ± 11.07 years (range: 3-42 years). The mean age at implant was 31.42 ± 14.7 years (range: 10-62 years). Etiology was non-lesional in 5 patients and lesional in 16 patients (cortical malformations n=2, ischemia n=8, tumor n=2, infection n=1 and tuberous sclerosis n=3). The mean seizure frequencies before VNS and at latest FU were 26.08 ± 29.73 and 7.54 ± 10.22, respectively ($p<0.0001$; Wilcoxon Signed Rank Test) (Figure 1). At latest FU, 11 cases (52.38%) were using the slow cycle, 8 (38.09%) the intermediate one and only 2 patients (14.28%) the fast cycle. Among patients with a FU longer than 3 years (n=16), 15 of them (93.75%) were using slow or intermediate cycles. When considering the subgroup of patients who reached a 75% of reduction of seizures number (n=12) nobody was using the fast cycle.

Discussion

Our results indicate that in patients "responders" to VNS the slow and intermediate cycles maintain the benefit of stimulation. We investigated this parameter only in the responder patients to avoid the interference of other possible confounding variables that influence the prognosis of these patients. We think that this observation is interesting because the stimulation cycle affects the duration of generator that is directly correlated to the cost of this therapy. When examining the literature we found that the latest published meta-analysis didn't take into account the role of this parameter [5] and that the evidence to support the use of a determined cycle to reduce seizure occurrence was found insufficient in a recent evidence-based guideline update [12]. Furthermore the role of stimulation cycle in VNS therapy was fully investigated only marginally [2,9-11]. Moreover these studies had a FU generally short (mean FU ranges from 3 to 15.8 months) (Table 2). While Labar [2] found that stimulation parameters did not affect seizure rates in their groups, Shermann and colleagues [9], evaluating two stimulation cycles (fast and slow cycles), evidenced as patients with stimulation-on period of 30 sec (slow cycle) had a significantly better seizure outcome than patients with stimulation-on periods of 7 sec (fast cycle). Moreover it has been showed that in the first 3 months of therapy, initial settings of 30 seconds on/3 minutes off are well tolerated, and produced the most 75% responders [11] and that patients in the settings of 30 sec on and 5 min off improve in their response over 1 year period [10]. In our study the mean FU was 80.42 ± 54.01 months and we found that in patients with a FU more than 3 years, all but one case were using the slow or intermediate cycle.

Conclusions

Our study has some limitations due to the limited number of patients and the retrospective nature of data. However based on our observations and the reported literature, in managing patients after VNS implantation, we suggest to start with the slow cycle and, if there is no response, to switch to intermediate one. At that stage the probability for the patient of being a responder with the fast cycle is very low. Obviously further studies that should be multicentric and randomized are needed.

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