NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of vagus nerve stimulation for refractory epilepsy in children

Introduction

This overview has been prepared to assist members of IPAC advise on the safety and efficacy of an interventional procedure previously reviewed by SERNIP. It is based on a rapid survey of published literature, review of the procedure by one or more specialist advisor(s) and review of the content of the SERNIP file. It should not be regarded as a definitive assessment of the procedure.

Procedure name

Vagus nerve stimulation (VNS)
Synonyms: vagal nerve stimulation

SERNIP procedure number

122

Specialty society

British Association of Paediatric Surgeons
Society of British Neurological Surgeons

Indication(s)

Vagus nerve stimulation is used in children and adults with epilepsy, particularly complex partial epilepsy that remains incapacitating despite maximal anti-epileptic medication. The technique has also been used in children with medically refractory encephalopathic seizures, idiopathic seizures, primary generalised epilepsy and the Lennox-Gastaut syndrome, which is a young onset epileptic disorder characterised by multiple seizures types and developmental delay.

Epilepsy prevalence is 2% to 5% worldwide (World Health Organisation estimate). About 5% to 30% of people with epilepsy have medically refractory complex partial seizures.[1] We found no prevalence estimates for medically refractory epilepsy in children.

Summary of procedure
A battery powered pulse generator device is implanted under the skin of the upper left chest. A wire is tunnelled under the skin and connected to the left vagus nerve in the neck (surgery time 45 minutes to 2 hours). Stimulation parameters (pulse width and frequency, current intensity, on/off cycles) are programmed into the pulse generator via a programming wand. Patients or carers may then switch the stimulator on and off by passing a magnet over the generator. The battery lasts 3-5 years and can be replaced under local anaesthetic. A typical treatment regimen might comprise intermittent stimulation for 30 seconds every 5 to 10 minutes throughout the day and night.

Drug therapy is, by definition, not an alternative for children with medically refractory epilepsy. However, the criteria for deciding whether a child is responding or refractory to medical therapy may vary among practitioners. Neurosurgery, such as lobectomy or callosotomy, is used in children with severe refractory epilepsy.

Literature review

Appraisal criteria
We included studies of vagal nerve stimulation (VNS) in children with refractory epilepsy (RE) or Lennox-Gastaut syndrome (LG). Studies with mixed age groups have only been included if children were analysed separately. We included for the purposes of description any systematic reviews and controlled studies and uncontrolled studies of 50 or more children. Smaller series and one non-English language study of uncertain size are listed in the annex. Non-systematic reviews were excluded.

List of studies found
We found two systematic reviews.[1,2] Neither identified controlled studies in children. The more recent review was the more up to date and inclusive and is described in the table.[2] We found no further controlled studies.

We found 17 case series. [4-22] Three of these series met inclusion criteria.[4-6]

Summary of key efficacy and safety findings

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Corabian P[2] Systematic review Primary sources: Medline, Embase, PubMed, Cochrane, best Evidence, ECRI, NHS CRD databases, relevant web sites. Search date 1998 Identified no controlled studies Identified 5 case series of VNS in children with RE [5,9,14,15,17] Identified 6 case series of VNS in children with LG [7,9,14,15,21, 22]	Concluded that efficacy yet to be established in children	Concluded that safety yet to be established in children	High quality systematic review. Literature search well described with list of databases searched and key words used. Bibliographies were searched for additional references Explicit inclusion and exclusion criteria for studies in the review No pooling of data. Noted that all studies uncontrolled and open-label. Age and indications varied within and among studies. Different stimulation parameters used in studies. Drugs co-administered Tools used to assess quality of life varied, as did follow-up periods

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Helmers SL[4] Retrospective case series (not cited in systematic review[2]) Six centres: Boston, Houston, Denver, Minnesota, New Orleans, Washington; USA. Implanted 1997 to December 1998, follow-up to March 1999. n=125 children with RE, (median age 12 years, range 3-18 years; 41 children <12 years) seizure types: • partial (n=59) • generalised seizures (n=23) • LG (n=43; see Frost[6] for analysis of these patients) 35 children had previous surgery: lobectomy (13); callosotomy (18); both (2). Children had tried mean 8.6 (range 2-17) different anticonvulsants before VNS. Children were taking a mean of 2.3 anticonvulsants at time of implant (range 1-5) Follow up: 3 months (n=95) 6 months (n=56) 9 months (n=12)	At 3 months (n=95), mean seizure frequency reduced by: • 36% from baseline for all groups (p<0.0001) • 27% for LG subgroup • 25% to 32% for other subgroups • 19% in children <12 years (n=41) Anticonvulsant use decreased in 10/95 (11%), unchanged in 65/95 (68%) at 3 months At 3 months, quality of life measures reported by patients or carers as 'better' or 'much better' for: • alertness 48% • seizure clustering 36% • verbal communication in post-ictal periods 27% • school achievements and mood 22% • memory in 14% • ambulation 5% At 6 months (n=56), mean seizure frequency reduced by 45% (p<0.0001). Similar reduction for children <12 years (n=20) Anticonvulsant use decreased in 9/56 (16%), unchanged in 33/56 (59%) at 6 months	Surgical complications: • voice alteration 58% • coughing 38% • ear pain 1% • increased drooling <1% - resolved spontaneously • increased hyperactivity in 'a few' children • left vocal cord paralysis causing moderate to severe dysphonia in 1 child, 'almost completely' resolved at 4 months • right sided weakness, incoordination requiring 3 emergency visits in 1 patient - resolved spontaneously Broken electrode leads in 3 patients No explants, no deaths, no status epilepticus	3 months: 30/125 dropped out 6 months: 69/125 lost to follow up Accuracy of reports of seizures depended on records by carers and patients

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Murphy JV[5] Retrospective case series (cited in systematic review[2]) Kansas City, USA. Date of surgery not stated (published 1999) n=60 children with RE (mean 13.5 years, range 3.5 to 18 years; 16 children <12 years). seizure types: • partial complex (n=34) • generalised tonic-clonic (n=16) • simple partial (n=4) • secondary generalised partial (n=6) 15 had previous surgery Follow up: at least 3 months	At 3 months (n=60), median seizure frequency reduced by 23% At 6 months (n=55), median seizure frequency reduced by 31%, although results exclude 3 children, who dropped out due to 'lack of efficacy' At 12 months (n=51), median seizure frequency reduced by 34% (n=51). At 18 months (n=46), median seizure frequency reduced by 42%	Complications: Device eroded through skin (1 child – no further information available); death due to aspiration pneumonia (1 child) Surgery required to repair leads, or replace defective generators in some patients (number not stated) Complications within 3 months • fever 27% • cough 25% • headache 23% • voice alteration 22% • vomiting 18% • pharyngitis 13% • nausea 12% Voice alteration reported in 15% at 6 months, 14% at 12 months and 13% at 8 months	Baseline data limited: neurological or mental status not stated, aetiology of epilepsy unknown in 40 patients 5 people excluded from 6 month analysis (2 listed in complications); 3 from lack of efficacy

Authors, location, date, patients	Key efficacy findings	Key safety findings	Key reliability and validity issues
Frost, M[6] Retrospective case series (not cited in systematic review[2]) Kansas City, USA. Six centres: Boston, Houston, Denver, Minnesota, New Orleans, Washington; USA. Implanted 1997 to December 1998, follow-up to March 1999 **Note: included same patients as Helmers,[4] but analysis specific to LG patients** n=50 children with LG (median age 13 years, range 5-27 years; 21 patients <12 years at implant) 6 children had previous surgery: lobectomy (1); callosotomy (5) Follow up: 1 month (n=46) 3 months (n=43) 6 months (n=24)	Median number of seizures reduced by: • 42% at 1 month • 58% at 3 months • 58% at 6 months ($p<0.0001$ for all comparisons with baseline) Quality of life improved for 'some' patients in study (no numbers stated) No patients seizure free after treatment	Seizures increased by 50% in 1/46 patients at 1 month; 3/43 patients at 3 months Complications (number of children): • wound infections at incision site (2) • transient pain at incision site (5) • voice alteration (22) • coughing (15) • paraesthesia during stimulation (4) • exertional dyspnoea (2) • decreased appetite (2) • hiccups (2) • dyspepsia (2) • dysphagia (1) • vomiting (1) • increased drooling (4 • hyperactivity (3) - resolved with altering medication and stimulation Quality of life reported as 'worse' in 2 patients	As for Helmers[4] Drop out 4 at one month (due to inadequate recording of information) Declining number of patients with time due to date cut off of study Quality of life data presented graphically; no absolute figures reported

Validity and generalisability of the studies
Case series were carried out in settings applicable to the UK. The larger studies were from the USA. Most studies were small and all lacked controls. Inclusion and exclusion criteria were not clear. Drop out rates were low for early follow up (up to 6 months), although the reason for drop out in some studies (complications or lack of efficacy) may have biased the results. We found no evidence for long term safety.

Bazian comments
The research base appears to be growing slowly, although publications are limited to a small number of groups. In adults, the systematic reviews concluded that VNS is both safe and effective.[1,2]

Specialist advisor's opinion / advisors' opinions
Specialist advice was sought from the Society of British Neurological Surgeons and the British Association of Paediatric Surgeons

Specialist Advisors advised that this procedure is:

- now established practice
- not technically difficult – rapid training
- the manufacturer (Cyberonics) runs register of cases

Issues for consideration by IPAC
None other than those discussed.

References

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6. Frost M, Gates J, Helmers SL, Wheless JW, Levisohn P, Tardo C et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. Epilepsia 2001; 42(9):1148-1152

Overview prepared by:
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Annex: references for relevant studies excluded from summary table

*indicates that study is cited in the more recent systematic review[2]

Reference	Number of children
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*Lundgren J, Ekberg O, Olsson R. Vagus nerve stimulation in 16 children with refractory epilepsy. Epilepsia 1998; 39(9):809-813.	16
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Farooqui S, Boswell W, Hemphill JM, Pearlman E. Vagus nerve stimulation in pediatric patients with intractable epilepsy: case series and operative technique. Am Surg 2001; 67(2):119-121.	5
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Nakken KO, Henriksen O, Roste GK, Lossius R. [Chronic intermittent vagal nerve stimulation - a new therapeutic approach in epilepsy]. [Norwegian]. Tidsskr Nor Laegeforen 2001; 121(13):1582-1585.	non English, n not known
Ben Menachem E, Hellstrom K, Waldton C, Augustinsson LE. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. Neurology 1999; 52(6):1265-1267	8
Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. J Child Neurol 2000; 15(8):509-512	13