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# Improved quality of life and cognition after early vagal nerve stimulator implantation in children

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ABSTRACT

*Objective:* In patients with drug-resistant epilepsy, reduction of seizure duration and frequency at an early age is beneficial. Vagal nerve stimulator (VNS) was shown to reduce seizure frequency and duration in children; however, data in children under the age of 12 years are sparse. The aim of this study was to compare seizure outcome and quality of life after early (≤5 years of age) and late (>5 years of age) implantation of VNS in children.
*Methods:* This study reviewed 45 consecutive children undergoing VNS implantation. Primary outcome measure was the reduction of seizure frequency. Secondary outcome measures were epilepsy outcome assessed by the McHugh and Engel classifications, reduction of antiepileptic drugs (AEDs), psychomotor development, and quality of life measured by the Pediatric Quality of Life (PEDSQL™) questionnaire and caregiver impression (CGI) scale. The mean follow-up time was 72.3 months (±39.8 months).
*Results:* Out of 45 patients included, in 14 (31.1%), VNS was implanted early and in 31, (68.9%) late. Reduction of seizure frequency, McHugh and Engel classifications, and reduction of AED were comparable in both groups. Quality of life measured by the CGI scale (2.1 ± 1.7 in the early group vs. 3.6 ± 1.6 in the late group; $p = 0.004$), as well as the difference of total PEDSQL™ Core scores (12.0 ± 24.0 in the early group vs. −5.2 ± 14.9 in the late group; $p = 0.01$) and cognitive PEDSQL™ Core (30.6 ± 32.0 in the early group vs. 2.4 ± 24.3 in the late group; $p = 0.03$) between preoperative and follow-up was significantly higher in the early implantation group.
*Conclusion:* Early VNS implantation in children leads to a significantly better quality of life and cognitive outcome compared with late implantation while reduction of seizure frequency and epilepsy outcome seems comparable. Therefore, in children with drug-resistant epilepsy, VNS implantation should be considered as early as possible.


## 1. Introduction

Epilepsy in children is a common disease. Seizure control in children is critical since it improves quality of life, cognitive function and facilitates developmental progress [1–3]. Approximately 33% of the children with epilepsy do not respond to medication, which is then defined as drug-resistant epilepsy [4]. In children with drug-resistant, nonlesional epilepsy, the implantation of a vagal nerve stimulator (VNS) was proposed as an adjuvant treatment, showing significant reduction in seizure frequency and duration [1–3,5–11]. In addition, VNS has shown to improve the quality of life and neuropsychological performance of these children and reduce the number of urgent hospitalizations [12–14]. Only very few studies evaluate the outcome of early VNS implantation in children. Those studies show similar effect or even superiority in outcome when VNS is implanted at an early age [2,6–8,11,15,16]. However, most studies compare the outcome in children above and under the age of 12 years while studies comparing implantation at a younger age are very sparse. We published the first study comparing implantation of VNS in children under and above the age of 5 years and showed comparable outcomes in seizure reduction, quality of life, and cognitive development [16]. However, our pilot study consisted of a rather small patient cohort and was probably

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underpowered. The aim of this study was to compare the seizure reduction rate, quality of life, and cognitive development in a larger cohort of children undergoing VNS implantation before and after the age of 5 years.

## 2. Methods

In this study, we reviewed the medical data of children (≤18 years of age) who were implanted with a Cyberonics®/Livanova® (Houston, Texas, USA) VNS (Demipulse Model 102 or (as of 2007) Demipulse Model 103) between the years 2010 and 2016 at the Children's University Hospital of Basel, Switzerland and between the years 1998 and 2016 at the Dana's Children Hospital, Medical Center Tel Aviv, Israel. This study is an extension of our pilot study on early VNS implantation in children published in 2018 [16]. None of the included patients showed an epileptic disorder which was characterized by an epileptogenic structural lesion ("lesional epilepsy") in the preoperative assessments. The primary outcome measure was response rate, following the equation: (seizure/month on VNS − baseline seizure/month) / (baseline seizure/month) × 100. "Responders" were defined as patients experiencing a seizure frequency reduction of 50% or more (adapted from Colicchio et al. [15]). Secondary outcome measures were cognitive function and quality of life measured with the Pediatric Quality of Life (PEDSQL™) Core questionnaire (edition 4.0) [17], quality of life measured by the caregiver impression (CGI) scale (Supplementary Table 1), reduction of antiepileptic drugs (AEDs), seizure outcome assessed by the McHugh and Engel classifications, surgical complications rate, and mortality. We did not assess for seizure type or seizure durations, since most children had many episodes per day mostly consisting of various seizure types and durations. For the statistical analysis, the McHugh and Engel scores were dichotomized into "good outcome" (McHugh or Engel score 1–3) and "bad outcome" (McHugh score 4–5, Engel score 4). The PEDSQL™ is a validated, standardized, and widely used questionnaire, addressed to the children, parents, or caregivers, obtaining the child's quality of life and cognitive development [17,18]. A PEDSQL™ Epilepsy questionnaire specifically for patients with epilepsy exists, however, patients under the age of 2 years cannot be assessed through this subset of questionnaire. Therefore, we refrained from using the PEDSQL™ Epilepsy questionnaire and used the more general PEDSQL™ Core questionnaire. The PEDSQL™ Core questionnaire evaluates four dimensions of the child's quality of life: physical function, emotional function, social function, and schooling function while the later three are composited together as psychological function. A separate questionnaire evaluates, in addition, the child's cognition. The scores are presented on scale between 0 and 100 while a higher score represents a better outcome. In order for us to be able to assess and compare the preoperative status of the child and the postoperative cognitive function and quality of life, the parents completed the PEDSQL™ twice, once assessing the child's condition 3 months preoperatively in a retrospective manner and once postoperatively in a prospective manner. This allowed us to evaluate if the treatment led to a progress in the quality of life and development of the child. Patients were divided into an early implantation group (patients ≤5 years of age at implantation) and a late implantation group (patients >5 years of age at implantation) and compared for primary and secondary outcome measures. Whenever possible, child's reporting was undertaken. However, most of the data are based on parental reporting, either due to the young age of the children or due to the disability of the child. The study protocol was approved by the local ethics committee (EKNZ, Basel, Switzerland and Helsinki Committee, Tel-Aviv Medical Center, Tel Aviv, Israel) while informed consent was obtained from each patient or the parents.

All statistical analyses were done using SPSS Statistics Version 21.0 (IBM Corp, Armonk, NY, USA 2012). Contingency tests were done using Fisher's exact test while all other calculations were done using the Mann–Whitney U test. A p value of $<0.05$ was considered significant.

## 3. Results

### 3.1. Patients' demographics

Out of 78 patients screened, we included 45 consecutive children (23 females, 51.1%) who underwent VNS implantation due to drug-

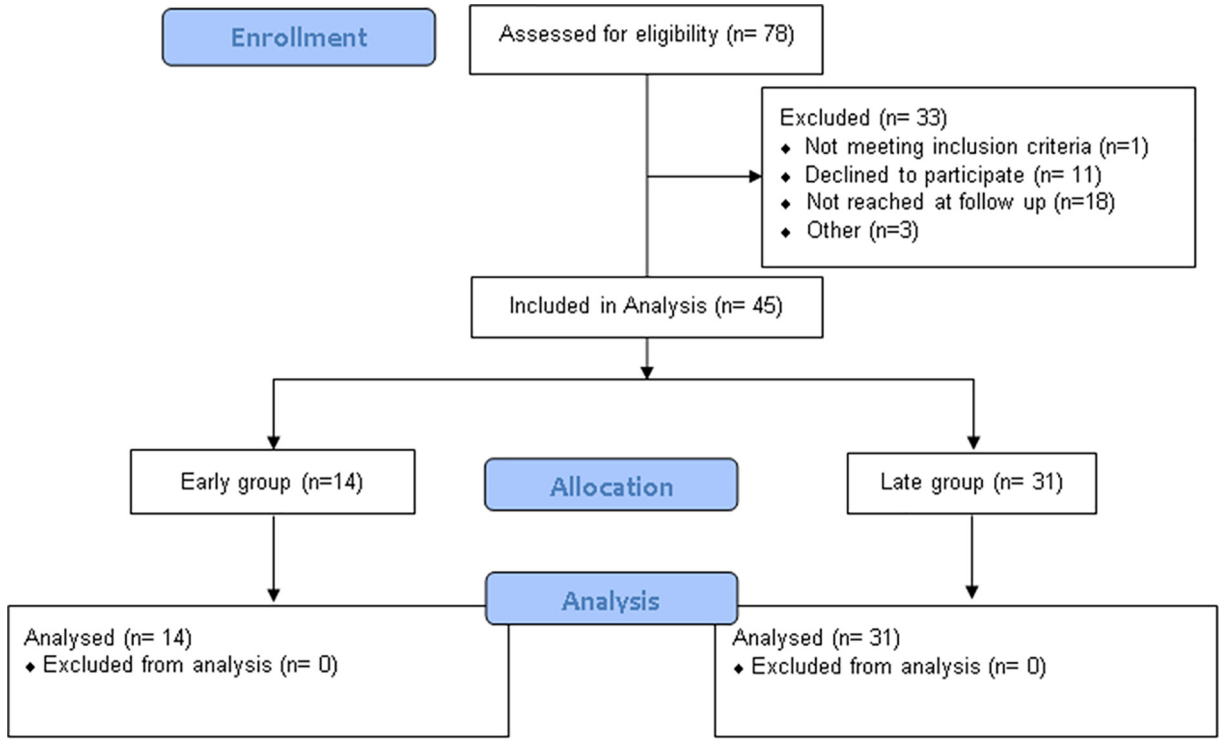


**Fig. 1.** Study flow chart.