Seizure 58 (2018) 120–126

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Clinical outcomes of VNS therapy with AspireSR® (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre

Preci Hamilton[a,1], Imad Soryal[a,*,1], Prince Dhahri[a], Welege Wimalachandra[a], Anna Leat[a], Denise Hughes[b], Nicole Toghill[a], James Hodson[c], Vijay Sawlani[a,b], Tom Hayton[a], Shanika Samarasekera[a], Manny Bagary[b], Dougall McCorry[a,b], Ramesh Chelvarajah[a,b]

[a] Complex Epilepsy and Surgery Service, Queen Elizabeth Hospital Birmingham, United Kingdom
[b] Regional Complex Epilepsy Service, The Barberry, Birmingham, United Kingdom
[c] Statistics Department, Institute of Translational Medicine, Queen Elizabeth Hospital Birmingham, United Kingdom

ARTICLE INFO

Article history:
Received 25 December 2017
Received in revised form 5 March 2018
Accepted 24 March 2018
Available online xxx

Keywords:
Vagal nerve stimulation (VNS)
AspireSR®
Automatic stimulation (AutoStim)
Pharmacoresistant epilepsy
Cardiac-based seizure detection (CBSD)

ABSTRACT

Purpose: To compare the efficacy of AspireSR® to preceding VNS battery models for battery replacements, and to determine the efficacy of the AspireSR® for new implants.
Methods: Data were collected retrospectively from patients with epilepsy who had VNS AspireSR® implanted over a three-year period between June 2014 and June 2017 by a single surgeon. Cases were divided into two cohorts, those in whom the VNS was a new insertion, and those in whom the VNS battery was changed from a previous model to AspireSR®. Within each group, the seizure burden was compared between the periods before and after insertion of AspireSR®.
Results: Fifty-one patients with a newly inserted AspireSR® VNS model had a significant reduction in seizure frequency ($p < 0.001$), with 59% (n = 30) reporting ≥50% reduction. Of the 62 patients who had an existing VNS, 53% (n = 33) reported ≥50% reduction in seizure burden when the original VNS was inserted. After the battery was changed to the AspireSR®, 71% (n = 44) reported a further reduction of ≥50% in their seizure burden. The size of this reduction was at least as large as that resulting from the insertion of their existing VNS in 98% (61/62) of patients.
Conclusion: The results suggest that approximately 70% of patients with existing VNS insertions could have significant additional benefit from cardiac based seizure detection and closed loop stimulation from the AspireSR® device. For new insertions, the AspireSR® device has efficacy in 59% of patients. The *'rule of thirds'* used in counseling patients may need to be modified accordingly.

1. Introduction

Vagal nerve stimulation (VNS) emerged in the 1980s as a treatment alternative for pharmacoresistant epilepsy that is not amenable to resective surgery [1]. Having gained approval by the United States Food and Drug Administration (FDA) in 1997, this modality has become an established neuromodulatory treatment option for this group of patients [2]. Implantable pulse generator (IPG) models have evolved over time, with the latest being the first closed-loop VNS device, AspireSR® (Seizure Response).

Cardiac-based seizure detection (CBSD) uses ictal tachycardia as a surrogate marker for seizure prediction [3–6]. The sudden tachycardia that is often associated with a seizure episode has triggered interest in CBSD and now the AspireSR® (model #106) has been demonstrated to have the ability to sense this ictal tachycardia as a proxy to an epileptic seizure and deliver a closed – loop electrical current to the vagus nerve [5–7]. This IPG may also be able to differentiate this ictal tachycardia from rise in heart rate due to other causes however this is yet to be proven [5].

* Corresponding author at: Queen Elizabeth Hospital Birmingham, United Kingdom.
E-mail addresses: preci.hamilton@lthtr.nhs.uk (P. Hamilton), imad.soryal@nhs.net, Imad.Soryal@nhs.net (I. Soryal), prince.dhahr@nhs.net (P. Dhahri), ibuddhika.wimalachandra@uhb.nhs.uk (W. Wimalachandra), anna.leat@uhb.nhs.uk (A. Leat), denise.hughes@uhb.nhs.uk (D. Hughes), nicole.toghill@uhb.nhs.uk (N. Toghill), james.hodson@uhb.nhs.uk (J. Hodson), vijay.sawlani@uhb.nhs.uk (V. Sawlani), tom.hayton@nhs.net (T. Hayton), shanika.samarasekera@uhb.nhs.uk (S. Samarasekera), m.bagary@nhs.net (M. Bagary), Dougall.Mccorry@uhb.nhs.uk (D. McCorry).
[1] Co-first authors.

https://doi.org/10.1016/j.seizure.2018.03.022

The traditionally held view is that one-third of implanted patients will have significant benefit of ≥50% seizure burden reduction, one-third of patients will have less meaningful benefit, and the final third will have little benefit. More recent large retrospective case series have reported that 8% become seizure free, approximately 20% will have >90% seizure reduction and approximately 70% have >50% reduction in seizure frequency [8]. We postulated that the AspireSR® would be better than previous VNS models at controlling seizures in patients with epilepsy who are considered to be pharmacoresistant.

The aim of this study is to compare the efficacy of the AspireSR® at a large complex epilepsy and surgery center with preceding VNS battery models for battery replacements and to determine the response to AspireSR® for new implants. We performed a retrospective analysis of all VNS AspireSR® insertions and battery changes over a three-year period.

2. Methodology

We retrospectively reviewed the electronic records of adult patients who had VNS AspireSR® implanted by a single surgeon over the three-year period June 2014 through to June 2017 at the Queen Elizabeth Hospital Birmingham, United Kingdom. Our study was divided into two separate cohorts, the first being those patients who had AspireSR® implanted as their first VNS model ("new insertions cohort") and the second being those who had VNS battery changed from a previous model to AspireSR® ("battery change cohort"). Supplemental telephone interviews were employed by the surgical team to trace eight patients in the battery change cohort whose follow-up details were not available electronically.

2.1. Seizure burden estimates & outcome classification

Seizure burden data were estimated using seizure frequency and severity as reported by patients and caregivers. Each patient's response to VNS therapy was classified according to McHugh classification using a combination of each patient's interpretation or that of the clinician as documented in the electronic database or reported during telephone interviews. The McHugh classification is a VNS-specific seizure burden response considering seizure frequency and severity changes after IPG insertion [9]. It divides response into five categories.

2.2. Device programming and interrogation parameters

Device interrogation and programming information were retrieved from a combination of outpatient clinic notes, operative notes and the hospital's Motion VNS Therapy v11.0 programmer used in the operating theatre and Epilepsy Service outpatient department. The latter was done by matching either the patient allocation number or serial number of the implanted device. These identification data were available in the patients' electronic file or in the operating theatre records. Key device information recorded included:

Normal mode; On Time and Off Time (used to derive duty cycle), Frequency, Pulse Width, Output Current, Total On Time

Magnet mode; On Time, Pulse Width, Output Current and Total On Time

AutoStim; On Time, Threshold, Output Current, Total On Time and whether this feature was turned On or Off.

2.3. Defining commencement of therapeutic stimulation

Commencement of therapeutic AspireSR® therapy was defined for the new insertion cohort as the time of attaining normal stimulation mode current of 1.5miliamperes (1.5 mA) and thereby completing the ramping up phase – the process of increasing stimulation to optimal levels.

In the battery change cohort, therapeutic AutoStim parameters is classified as being achieved when attaining any of the following:

i Two incremental increases in stimulation current
ii Two incremental decreases in threshold heart rate detection
iii No further adjustment in device parameters was warranted.

Where none of the above information was available, this period was assumed to be six weeks.

2.4. Comparison periods

The periods being considered in the analysis of the two cohorts are shown in Fig. 1. In each case, for the periods after the insertion of a VNS, seizure burdens were recorded once therapeutic stimulation was achieved. For the new insertion cohort, the pre-VNS seizure burden was compared to the post- AspireSR® burden. For the battery change cohort, three periods were used: pre-VNS, post-initial VNS and post-AspireSR®. Comparisons were made between the first and second periods, to assess the improvement resulting from the initial VNS, and between the second and third periods, to assess any subsequent improvement resulting from the AspireSR®. The changes in the estimated yearly seizure frequency were aligned to the McHugh classification of VNS outcomes [9]. Reported seizure frequencies were converted to a common denominator (i.e. seizures per year), prior to analysis. Where patients reported their seizure frequency as a range, the midpoint was used. Thus we extrapolated for those patients who were followed up for less than one year.

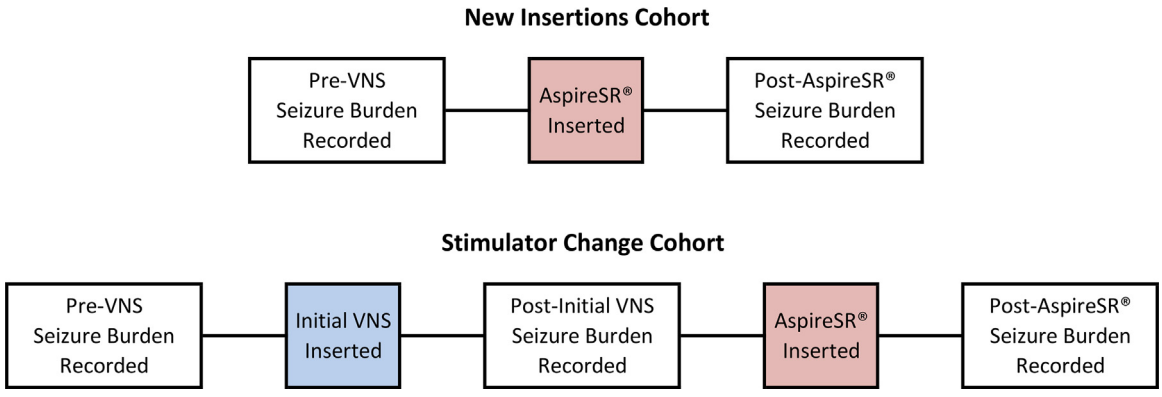

Fig. 1. Study design.

The device programming parameters were used to derive the duty cycle at which each device was being operated, and comparisons were made between pre- and post-AspireSR® therapy, to assess if a change in duty cycle could have influenced the outcome in the cohort of patients who demonstrated significant benefit (≥50% seizure burden reduction) after battery change to AspireSR®.

2.5. Theory & calculation

Estimated yearly seizure frequencies were found to follow skewed distributions, and so these were reported as medians with interquartile ranges (IQRs) and compared between periods using Wilcoxon's Signed-Rank Tests. In the battery change cohort, the post-initial VNS and post-AspireSR® improvements were then classified, based on the McHugh classification of VNS outcomes. The resulting values were then compared, to assess whether those patients who expressed an improvement after their initial VNS insertion tended to report similar improvements after the battery was changed to AspireSR®.

All analyses were performed using IBM SPSS Statistics 22 (IBM Corp. Armonk, NY). Patients with missing data were excluded on a per-analysis basis. A p-value < 0.05 was deemed to be indicative of statistical significance throughout.

2.6. Surgical technique

All patients had a left cervical skin crease incision and the battery secured in a left anterior chest wall subcutaneous pouch, except for one patient who had an interscapular IPG placed. We did not find it necessary to extend the incision to accommodate the larger AspireSR® battery as Schneider had found when replacing a Demipulse® model [6]. For these battery change cases, we used the previous incision, and developed a more caudal subcutaneous pocket regardless of the battery model being replaced.

A video record of our unit's surgical technique for new implant procedures is available for review at LivaNova Data on file (video upon request).

3. Results

3.1. Patient demographics

Our cohort consisted of 151 patients treated with AspireSR® VNS therapy over the three- year period. Three were excluded as lead revisions, leaving 77 new insertions and 71 battery changes. By the end of follow up, 26 (34%) of the new insertion cohort were still undergoing ramping up, and nine (13%) of the battery change cohort were having their AutoStim parameters adjusted. After excluding these patients, a total of 113 were included in the study, made up of 51 new insertions and 62 battery changes. The study flowchart is reported in Fig. 2.

For the 113 patients studied, the median age at initiation of AspireSR® therapy was 37 years (range: 19–74 years), and 51% of patients were males (n = 24 new insertions and n = 34 battery changes). The median follow- up duration of AspireSR® therapy was 17.3 months (range: 1–32 months) in the new insertion cohort and 19.9 months (range: 0.5–37.5 months) in the battery change cohort.

3.2. Outcomes in the AspireSR® new insertion cohort

Prior to AspireSR® VNS therapy, the 51 patients in the new insertion cohort reported a median of 192 (IQR: 48-720) seizures per year. This reduced significantly ($p < 0.001$, Table 1) post-AspireSR® therapy, to a median of 64 per year (IQR: 18-216). Data were not available for the post-AspireSR® seizure frequency in two patients, hence these were excluded from the above analysis. Both of these patients reported a 1–49% reduction in seizure burden by their qualitative interpretation despite not being able to report estimated seizure frequencies.

Changes in seizure burden after new AspireSR® insertions are shown in Fig. 3. A total of 59% (n = 30) of the cohort reported ≥50% reduction in seizure burden post-AspireSR® therapy. Of these, 21 (41% of the cohort) reported ≥80% reduction in seizure burden. Three patients (6% of the cohort) report having had no seizures in two, seven and 15 months after completing ramping up of VNS therapy.

Among the poor responders in this cohort, eight patients (16%) at best had their seizures dampened or aborted with swiping of the magnet of whom five (10% of the cohort) reported no antiepileptic benefit from VNS therapy.

3.3. Outcomes in the AspireSR® battery change cohort

Prior to VNS therapy, the 62 patients in this cohort had a median of 336 seizures per year (IQR: 84-1680). Following initial VNS insertion, this decreased significantly ($p < 0.001$, Table 1) to a median of 90 per year (IQR: 12-672), with 53% (n = 33) of patients reporting ≥50% reduction in seizure burden.

When the battery was changed to the AspireSR®, patients reported a further significant reduction in seizure burden

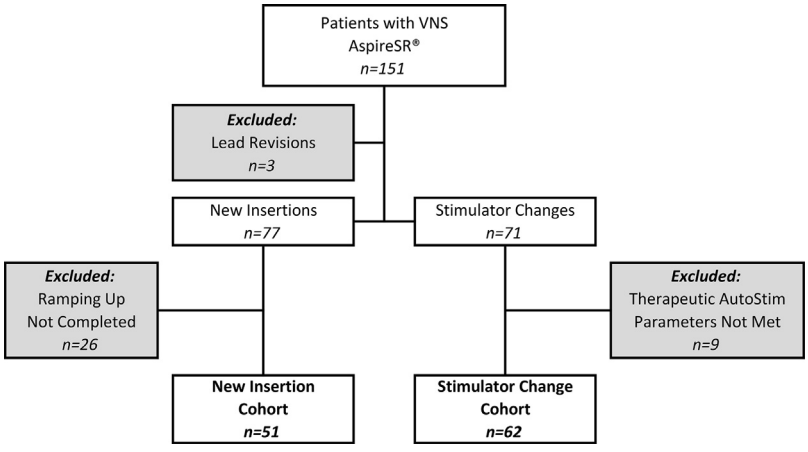

Fig. 2. Study flowchart.

Table 1
Comparison of seizure counts after optimized VNS therapy with implanted AspireSR®.

	N	Number of Seizures per Year Median (IQR)
New Insertions Cohort (N = 51)		
Pre-VNS	51	192 (48, 720)
Post-AspireSR®	49	64 (18, 216)
Change in Seizures (Pre-VNS to Post-AspireSR®)	*49*	*−30 (−348, −8)*
p-Value (Pre-VNS to Post-AspireSR®)		**<0.001**
Battery Change Cohort (N = 62)		
Pre-VNS	61	336 (84, 1680)
Post-Initial VNS	61	90 (12, 672)
Change in Seizures (Pre-VNS to Post-Initial VNS)	*60*	*−114 (−579, −10)*
p-Value (Pre-VNS to Post-Initial VNS)		**<0.001**
Post-AspireSR®	59	72 (12, 480)
Change in Seizures (Post-Initial VNS to Post-AspireSR®)	*59*	*0 (−42, 0)*
p-Value (Post-Initial VNS ® to Post-AspireSR®)		**<0.001**

In the new insertions cohort, data were not available for two patients in the Post-AspireSR® period, hence these were excluded from the calculation of the medians and comparisons between the periods. In the battery change cohort, data were not available for one patient each for the pre-VNS and post-initial VNS periods, and for three patiens in the Post-AspireSR® period, hence these were excluded from the calculation of the medians and comparisons between the associated periods. p-Values are from Wilcoxon's tests where statistical significance is defined as $p < 0.05$

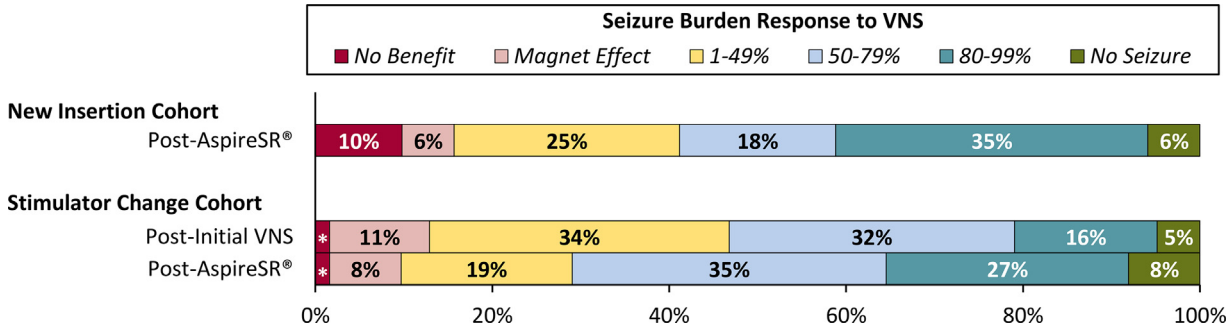

Fig. 3. Seizure burden response to VNS in the two cohorts.

($p < 0.001$), to a median of 72 seizures per year (IQR: 12-480), with 71% (n = 44) reporting ≥50% improvement over their initial VNS.

Duty cycles were recorded in 43 of the 44 patients who reported ≥50% improvement in seizure burden with the AspireSR®. Of these, 74% (N = 32) required no change to their duty cycle from previous settings. Four (9%) patients had their duty cycle stepped down. The first of these stepped down from 44% to 35% to facilitate the AutoStim feature of this new model. The second patient originally had his pre AspireSR® parameters adjusted to prolong battery life and efforts to return to initial parameters post AspireSR® were not tolerated, as he experienced coughing. As such, his device was programmed at 16% duty cycle down from 19% pre AspireSR®. These translate into 20% and 19% less work, respectively, by the AspireSR® compared to the replaced models, without losing the previous benefit gained from VNS therapy. The rationale for the duty cycle step down in the other two patients was unclear.

The remaining seven (16%) patients with significant benefit had the device duty cycle turned up, with a median increase of 33% (range: 21–100%) relative to that of their previous VNS. Five of these were in an attempt to further improve on seizure reduction; one was to facilitate further antiepileptic drug reduction and one successfully targeted benefit in hyperactivity and attention deficit.

A comparison of the improvements resulting from the two VNS therapies is reported in Table 2. The improvement in McHugh classification associated with the AspireSR® was found to be significantly greater than that for a patient's previous VNS ($p < 0.001$), with 31% (n = 19) of patients seeing a greater response to the AspireSR® than their previous VNS. Of the seven patients who only had a magnet swipe benefit from their initial VNS, two (29%) reported improvements in seizure burden after changing the battery to AspireSR®. The swipe benefit was retained after the battery change for the remaining five patients.

Only one patient reported a smaller benefit with AspireSR® therapy, compared to their initial VNS. This 32 year-old woman who has Tuberous Sclerosis (TS) reported a 50–79% reduction in seizure burden after initial VNS, which was followed by <50% improvement after the battery change to the AspireSR®. Interrogation of her device revealed extremely high impedance (>10 000 Ω) and that the device was delivering Output Current of only 0.5 mA, despite AutoStim being programmed at 1.125 mA. This high impedance suggested malfunctioning of the lead from a previous model that was originally placed in 1999 and she has been offered lead revision surgery. In addition, a single patient, a 21 year- old woman with severe Intellectual Disability (ID), reported no antiepileptic benefit from either initial VNS therapy, or after a battery change to AspireSR®, although she did maintain benefits to cognition and challenging behaviour attributed to VNS.

3.4. Procedural complications

Of the total 151 patients with AspireSR®, there were four cases (2.6%) of transient vocal cord paresis, all with complete resolution within 4–6 months and one case of lead migration (0.7%) suspected after a severe convulsive seizure soon after implant insertion requiring revision surgery. There were no reported cases of post-operative haemorrhage or surgical site infection in our cohort of patients.

Table 2
Hamilton-Soryal Actuarial Table of AspireSR® VNS battery change outcomes: Comparisons of the efficacy of initial VNS and AspireSR®.(For interpretation of the references to color in this Table legend, the reader is referred to the web version of this article.)

		Post-AspireSR® Therapy						
		Total N	**No Benefit**	**Magnet Effect**	**1-49%**	**50-79%**	**80-99%**	**No Seizure**
Post-Initial VNS Therapy	**No Benefit**	*1*	1 (100%)	-	-	-	-	-
	Magnet Effect	*7*	-	5 (71%)	1 (14%)	-	1 (14%)	-
	1-49%	*21*	-	-	10 (48%)	8 (38%)	3 (14%)	-
	50-79%	*20*	-	-	1 (5%)	14 (70%)	4 (20%)	1 (5%)
	80-99%	*10*	-	-	-	-	9 (90%)	1 (10%)
	No Seizure	*3*	-	-	-	-	-	3 (100%)
	Total N		*1*	*5*	*12*	*22*	*17*	*5*

The diagonal (grey cells) represents those patients where the responses to the initial VNS and AspireSR® therapies were in the same McHugh class. Cells above this (green) are where patients had a larger proportional response to the AspireSR® battery than the initial VNS, whilst the cell below the diagonal (red) indicator superior response to the initial VNS over the AspireSR®. Percentages are calculated based on the row totals. The response to the AspireSR® was found to be significantly greater than that of the initial VNS (Wilcoxon's test: $p < 0.001$).

4. Discussion

VNS was introduced in the 198Os and was not approved by the FDA until a decade later [1,2]. Now three decades on, VNS is the main neuromodulatory treatment option for medically refractory epilepsy not amenable to resective surgery.

The reporting of outcome measures in epilepsy is of paramount importance for any treatment modality and this holds true for vagal nerve therapy. There have been a number of publications comparing the VNS outcomes among different patient populations [8–12]. We compared our experience with AspireSR® not only to our pre-AspireSR® experience, but also with the existing literature [8,9,13,14]. Our population consisted of a mixture of seizure types and we did not differentiate outcome based on gender, seizure type or laterality as Chen and colleagues have previously done nor did we differentiate based on age or concomitant co-morbidities [4].

We found that battery change to AspireSR® resulted in significant reduction in seizure burden (≥50% reduction) in 71% of cases, which is greater than reported in the available literature for both adult and pediatric VNS population to date. This is evident earlier with AspireSR® treatment as, at a mean follow up of 13 months, 59% of our new insertion cohort had already reported this significant degree of benefit (see Fig. 4).

4.1. Patient with deteriorating seizure control following AspireSR® therapy

We identified one patient with deteriorating seizure control following VNS battery change to AspireSR®. This patient had a lead malfunction from a previous IPG model and made an informed choice not to undertake lead revision surgery after being counseled about the risks of the operation, which included up to 22% risk of

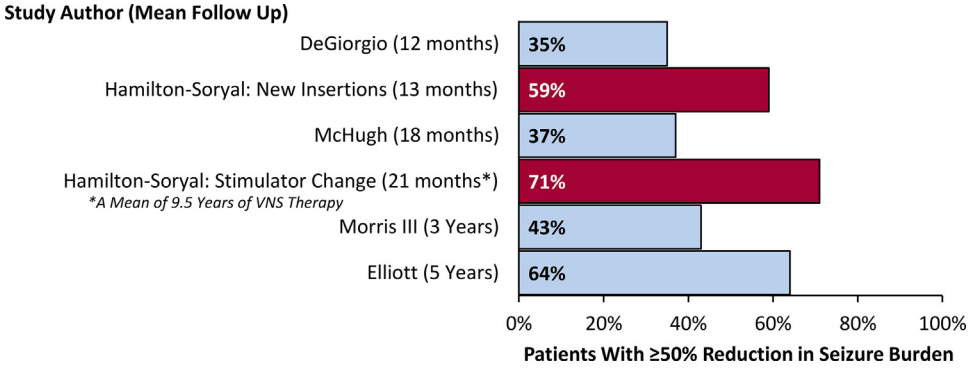

Fig. 4. Comparison of the rates of significant seizure burden control (i.e. ≥50% reduction) resulting from AspireSR® insertion in this study (red bars) and the prevailing literature. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

permanent vocal cord palsy. She commenced targeted therapy with Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, for renal Angiomyolipomas on the background of Tuberous Sclerosis with Subependymal Giant Cell Astrocytomas (SEGAs) based on the EXIST trials [15–17].

4.2. AspireSR® battery change in a non-responder

VNS battery change to AspireSR® was offered to one patient who previously had no antiepileptic benefit from VNS therapy. This patient who had severe Intellectual Disability (ID) reported significant benefit attributed to VNS for improved cognition and behaviour. She maintained this degree of the widely accepted benefit of VNS therapy in this community of patients but continued to have no antiepileptic benefit after the battery was changed to the AspireSR® [18,19].

4.3. Patient counseling-modification of the 'rule of thirds'

We routinely categorize our VNS implanted patients' outcomes according to the McHugh classification system. In light of our findings, the information presented to patients may need to be modified as we report that, with battery change to AspireSR®, approximately one-third (29%) of patients will have <50% benefit, one-third (35%) will have 50–79% benefit and another one–third (35%) will have even ≥80% benefit (See Fig. 3). The proportion of patients who did not benefit was found to be negligible (<2%).

Although this is a retrospective study with small sample size, our findings suggest that patients who reported 1–49% reduction in seizure burden with a device prior to AspireSR® should be considered for a battery change, as 52% of this sub-cohort (n = 11) achieved clinically significant additional benefit (See Table 2). This is an important finding but requires replication by other studies.

In our discussion with patients, we abbreviate the automatic stimulation mode as *'automatic magnet swipe.'* The inherent ability of the AspireSR® to detect the ictal tachycardia associated with four-fifths of all seizures is a significant advancement, as delivering an on-demand electrical stimulation can dampen or abort a seizure without any active effort by the patient or care giver [5]. For example, one of our patients improved from McHugh class IV to McHugh class III, for which we believe that AutoStim of the AspireSR® is primarily responsible. This is supported by the almost 20% Total On Time of the device being accounted for by AutoStim compared to <1% by the magnet in this index patient. In our study population, there was no increase in duty cycle in 83% of those who attained significant benefit (≥50% seizure burden reduction) after battery change to AspireSR®. This improvement in seizure control is likely due to the AutoStim feature inherent to the VNS AspireSR® model, as there was no increase in duty cycle.

4.4. Limitations & generalizability

Our study was a retrospective analysis and we reported patients' and carers' interpretation of their response to VNS therapy rather than by prospectively collected seizure diaries or a formal quality of life assessment tool. This retrospective seizure reporting was therefore a potential source of recall bias. Similarly, the lack of blinding and randomization could have resulted in selection bias as patients who were more likely to have had benefit from VNS therapy were offered treatment with AspireSR®. Although we compared seizure burden at different periods, we did not compare our CBSD period with another group that is being treated concurrently with VNS other than CBSD IPG. Whilst we have not looked at concurrent medication changes, the VNS is used as an adjunct usually with no changes to medications within the first 12 months rather than as a replacement for medications.

Strengths of our study include the careful selection of patients for VNS therapy through a MDT process to exclude patients with misdiagnosis and the fact that a consistent approach to VNS programming was applied. The actuarial table presented for our battery change cohort may become applicable to individual patients as a predictor of potential response to CBSD IPG such as the AspireSR®, as a function of their response to previous VNS model(s).

5. Conclusion

In our study, the 59% response rate for new implants at the 50% improvement in seizure frequency threshold were better than reported in most previously published studies, although in line with outcomes reported by Elliot et al. (2011). In addition, patients experience meaningful improvement sooner with this cardiac-based seizure detection VNS therapy. VNS therapy with CBSD IPG (AspireSR®) achieved a greater seizure control benefit over a mean of 13 months duration of therapy than reported figures achieved after longer treatment duration of up to five years.

In addition, 71% of our study population reported an additional improvement in seizure control at the 50% threshold for improved seizure frequency following battery change from previous IPG models to the AspireSR® IPG. The majority (74%) did not require a change to the duty cycle. An additional 18% of those who underwent a battery change experienced ≥50% seizure reduction response over a mean of 21 months of AspireSR® therapy.

The closed – loop cycle is not dependent on patient or caregiver compliance as it is an automated system. This device improved the number of good responders, while reducing the number of poor responders to VNS therapy. The '*rule of thirds*' when applied to patient counseling could be revised accordingly.

Declaration of interest

Mr. Ramesh Chelvarajah declares that he receives speaker fees from Cyberonics Inc. The remaining authors have no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

[1] Penry J.K., Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. Epilepsia 1990;31(Suppl. 2): S40–43.
[2] Ogbonnaya S, Kaliaperumal C. Vagal nerve stimulator: evolving trends. J Nat Sci Biol Med 2013;4(1):8–13.
[3] Chen Wei, Guo Chang-Li, Zhang Pei-Song, Liu Chong, Qiao Hui, Zhang Jian-Guo, et al. Heart rate changes in partial seizures: analysis of influencing factors among refractory patients. BMC Neurol 2014;14:135.
[4] Chen W, Zhang XT, Guo CL, Zhang SJ, Zeng XW, Meng FG. Comparison of heart rate changes with ictal tachycardia seizures in adults and children. Childs Nerv Syst 2016;32(4):689–95.
[5] Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure 2014;23(7):496–505.
[6] Schneider UC, Bohlmann K, Vajkoczy P, Straub HB. Implantation of a new Vagus Nerve Stimulation (VNS) Therapy(R) generator, AspireSR(R): considerations and recommendations during implantation and replacement surgery-comparison to a traditional system. Acta Neurochir (Wien) 2015;157(4):721–8.

[7] Fisher RS, Afra P, Macken M, Minecan DN, Bagic A, Benbadis SR. Automatic vagus nerve stimulation triggered by ictal tachycardia: clinical outcomes and device performance–the U.S. E-37 trial. Neuromodulation 2016;19(2):188–95.
[8] Elliott Robert E, Morsi Amr, Kalhorn Stephen P, Marcus Joshua, Sellin Jonathan, Kang Matthew, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav 2011;20(1):57–63.
[9] McHugh John C, Singh Harsh W, Phillips Jack, Murphy Kevin, Doherty Colin P, Delanty Norman. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. Epilepsia 2007;48(2):375–8.
[10] Elliott Robert E, Morsi Amr, Tanweer Omar, Grobelny Bartosz, Geller Eric, Carlson Chad, et al. Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years. Epilepsy Behav 2011;20(3):478–83.
[11] Elliott Robert E, Rodgers Shaun D, Bassani Luigi, Morsi Amr, Geller Eric B, Carlson Chad, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. J Neurosurg Pediatr 2011;7(5):491–500.
[12] Rodgers Will P, Durnford Andrew J, Kirkham Fenella J, Whitney Andrea, Mullee Mark A, Gray William P. Interrater reliability of Engel: International League Against Epilepsy, and McHugh seizure outcome classifications following vagus nerve stimulator implantation. J Neurosurg Pediatr 2012;10(3):226–9.
[13] DeGiorgio CM, Schachter SC, Handforth A, Salinsky M, Thompson J, Uthman B, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 2000;41(9):1195–200.
[14] Morris 3rd GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology 1999;53(8):1731–5.
[15] Bissler John J, Kingswood J Christopher, Radzikowska Elzbieta, Zonnenberg Bernard A, Frost Michael, Belousova Elena, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2013;381(9869):817–24.
[16] French Jacqueline A, Lawson John A, Yapici Zuhal, Ikeda Hiroko, Polster Tilman, Nabbout Rima, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet 2016;388(10056):2153–63.
[17] Kingswood J Chris, Jozwiak Sergiusz, Belousova Elena D, Frost Michael D, Kuperman Rachel A, Bebin E Martina, et al. The effect of everolimus on renal angiomyolipoma in patients with tuberous sclerosis complex being treated for subependymal giant cell astrocytoma: subgroup results from the randomized, placebo-controlled, Phase 3 trial EXIST-1. Nephrol Dial Transplant 2014;29(6):1203–10.
[18] Hallbook Tove, Lundgren Johan, Stjernqvist Karin, Blennow Gosta, Stromblad Lars-Goran, Rosen Ingmar. Vagus nerve stimulation in 15 children with therapy resistant epilepsy; its impact on cognition: quality of life, behaviour and mood. Seizure 2005;14(7):504–13.
[19] Lund C, Kostov H, Blomskjold B, Nakken KO. Efficacy and tolerability of long-term treatment with vagus nerve stimulation in adolescents and adults with refractory epilepsy and learning disabilities. Seizure 2011;20(1):34–7.