

Summary

- ✓ **The NeuRx DPS is a laparoscopically implanted device that provides ventilatory support.**
- ✓ **This device stimulates the diaphragm muscle, rather than the phrenic nerve, and is intended to lead to less risk of nerve damage than other therapies.**
- ✓ **This technology provides an alternative to mechanical ventilation, and allows patients to increase day-to-day freedom and minimize the risk of respiratory infection.**
- ✓ **The NeuRx DPS safety profile is based on clinical testing, which began with clinical trials starting in 2000. It has the potential to reduce costs, but this has not been well established.**

Background

Tetraplegia is the loss of voluntary movement and sensation affecting all four limbs. This disorder is usually caused by damage to the cervical spinal cord. Spinal cord injury (SCI) occurs when trauma or disease damages the spinal cord and results in partial or complete paralysis. The degree of paralysis depends on the level and severity of injury. Injury in the cervical part of the spine (neck, vertebrae C1-T1) characterizes tetraplegia (formerly called quadriplegia). People with tetraplegia experience a loss of feeling, and/or movement in their head, neck, shoulders, upper chest, arms, hands, and/or fingers.¹ Many of these patients develop trouble breathing and require mechanical ventilation support even if their lungs, chest wall, and respiratory muscles are usually physiologically normal.² Mortality and morbidity prevalence rates are higher for ventilator-dependent persons.³ At the age of forty, life expectancy is reduced to 11 years.³⁻⁵

The annual incidence of SCI in Canada ranges from 900 to 1,200 cases. The prevalence of SCI in Canada is estimated to be between 36,000 to 41,000 people.^{5,6} Eighty-four per cent of injuries occur in people under the age of 34.⁵ The most common causes of SCI in Canada are road crashes (46.5%), falls (16.5%), and medical conditions (10.8%).⁵ Tetraplegia accounts for 50% of SCI cases,^{5,6} equal to 18,000 to 20,500 Canadians.

The Technology

NeuRx DPS is a diaphragm pacing stimulator that works by providing an electrical stimulus to the diaphragm, initiating movement and allowing patients to breathe.⁷ Electrodes are implanted in the diaphragm muscle through minimally invasive laparoscopic surgery. The electrodes are connected to a four-channel, battery-powered external pulse generator through a cable and a connector that exit from the patient's chest.⁷

The skin at the exit site must be cleaned with alcohol, and covered with a gauze dressing. The dressing should be changed every three days, or more frequently if the dressing becomes wet or soiled. The surface of the stimulator may be cleaned and disinfected with a bleach solution or rubbing alcohol. The surface of the cables may be cleaned with a mild anti-bacterial hand soap solution.

The pulse generator provides electrical stimulation to the internally implanted electrode. This prompts contractions of the diaphragm muscle that stimulates movement and causes the patient to inhale.⁷ The battery-operated stimulator is small enough to be placed in a pocket or attached to a belt.

The electrodes are implanted in an outpatient setting. The surgery typically takes less than 2.5 hours.⁸ Following a recovery period of a week or so, the patient is required to return to hospital for the initiation of stimulation. Patients and caregivers can be trained in the use of the NeuRx DPS. The device is intended to alleviate dependence on mechanical ventilators, reduce the need for clinical supervision, increase patient's day-to-day freedom, and minimize the risk of

respiratory infection.⁹ The equipment is smaller and more portable than a mechanical ventilator.

The device is also intended to allow for more normal speech patterns and may help patients to regain the senses of taste and smell, which can weaken with ventilator support. It is also intended to reduce the risk of damage to the phrenic nerve because the electrodes are not attached to it.

Regulatory Status

The NeuRx DPS is manufactured by Synapse Biomedical Inc. It received approval by the US Food and Drug Administration (FDA) in June 2008 for patients with stable, high spinal cord injuries with stimlatable diaphragms, but who lack control of their diaphragms.⁷ The FDA decision was made following clinical trials starting in 2000 under an Investigational Device Exemption application. In the US, the procedure is covered by Medicare, Medicaid, or private insurance.¹⁰

The NeuRx DPS has not been approved for use by Health Canada. However, it is being used as part of a clinical trial in Canada at the Vancouver Coastal Health Research Institute under a Health Canada clinical trial application.¹¹

The NeuRx DPS was licenced for use in Europe in November 2007, and is approved for treating patients with diaphragm dysfunction.¹²

Patient Group

The NeuRx DPS is intended for use in spinal cord injury patients who cannot voluntarily control their diaphragms, but whose diaphragms are able to be stimulated. Normal bilateral phrenic nerve function below the level of the spinal cord injury is required. The device is indicated to allow patients to breathe without the assistance of a mechanical ventilator for at least four continuous hours a day. In the US, it is currently being marketed to patients 18 years of age or older.¹² Patients are screened for significant underlying lung, chest wall, or primary muscle diseases to determine their suitability for this device.

Current Practice

For patients who have stimlatable diaphragms, conventional diaphragmatic pacing/phrenic nerve

pacing is available. This modality involves the direct application of radiofrequency stimulation to the phrenic nerve, which activates diaphragm contractions. Diaphragmatic pacing was developed in 1964. This surgery is associated with a risk of phrenic nerve damage and muscle fatigue, which may occur at the time of surgery or due to scar formation and/or tension on the nerve following surgery. Damage to the phrenic nerve could potentially invoke respiratory failure through inadequate inspired volume generation.^{13,14} For the last 20 years, conventional phrenic nerve pacing has represented the gold standard of clinical care for patients with diaphragmatic paralysis.¹³

The placement of phrenic nerve electrodes can be performed through the neck or the chest. When this procedure is performed through the chest, a thoracotomy is required. This is a surgical rather than a laparoscopic procedure and its approach is associated with risks relating to the incision, the medical condition of the patient, and the administration of anesthesia. A thoracotomy is also associated with significant perioperative morbidity, requiring an inpatient hospital stay and high costs.

However, there is some evidence that a larger portion of the phrenic nerve may be stimulated by the chest approach, as a small branch of the phrenic nerve joins the main nerve trunk only after it enters the chest cavity.¹⁵

The neck placement of the electrodes is less complicated and risky than a thoracotomy and, for some patients, can be performed on an outpatient basis. However, movement of the neck can place the electrodes under mechanical stress, resulting in a possible nerve injury and/or poor electrode contact and ineffective stimulation. In addition, other neighbouring nerves located close to the electrodes may inadvertently be activated, resulting in pain or unwanted neck or shoulder musculature movement. Consequently, the thoracic approach is the preferred method for implanting electrodes.¹⁶

Compared to diaphragmatic pacing, mechanical ventilation via a tracheostomy is associated with increased rates of infections, and tracheal injuries. Patient mobility is also limited because patients are tethered to breathing apparatus. Other alternatives to conventional phrenic nerve pacing are the non-invasive positive pressure, pneumobelt, and rocking bed ventilation systems.

The Evidence

The Summary of Safety presented to the FDA is the most complete report available covering both clinical and safety data.^{7,17} Other study publications relate to the same prospective observational study.^{2,8,13,18}

Reports of the one available study describe a single cohort of 50 patients with tetraplegia (aged 18 to 74 years), with a time from injury ranging from three months to 27 years. The average study follow-up was 1.7 ± 1.4 years. The length of the conditioning phase was variable. It ranged from 1 week for 18-20 year olds on mechanical ventilation for less than 1 year, to 14 weeks for 40-50 year olds on a ventilator for greater than 5 years. The success rate was 96%, where success was defined as ongoing use for at least four hours with an acceptable tidal volume. At the end of the study, 88% of patients were regularly using the device. More than 50% of the sample could use the DPS for 24 hours a day.¹⁹

Patients reported improved sense of smell, more comfortable breathing, improved speech, greater independence, and the elimination of fear of disconnection from a mechanical ventilator.¹³

Adverse Effects

In the same study (n = 50), the most common adverse event reported was capnothorax (42%). This complication is associated with the implantation of the electrodes⁷ and occurs when air tracks into the pleural cavity due to carbon dioxide used to inflate the abdomen during surgery. The incidence of capnothorax during the implantation of the NeuRx DPS is similar to that associated with other laparoscopic procedures.⁷

Equipment failure occurred in 24% of patients. Broken external wires account for 14% of these cases and they were either replaced or repaired at home or at an office visit. Breakage of anode leads accounted for 6% of these cases and necessitated a return to mechanical ventilation until they were repaired. External stimulator failure affected 4% of the patient population and required a return to mechanical ventilation until replacements were provided.⁷

Localized infections occurred at an incidence rate of 4%. Six per cent of patients reported pain or discomfort with stimulation in the first phases of the initiation period. Six per cent of patients had incidents of aspirations during pacing.

The post-surgery death rate was 8%, although this was perceived to be not directly related to the device.⁷

These patients achieved a tidal volume greater than the baseline and more than four hours of continuous use of the device. No interaction has been detected between the DPS system and cardiac pacemakers.⁸

While laparoscopic surgery is much less invasive than thoracotomy, there are some other associated risks, such as the development of pneumothorax and subcutaneous emphysema.¹³

Administration and Cost

The cost for the NeuRx DPS procedure is approximately C\$24,000.¹¹ The equipment itself costs C\$11,440.¹¹ In comparison, the cost of a conventional bilateral phrenic nerve pacing system is approximately C\$61,000 to 74,000.^{20,21} There are also minor costs for battery and external cable replacement.¹⁸

No cost-effectiveness studies have compared DPS with alternatives, although it is believed direct costs will be reduced, as laparoscopic surgery is performed in outpatient settings with an expected maximum length of hospital stay of one day. Compared to mechanical ventilation, DPS could reduce the risk of complication and need of nursing assistance,¹⁶ with an additional impact on cost.

Investigators reported a saving of C\$12,850 monthly (in 2007 dollars) for one patient successfully weaned off a ventilator for full-time pacing.^{11,18} In addition, DPS may provide indirect benefits to society regarding increased patient mobility and overall improvement of well-being due to fewer difficulties in communicating and, therefore, better social interaction. The device also reduces the burden of care for family members and allows more housing options.⁸

Some cost studies that compare conventional DPS systems to tracheostomy ventilation have already been conducted, and they demonstrated a significant saving in the post-surgery phase,²² suggesting a survival advantage.²³

Concurrent Developments

Adaptations of the device are being implemented and routine aspects of the operation are being optimized following feedback from surgeons.²⁴ Clinical trials on the implantation of NeuRx DPS in amyotrophic lateral

sclerosis (ALS) patients are underway in the US and Europe.^{7,25}

Protocols for the implantation of NeuRx DPS in children and the optimal implantation time after injury are in development.^{8,13} The use of different DPS devices in children suffering from Congenital Central Hypoventilation Syndrome is currently under investigation.^{13,14}

Other expected extensions of the use of the NeuRx DPS are muscular dystrophies, and post-polio and hypoventilation syndromes.¹⁸ Its use in patients with progressive neuromuscular disease, such as motor neuron disease, seems more uncertain.²⁶

A totally implantable system with radiofrequency-powered pulse generators similar to that used in conventional DPS (and which are currently used with phrenic nerve pacing) and combined intercostal and diaphragm pacing systems is under development.¹⁶ It is believed that a fully implantable system could eliminate the risk of infection and remove the inconvenience of the wires that exit the body.¹³ A future system could include a battery that is recharged through the skin or a battery that does not require recharging for a minimum of ten years.

Potential methods to activate expiratory muscles are still to be optimized and include magnetic stimulation, surface abdominal muscle stimulation, and electrical stimulation in the region of the lower thoracic spinal cord.¹⁶

Rate of Technology Diffusion

Since the NeuRx DPS approach is intended to provide several clinical advantages to the traditional phrenic stimulation technique, the impact on patient acceptability of the procedure could be significant. The NeuRx DPS can be implanted laparoscopically in an outpatient setting, which could reduce costs, serious morbidity and inconvenience compared to a conventional phrenic nerve approach that usually requires a thoracotomy. The NeuRx DPS does not risk injury to the phrenic nerve, which could invoke respiratory failure.

The potential extension of the use of NeuRx DPS to other pathologies (such as ALS patients) and to other ages (i.e., children) will also be associated with an increase in demand.

Implementation Issues

The published data available on NeuRx DPS comprised only ongoing prospective studies with a mean follow up of 1.7 years.^{17,26} Long-term effects of the device are still being investigated. Importantly, there is also a lack of data in terms of comparison with the existing diaphragm pacing procedures. The device's portability and autonomy of use, after the initiating and training phase, has showed a positive impact on patient lifestyle and on burden of care for family members compared to mechanical ventilation. There are currently no evidence-based recommendations regarding appropriate strategies for ventilator support for tetraplegic patients. Laparoscopic implantation requires planning and training sessions for surgeons.

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