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Quality of life after vagal nerve stimulator insertion

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ABSTRACT – *Aim.* Assess quality-of-life after vagal nerve stimulation and determine patient characteristics associated with improvement in quality-of-life. *Methods.* Sixteen patients (11 children, 5 adults) who had vagal nerve stimulation at our center were studied. Quality-of-life was assessed pre- and post-vagal nerve stimulation using the Quality-of-Life in Childhood Epilepsy questionnaire for children and the Epilepsy Surgery Inventory-55 for adults. *Results.* Sixteen patients who did not qualify for resective surgery were included; seven (43.75%) were males and 9 (56.25%) were females. Mean age at onset of seizures was 3.96 ± 4.00 years and at surgery was 15.78 ± 10.78. Follow-up time was 1.26 ± 0.92 years. Fourteen patients (87.5%) were mentally retarded. Ten (62.5%) had cryptogenic etiology and 6 patients (37.5%) symptomatic etiology. Fifty percent had localization-related epilepsy. Six of 7 patients with generalized cryptogenic etiology (85.71%) had Lennox-Gastaut syndrome. Seizures dropped from 122.31 ± 159.49 to 67.84 ± 88.22 seizures/month. Seizure reduction (> 50%) correlated with improvement in total quality-of-life ($p = 0.034$). Post-vagal nerve stimulation, the total group scored significantly higher in the social domain ($p = 0.039$). In patients with localization-related epilepsy, significant improvements were detected in the social domain ($p = 0.049$) and in total quality-of-life ($p = 0.042$). *Conclusion.* Despite a diverse and small population size, we observed significant improvements in the social domain 1.26 years post-vagal nerve stimulation. In addition, there was an improvement in total quality-of-life amongst patients with partial seizures. Finally, seizure reduction was associated with quality-of-life improvement. Our results support previous studies from the West reporting improvement in quality-of-life following vagal nerve stimulation, contradict those studies that did not show such differences, and are the first coming from a developing country.

Key words: quality of life, vagal nerve stimulator, epilepsy surgery, drug resistance

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Pharmacoresistant epilepsy is a disabling disease that affects about 30% of the epileptic population (Kwan and Brodie, 2000). Of those who end up with medically uncontrolled seizures and are then referred for preoperative evaluation, only 23-46% are good candidates for epilepsy surgery (Boon

et al. 1999, Scott *et al*. 1999). Two thirds of surgically treated patients may benefit from these procedures (Engel 1987).

Failure to localize the "epileptogenic zone" or inability to remove an epileptic focus due to its location within a critical part of the brain precludes resective surgery as a therapeutic option. In those instances, cure of epilepsy might not be the goal of subsequent management, and only palliative measures should be considered (i.e ketogenic diet and vagus nerve stimulation).

In 1989, a vagus nerve stimulator (VNS) was first implanted in a human subject. Since then, many series of patients reported the efficacy of VNS in controlling drug-resistant epilepsy. The majority of authors agreed on the potential of VNS to reduce seizure frequency and sometimes to decrease generalization, the most offending aspect of their epilepsy profile interfering with daily activities (Patwardhan *et al*. 2000, Amar *et al*. 2004).

Nevertheless, the validity of such an expensive device should be assessed by surgical outcomes and its ability to improve quality of life. VNS is not a surgical option that is expected to render a patient seizure-free. A prior study has shown that partial resolution of epilepsy after surgical resection might worsen the psychosocial outcome when compared to the preoperative baseline (Seidman-Ripley *et al*. 1993); hence, the importance of studying the outcome of surgical interventions that do not offer seizure freedom. Whereas some studies have shown significant improvements in QOL (Cramer *et al*. 2001, Hallbook *et al*. 2005, Ergene *et al*. 2001, Patwardhan *et al*. 2000), others have detected no changes (Parker *et al*. 1999, Morrow *et al*. 2000, Chavel *et al*. 2003). All of these studies were reported from developed countries; thus the need for further studies in multiple populations since psychosocial factors and support systems for patients with epilepsy can be population-dependent (Buck *et al*. 1999, Mikati *et al*. 2006).

Our objective was to assess overall QOL after VNS insertion and acquire a comprehensive understanding of the impact of VNS on the social, health, emotional, and physical domains using age- and epilepsy-specific instruments.

Methods

Sixteen consecutive patients who underwent left VNS implantation for intractable epilepsy from August 2003 to November 2007 at the American University of Beirut-Medical Center (AUB-MC) were included. All patients had undergone pre-surgical evaluation and were found to be inadequate candidates for resective surgery due to inability to localize a single epileptic focus or due to location of the focus in an eloquent area of the brain where cognitive or motor impairments could result if the focus was resected.

VNS surgery was performed in the standard fashion under general anesthesia for all patients. Duration of hospitalization was no longer than 48 hours, with patients routinely discharged home the first postoperative day. The stimulator was turned on and programmed by the neurologist 1 to 2 weeks after surgery. All patients were set on a certain stimulation protocol: current output 0.25 mA with a stepwise increment by 0.25 mA per week until the target point of 2 mA is achieved. The stimulation frequency was set at 30 Hz; pulse width, 250 ms; signal on time, 30 s; and signal off time, 5 min. Meanwhile, the parameters were titrated against the side effects and seizure control. The signs of adverse effects from stimulation and the use of the magnet in the setting of acute seizure control were all explained to the caregivers.

The study was accepted by the ethics committee and informed consent was obtained from the patient or the parents. Data on pre- and post-operative seizure frequency, duration, severity, and type, age at onset and at surgery, etiology, and pre- and post-operative antiepileptic drugs were collected from outpatient visits and through interviews when needed. Mental status was assessed using IQ testing (Wechsler Adult Intelligence Scale-III and the Wechsler Intelligence Scale for Children) and the Denver Developmental test.

QOL was assessed in adults (> 18 years old) using the Epilepsy Surgery Inventory-55 (ESI-55) questionnaire containing 55 items (Vickrey *et al*. 1992). The 55 QOL items were divided into three domains:

1. *The "well being" domain* included six scales: health perception (9 items), change in health (1 item), energy/fatigue (4 items), emotional well-being (5 items), pain (2 items), and overall QOL (2 items);
2. *The "functioning" domain* included three scales: physical function (10 items), social functioning (2 items), and cognitive function (5 items);
3. *The "role-limitation" domain* included three scales: role limitation due to physical (5 items), emotional (5 items), and memory problems (5 items).

The recorded numeric value of each item was scored on a 0 to 100 range. Scores stood for the percentage of the total possible score achieved. Items in the same scale were averaged together to create the 11 scale mean scores, and a total composite score for each of the three domains. A total ESI-55 score was generated from the average score of the three domains.

In pediatric patients (< 18 years old), seizure severity and the side effects of the antiepileptic drugs were assessed using the Hague Seizure Severity Scale (HASS) and the Hague Side Effects Scale (HASES). QOL was assessed using the Child Epilepsy Questionnaire Parental Form (CEQ-P [II]) (*i.e.* Quality-of-Life in Childhood Epilepsy Questionnaire QOLCE) (Sabaz *et al*. 2000). It included 91 items under seven main domains; overall QOL (1 item), general health (1 item), physical activities (12), emo-

tional well-being (19), social functioning (12), behavioral functioning (23), and cognitive functioning (23) domains. A linear score out of 100 was generated for each item. Pre- and post-operative average scores for HASS, HASES, and for each domain in the QOLCE were obtained. A total QOLCE score was produced from the average scores of the domains. QOL questionnaires were administered pre- and post-VNS and were filled by the patient or guardians depending on the mental status and age. QOL questionnaires were comprehensively translated into Arabic through a professional translator to ensure accuracy. The reliability of the Arabic version of the ESI-55 was tested as part of a Masters thesis of an MPH student. It has already been used in two of our previously published articles (Mikati *et al*. 2004 and Mikati *et al*. 2006). We performed extensive field testing and reliability testing on Lebanese patients after translation of the QOLCE questionnaire including back translation, inter-rater and test-retest procedures (Mikati *et al*. 2008, Mikati and Rahi, 2008).

For analysis of the whole group, adults and children, and of patients with localization related or generalized epilepsy, questionnaire items assessing similar outcomes of QOL were grouped together under 7 domains; Overall QOL (includes ESI-55 questions 2 and 48 and QOLCE section 7.1), Energy/Fatigue (ESI-55 questions 25, 29, 31 and 33 and QOLCE section 1.2 a, b), Physical domain (ESI-55 questions 4-13 and QOLCE section 1.1 a-j), Emotional Well Being (ESI-55 questions 26-28, 30 and 32 and QOLCE section 2.1 a-s), Cognitive (ESI-55 questions 35, 36, 38, 49, 50 and QOLCE section 3.1 a-w), Social (ESI-55 questions 24, 34 and QOLCE section 4.1, 4.2, 4.3), and General Health (ESI-55 questions 1, 3, 37, 39-47 and QOLCE section 6.1). The total QOL score was generated from the average of these 7 domains.

A power analysis was done using PASS 2008. Data were entered and analyzed using SPSS version 15.0 for Windows. Mean QOL scores before and after VNS were compared using Student's paired t-test and McNemar's test. Bivariate analysis was performed to find factors that correlated with improvement in total QOL scores. P values ≤ 0.05 were considered statistically significant. ANOVA was used to compare differences in seizure reduction in the semi-quantitative analysis of the open-ended questions.

Results

Demographics

Sixteen patients were included in the study; 5 young adults (19 to 38 years) and 11 children (5 to 18 years). Seven (43.75%) were males and 9 (56.25%) females. All approached patients participated. Mean age of onset of seizures was 3.96 ± 4.00 years (1 hour to 11 years), mean age at surgery was 15.78 ± 10.78 years (5 to 38 years), and mean follow-up time was 1.26 ± 0.92 years (0.4 to 3.9 years). Fourteen patients (87.5%) were mentally retarded. Ten (62.5%) had cryptogenic etiology and 6 patients (37.5%) had symptomatic etiologies; of these,1 patient had tuberous sclerosis, 1 patient had dysgenesis, 1 patient had probable polymicrogyri, 1 patient had left schizencephaly, and 2 patients had herpes encephalitis *(table 1)*. Fifty percent of the patients had localization-related epilepsy and 50% had generalized epilepsy. Six out of 7 patients (85.71%) with generalized cryptogenic etiology had Lennox Gastaut Syndrome (LGS) *(table 1)*.

Mean seizure frequency was 122.31 ± 159.49 seizures/month before VNS. An a priori power analysis with a hypothesized decrease in seizure frequency by 50% revealed a sample size of 44 needed for a power of 0.80. Mean seizure frequency after VNS was 67.84 ± 88.22 seizures/month. Two patients were able to decrease their total anti-epileptic medications by one medication each, while one patient had to have an additional two medications added. Thirteen patients had no change in their number of anti-epileptic medications *(table 2)*. Seizure frequency before and after insertion of VNS were compared using the McNemar's test and the Student's paired t-test. McNemar's test showed that VNS was associated with a significant drop in seizures ($p = 0.004$), while the t-test did not achieve statistical significance ($p = 0.155$). The lack of statistical significance is apparently attributable to one outlier that experienced an increase in seizure frequency of 175% post-VNS placement. Excluding this patient from the analysis resulted in a p value on the t test of 0.053.

Quality of life

An *a priori* power analysis using a pre-VNS QOL mean score of 45.1478, and an effect size of 50% improvement revealed a sample size of 6 needed for power of 0.8. After VNS insertion, patients scored significantly higher in the social domain ($p = 0.039$). There were no statistically significant differences in overall QOL, energy/fatigue, physical, emotional, cognitive, health domains and total QOL before and after VNS insertion ($p = 0.469$, 0.306, 0.459, 0.641, 0.467, 0.091, 0.136 respectively) *(figure 1)*.

Seizure reduction (> 50% reduction) was associated with improvement in total QOL ($p = 0.034$). Age at surgery and age of epilepsy onset, mental retardation, epilepsy type, follow-up duration, etiology, pre-seizure frequency, seizure severity, seizure duration, number of medications before VNS and after VNS insertion, total QOL scores before VNS insertion, sex, and socioeconomic-status did not correlate with improvement in total QOL ($p > 0.072$).

Subgroup analysis

The patients were analyzed in subgroups to assess for QOL differences within more homogeneous subsets.

Table 1. Demographics of the study group.

Patient	Sex	Age at surgery (year)	Age at epilepsy onset (year)	Socio-economic-Status	VNS Current (mA)	Seizure Type	Etiology	Mental Status
1	F	17.00	11.00	High	< 2	SPS, CPS, Secondary Generalized	Dysgenesis	MR
2	F	18.00	7.00	High	≥ 2	Generalized, atonic, absence, GTC, LGS	Cryptogenic	MR
3	F	5.00	.80	Middle	≥ 2	SPS, CPS, Secondary Generalized	Cryptogenic	Not MR
4	F	5.00	.40	Middle	≥ 2	CPS	Cryptogenic	MR
5	M	38.00	8.00	High	< 2	Generalized, GTC, LGS	Cryptogenic	MR
6	F	19.00	.80	Middle	> 2	Generalized, tonic, absence, myoclonic LGS	Cryptogenic	MR
7	F	11.00	5.00	High	< 2	Generalized, tonic, GTC, myoclonic, absence, LGS	Cryptogenic	MR
8	M	13.00	.70	Middle	< 2	Generalized, tonic, clonic	Cryptogenic	MR
9	M	8.40	.40	Middle	< 2	Generalized, GTC	probable polymicrogyri	MR
10	M	6.00	1.30	Low	≥ 2	CPS, Secondary Generalized	Tuberous Sclerosis	MR
11	M	31.00	11.00	Middle	< 2	SPS, CPS, Secondary Generalized	Cyptogenic temporal epilepsy R/O bilateral	Not MR
12	M	36.00	9.00	Middle	≥ 2	Generalized, GTC, absence, myoclonic, LGS	Cryptogenic	MR
13	F	19.00	.90	High	< 2	Generalized, atonic, absence, myoclonic, tonic, LGS	Cryptogenic	MR
14	M	12.00	4.00	Low	< 2	CPS, Secondary Generalized	Herpes Encephalitits	MR
15	F	7.00	First hour of life	Low	< 2	CPS	Left Schizencephaly	MR
16	F	7.00	3.00	Low	< 2	CPS	Herpes Encephalitits	MR

CPS: complex partial seizures; GTC: generalized tonic-clonic; SPS: simple partial seizures; MR: mentally retarded.

Table 2. Seizure outcome after VNS implantation.

Patient	Follow-up (years)	Number of medications Pre-VNS /Post-VNS	Seizure frequency Pre-VNS/Post-VNS/%reduction (seizure/month)	Seizure Severity	Seizure duration Pre-VNS/Post-VNS (seconds)
1	1.50	3/2	10/2/80%	Milder	150/60
2	1.80	2/2	75/30/60%	Milder	5/5
3	1.40	2/2	1/0/100%	Seizure free	65/0
4	1.20	2/2	4/4/0%	Same	120/120
5	3.90	3/5	80/75/6.25%	Same	30/300
6	2.40	4/4	600/90/85%	Milder	20/2
7	0.80	2/2	135/105/22.22%	Same	120/120
8	0.80	3/3	15/6/60%	Milder	60/30
9	0.70	3/3	4/3.5/12.5%	Milder	60/60
10	0.80	1/1	154/105/31.81%	Milder	2.5/30
11	0.90	4/4	120/12/90%	Milder	30/30
12	0.70	3/2	360/180/50%	Milder	150/10
13	2.00	3/3	120/330/-175%	Stronger	90/90
14	0.40	3/3	64/34/46.88%	Same	1.5/1.5
15	0.40	3/3	210/105/50%	Milder	300/1.5
16	0.40	3/3	5/4/20%	Milder	90/30

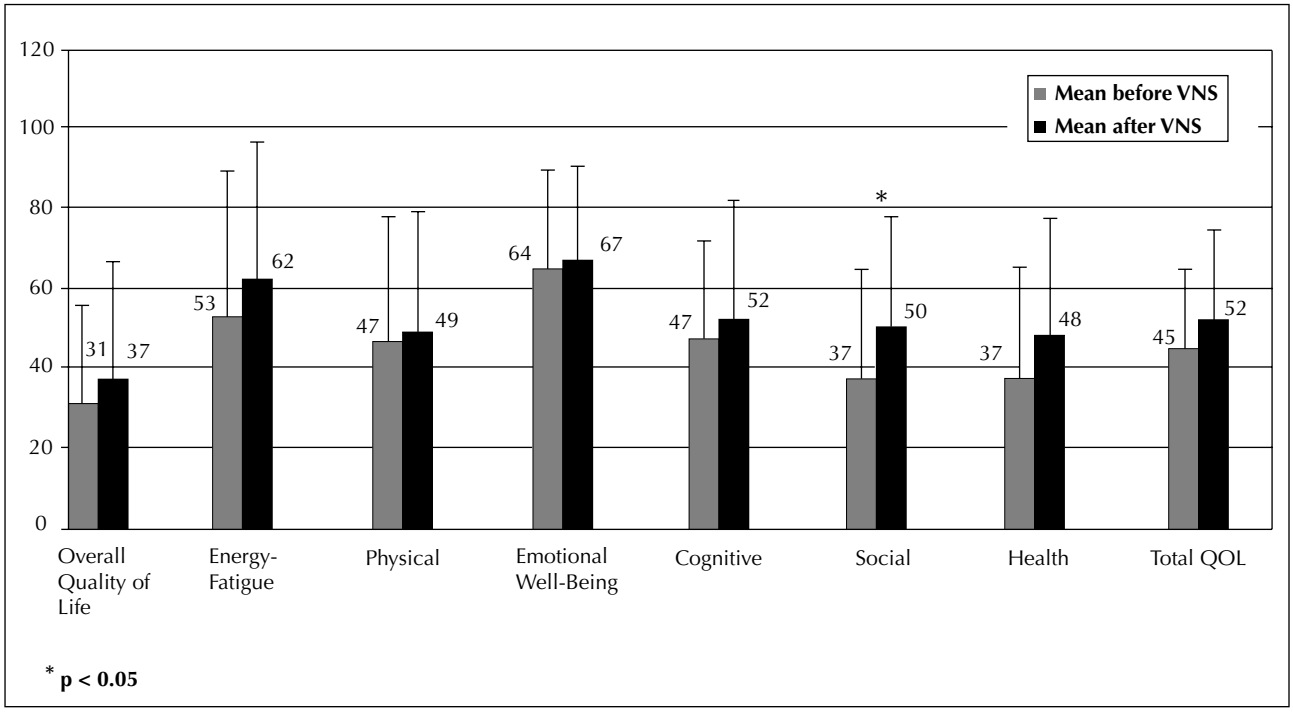

Figure 1. QOL results for the whole group.

Patients were separated by age and also by type of epilepsy (localization-related *vs* generalized).

Effect of Age

Ages 5-18 years

Mean age of seizure onset and at surgery for the pediatric group were 3.05 ± 3.47 years (1 hour-11 years) and 9.95 ± 4.62 years (5-18 years), respectively. Mean follow-up time was 0.93 ± 0.48 years (0.4-1.8 years). Mean seizure reduction was 43.95% (0-100%). Seizure frequency before VNS insertion (61.55 ± 73.81 seizures/month) significantly decreased after VNS insertion (36.23 ± 45.58 seizures/month) ($p = 0.026$). There were no significant differences in the QOL domains before and after VNS insertion ($p > 0.056$) (data not shown).

Ages 19-39 years

Mean age of seizure onset for the adult group was 5.94 ± 4.77 years (0.8-11 years), mean age at surgery was 28.60 ± 9.13 years (19-38 years), and mean follow-up time was 1.98 ± 1.29 years (0.7-3.9 years). Mean seizure reduction was 11.25% (- 175% to 90%). Seizure frequency before VNS insertion was 256.00 ± 221.99 seizure/month and after VNS insertion it was 137.40 ± 123.26 seizures/month. The decrease in seizure frequency after VNS insertion was not significant ($p = 0.371$). There were no significant differences in the QOL domains before and after VNS insertion ($p > 0.141$) (data not shown).

Effect of type of epilepsy

Localization-related epilepsy

Mean age of seizure onset for patients with localization-related epilepsy was 3.94 ± 4.56 years (1 hour – 11 years), mean age at surgery was 11.25 ± 8.99 years (5-31 years), and mean follow-up time was 0.88 ± 0.46 years (0.4-1.5 years). Mean seizure reduction was 52.34% (0-100%). Seizure frequency before VNS insertion was 71.00 ± 81.18 seizures/month and after VNS insertion it was 33.25 ± 45.58 seizures/month. The decrease in seizure frequency after VNS insertion did not reach significance ($p = 0.052$).

There was a statistically significant improvement in the social domain ($p = 0.049$) and in the total QOL scores ($p = 0.042$). No statistically significant differences were found in the other domains of QOL after VNS insertion ($p > 0.082$) *(figure 2)*.

Generalized epilepsy

Mean age of seizure onset for patients with generalized epilepsy was 3.98 ± 3.68 years (0.4-9 years), mean age at surgery was 20.30 ± 11.02 years (8.4-38 years), and mean follow-up time was 1.64 ± 1.14 years (0.7-3.9 years). Mean seizure reduction was 15.12% (- 175% to 85%). Seizure frequency before VNS insertion was 173.63 ± 204.70 seizures/month and after VNS insertion it was 102.44 ± 108.92 seizures/month. The decrease in seizure frequency after VNS insertion was not significant ($p = 0.362$).

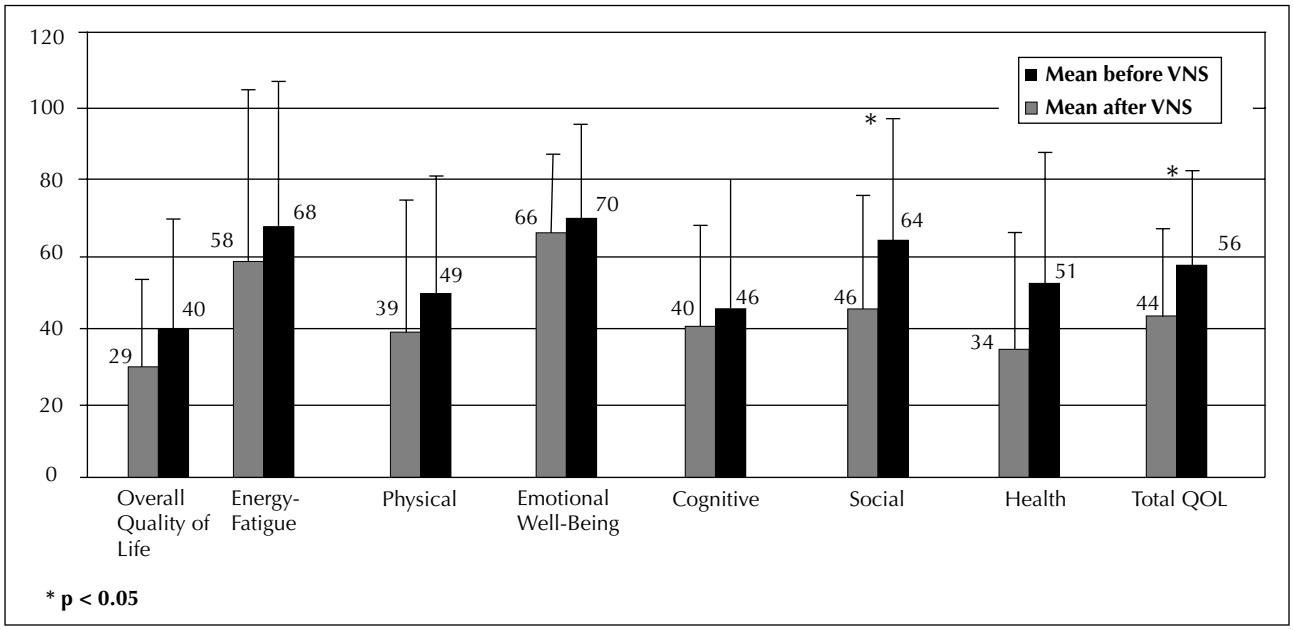

Figure 2. QOL results for patients with localization-related epilepsy (n = 8).

There were no statistically significant differences in the QOL domains after VNS insertion (p > 0.228) *(figure 3)*.
There were no statistically significant differences between patients with localization-related and generalized epilepsy in seizure reduction (p = 0.255), duration of follow-up (p = 0.111), VNS current (p = 1.000), seizure severity (p = 0.572), number of AEDs pre- and post-VNS (p = 0.537 and 0.334 respectively), SES (p = 0.064), sex (p = 1.000), mental retardation (p = 0.467), age at surgery and at seizure onset (p = 0.093 and 0.986, respectively).

Semi-quantitative analysis of the open-ended questions

Of the 16 patients, positive comments were recorded in 9, negative comments in 4, and neutral comments were recorded in 3 patients.
There were no significant differences in seizure reduction and in changes in the cognitive domain among patients/caregivers who commented positively, negatively, or neutrally on QOL after VNS implantation (ANOVA p = 0.336 and 0.451, respectively).

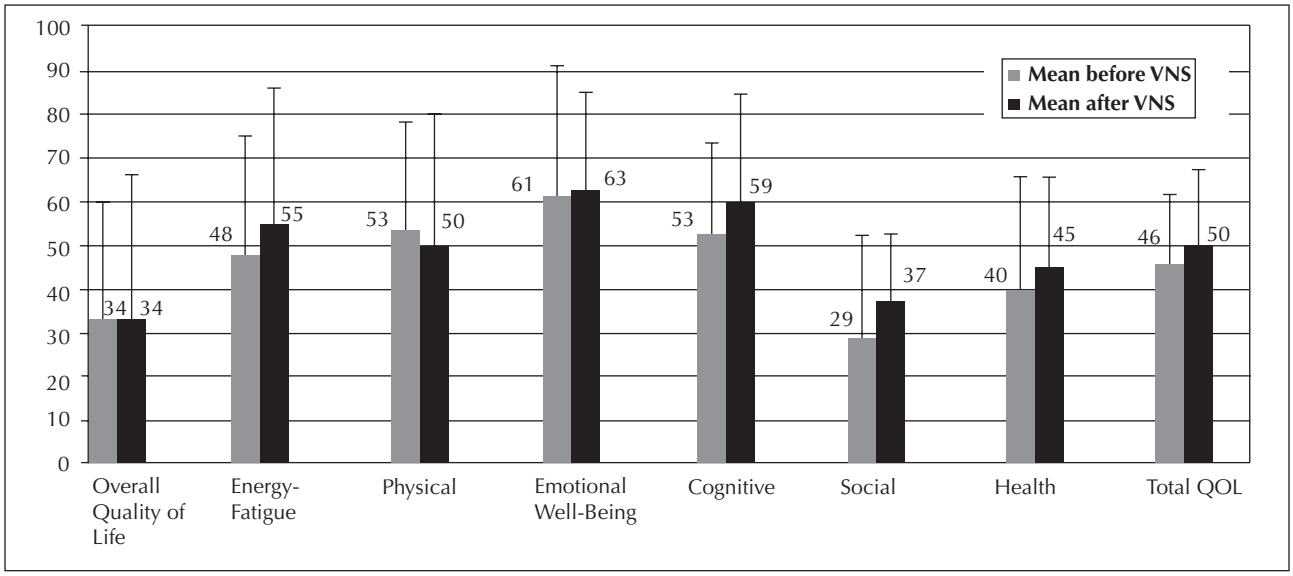

Figure 3. QOL results for patients with generalized epilepsy (n = 8).

Discussion

The current study reports statistically significant improvement in the social domain in all patients and in the social domain as well as in the total QOL in patients with partial seizures 1.26 years after VNS implantation. Decreased seizure frequency reflected positively on patients' social domain, probably by allowing them to participate in more social activities, decreasing stigmatization, and improving patients' relationships with family and friends. Improvements in QOL were also reflected qualitatively whereby the majority of patients commented positively on their QOL following VNS. Larger numbers and longer follow up periods may show additional improvements in other QOL domains.

Our results agree with those of Cramer (2001) who reported significant improvement in the social aspects domain 3 months after VNS insertion and also with Rychlicki *et al.* (2006) who found a significant improvement in QOL and a trend towards improvement ($p = 0.05$) in the sociability domain 18 months after VNS implantation. Similar to our results, several studies also detected improvements in QOL after VNS implantation with follow-up duration ranging from 3 months to 1 year (Patwardhan *et al.* 2000, Ergene *et al.* 2001, Hallbook *et al.* 2005). Other studies also found improvements in QOL in some patients after VNS insertion; however no statistical analysis was performed in these studies (Hornig *et al.* 1997, Lundgen *et al.* 1998, Frost *et al.* 2001, Helmers *et al.* 2001, Kirse *et al.* 2002, Nagarian *et al.* 2002, Larysz *et al.* 2007, You *et al.* 2007).

In patients with partial epilepsy, we detected statistically significant improvements in total QOL scores and the social domain, while no significant changes in QOL were found in patients with generalized epilepsy. Our results agree with Handforth *et al.* (1998) who reported significant improvements in global evaluation scores 12 to 16 weeks after VNS implantation in patients with partial onset seizures.

Other investigators, however, did not find similar improvements in QOL after VNS. Unchanged QOL, except in the general behavior domain and perceived treatment side effects, was reported by Parker *et al.* (1999) 1 year after VNS insertion in patients with both generalized and partial epilepsy. In patients with localization-related epilepsy, Morrow *et al.* (2000) reported that overall QOL, social, and work activities limitations did not change 12 months after VNS implantation. Also, Chavel *et al.* (2003) found no statistically significant changes in QOL 12-24 months after VNS implantation in patients with partial onset epilepsy.

We also found seizure reduction (> 50%) to be the only factor to correlate with improvement in total QOL. Similarly, Dodrill *et al.* (2001) found that a seizure reduction of at least 50% was associated with improved cognitive functioning and adjustment in medical care. While Cramer (2001) found that seizure reduction (≥ 50%) was only associated with improvement in energy, rather than in overall QOL, others found seizure severity (Hallbook *et al.* 2005), duration of epilepsy < 5 years, seizure onset > 1 year, and longer follow-up periods (> 12 months) (Patwardhan *et al.* 2000) to be associated with improved QOL. Other studies, however, did not find a correlation between improvement in QOL and seizure reduction (Lundgren *et al.* 1998, Parker *et al.* 1999, Ergene *et al.* 2001, Chavel *et al.* 2003), seizure severity (Lundgren *et al.* 1998, Ergene *et al.* 2001), or increased level of alertness (Ergene *et al.* 2001).

Our study has the following limitations:

– due to the number of patients studied, the power to detect significant differences in some QOL domains was low; however; it was sufficient to detect significant improvement in total QOL for localization-related epilepsy and in the social domain for the entire study population as described above. Likewise, despite a heterogeneous population, given the differences in age, epilepsy type, and cognitive level, this statistical significance was still present. The small patient number and the outlier may have contributed to our not finding significance in some analyses particularly when looking at the subgroups;

– our mean follow-up time was only 1.26 years; however, it is long enough to detect significant differences. Various studies reported improvements with a follow-up period ranging from 3 months to 31 months;

– scores from corresponding domains from the pediatric and adult questionnaires were combined for the purpose of statistical analysis. However, the questionnaires measure the same aspects of QOL in the two different age groups.

Our study has the following advantages:

– we assessed patients' QOL using the ESI-55 and QOLCE questionnaires. These tools are effective in measuring clinical (using HASS and HASES) as well as QOL outcomes, and both were proven to be reliable and valid measurements of therapy outcome (Vickrey *et al.* 1992, Sabaz *et al.* 2000, Sabaz *et al.* 2006, Mikati *et al.* 2008.);

– this study is the first of its kind in the Middle Eastern population. QOL differs among different populations (Buck *et al.* 1999); thus, collecting data from different populations allows determination and comparisons of population-specific needs;

– before and after comparisons in our study allowed for the control of individual factors and for the assessment of change related to VNS insertion;

– patients were assessed through interviews which added a qualitative feature to our study. □

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