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Amyotrophic lateral sclerosis: the Midwestern surgical experience with the diaphragm pacing stimulation system shows that general anesthesia can be safely performed

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Abstract

BACKGROUND: There is a paucity of literature concerning general anesthesia and surgery in patients with amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). This report summarizes the largest series of surgical cases in ALS during multicenter prospective trials of the laparoscopic diaphragm pacing system (DPS) to delay respiratory failure.

METHOD: The overall strategy outlined includes the use of rapidly reversible short-acting analgesic and amnestic agents with no neuromuscular relaxants.

RESULTS: Fifty-one patients were implanted from March 2005 to March 2008 at 2 sites. Age at implantation ranged from 42 to 73 years and the percent predicted forced vital capacity (FVC) ranged from 20% to 87%. On preoperative blood gases, Pco₂ was as high as 60. Using this protocol, there were no failures to extubate or 30-day mortalities. The DPS system increases the respiratory system compliance by decreasing posterior lobe atelectasis and can stimulate respirations at the end of each case.

CONCLUSIONS: Laparoscopic surgery with general anesthesia can be safely performed in patients with ALS undergoing DPS.

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Dr. Onders, University Hospitals of Cleveland, and Case Western Reserve University School of Medicine have intellectual property rights involved with the diaphragm pacing system and equity in Synapse Biomedical who manufactures the device.

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Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a relentlessly progressive and fatal disease, characterized by motor neuron degeneration of the cerebral cortex, brainstem, and spinal cord of unknown etiology. The targeted neurons include the upper motor neurons (UMNs) in the brain and lower motor neurons (LMNs) in the brainstem and spinal cord. The average lifespan of ALS patients from time of symptom onset is only 3 to 5 years. Although ALS has no direct effect on the lungs, it has devastating effects on the mechanical function of the respiratory system. ALS

affects all of the major respiratory muscle groups: upper airway muscles, expiratory muscles, and inspiratory muscles. Therefore, all patients with ALS are at significant risk for respiratory complications. Progressive inspiratory muscle weakness in ALS inevitably leads to inability to clear secretions, carbon dioxide retention, and hypercarbic respiratory failure, the major cause of death in ALS. Pulmonary complications and respiratory failure are reported to be responsible for at least 84% of deaths in ALS.¹

Even though there are slightly more than 5,000 new cases of ALS diagnosed each year in the United States, there is a paucity of literature concerning general anesthesia and surgery in patients with the disease. Historically, surgery has been considered high risk because of the significant and progressive respiratory insufficiency in ALS patients. Only several case reports are available in the literature, all of which recommend local-regional anesthetic techniques in ALS patients due to the heightened risk of general anesthesia.²⁻⁴ Even during percutaneous endoscopic gastrostomy tube placement, 30-day mortality rates are reported to be as high as 25%.⁵

The diaphragm pacing system (DPS) involves laparoscopic mapping of the motor point of each hemi-diaphragm to identify the optimal point where stimulation provides maximal contraction of the diaphragm.^{6,7} At this location electrodes are implanted that are then routed percutaneously to a control unit that provides the stimulus to provide respiration. DPS was developed initially to provide natural negative pressure ventilation in spinal cord-injured (SCI) patients on positive pressure mechanical ventilators. In multicenter trials of SCI patients, 98% of patients were liberated from their ventilators with the DPS system, which led to US Food and Drug Administration (FDA) approval of the DPS for this indication in 2008.⁸⁻¹⁰ The results in SCI patients led to the formulation of research plans to implant the DPS in ALS patients to delay the need for mechanical ventilators. Tracheostomy and mechanical ventilators would be the usual end result of respiratory failure, but most ALS patients in the United States choose death over this option. The goal of DPS implantation in ALS before tracheostomy is to maintain diaphragm strength, convert diaphragm muscle from the fast-twitch type IIb to slow-twitch type I and perhaps have a trophic effect that allows the phrenic motor neurons to live longer. This improvement may be identified by a decreasing rate of decline in the forced vital capacity (FVC) after implantation of DPS. Prior to the first surgical implantation of patients with DPS, a perioperative management plan was developed to decrease the presumptive risks of general anesthesia and laparoscopic surgery and has been the basis of management since the onset of the trial.

The initial pilot study results were positive in showing that the DPS system has significantly decreased the decline of FVC from 2.4% preimplant to .9% per month postimplant extrapolating to a 24-month improvement in survival.¹¹ This led to a multicenter worldwide trial at 11 sites that is still

ongoing. This report summarizes the perioperative management used at the 2 Midwestern implantation sites to dispel the belief that surgery in patients with ALS cannot be performed safely. This is the largest series of general anesthesia and surgery to be reported in ALS patients.

Patients and Methods

This is a prospective evaluation of all ALS patients implanted with the DPS system from March 2005 until March 2008 at University Hospitals Case Medical Center (UHCMC), Cleveland, OH, and Henry Ford Health System (HFHS), Detroit, MI. This was undertaken under FDA Investigational Device Exemption (IDE) G040142 and both sites institutional review boards (IRBs) approved the investigations. The study was registered at <http://www.clinicaltrials.gov> with the specific identifier NCT00420719. The patients being reported were involved in 3 separate IRB trials under the same IDE with some overlap of the trials. One of the primary inclusion criteria was a FVC above 50% predicted at enrollment and 45% at implantation because of the concern for taking a patient with severe respiratory dysfunction to surgery. The first group was a safety and feasibility trial to confirm that implantation and stimulation would not have any adverse effects. The second group involved the compassionate use of DPS in patients who had a predicted FVC below the inclusion criteria of the other trials. The third group of patients was involved in the initial aspect of a multicenter pivotal trial that will eventually consist of 100 patients. Since ALS patients are such a heterogeneous group, the trial was designed so that each patient would be their own control. Therefore, in the first and third groups of patients, subjects were evaluated 3 times with a battery of tests constituting the lead-in before surgical implantation. After surgical implantation and diaphragm conditioning, the patients underwent the same tests every 4 to 12 weeks for 1 year from enrollment. The tests over the course of the trial for these 2 groups of patients included the SF-36, amyotrophic lateral sclerosis functional rating scale-revised (ALSFR)-r scoring, phrenic nerve studies, diaphragm ultrasound thickness, fluoroscopic sniff tests, pulmonary function tests, arterial blood gases, laboratory tests, and electrode characterizations including electromyographic assessments. The primary end point of the pivotal trial is to assess the rate of decline of FVC before and after implantation of DPS and to assess the effect of DPS on survival.

The results of the long-term multicenter trial are incomplete as the trial is still on going. The goal of this study is to outline the perioperative results of 2 of the centers using a standard perioperative management plan. The plan is separated into 3 parts: preoperative planning, intraoperative management, and immediate postoperative management. The patient characteristics and perioperative results will be reported using this management plan.

Preoperative planning

Because of the nature of their progressive disease, ALS patients should undergo thorough evaluation before surgery. ALS patients are limited in physical activity, so assessment of underlying coronary disease may need more formal cardiac testing based on the patient's risk assessment. All patients undergo complete pulmonary function testing to assess FVC. Except in several compassionate use cases of DPS, patients were excluded from surgery if their FVC was below 45% predicted because of the possible increased risk of failure to extubate at the end of the case. Arterial blood gases are obtained to assess for underlying hypercarbia from hypoventilation.

The practice Parameter of the American Academy of Neurology suggests that all patients with ALS and respiratory symptoms or a FVC of less than 50% should be offered noninvasive positive pressure ventilation (NPPV).¹² It is important if patients meet these criteria that they are started on this therapy before surgery so that they can develop tolerance to the mask before needing it in the immediate postoperative time period.

Intraoperative management

Patients receive routine deep venous thrombosis prophylaxis with sequential leg compression devices and have appropriate warming apparatuses placed. Since electrodes are being implanted and some patients will have a contaminated case with simultaneous placement of gastrostomy tubes, preincision antibiotics are given to all patients.

Because muscle stimulation has to be performed to identify optimal implantation site of electrodes, no neuromuscular relaxants (paralyzing agents) are used. Succinylcholine is strictly contraindicated in patients with ALS because of the UMN involvement leading to denervated muscles with increased acetylcholine receptors contributing to this succinylcholine-triggered hyperkalemia.¹³ Preemptive local anesthetic is placed in all planned incisions to decrease need for intraoperative narcotics and decrease muscle spasms in patients with more UMN involvement. The overall strategy is to use rapid reversible short-acting analgesic and amnestic agents. Premedication is provided with midazolam, which is an anxiolytic that also decreases intraoperative muscle spasms. Induction is done with propofol and remifentanyl infusion. Propofol is an intravenous amnestic agent. Remifentanyl is an intravenous ultra-short-acting narcotic used for both induction and maintenance of anesthesia. This agent is a potent narcotic that depresses the respiratory drive, which facilitates diaphragm mapping because the patient will not try to augment respiration. Because of the ultrashort action of remifentanyl, patients resume their normal respirations minutes after discontinuation of the drug. Remifentanyl infusion is made with 1 mg in 40 mL of fluid and an initial bolus of .5 to 1.0 μg /kg and maintenance rate of .1 to .2 μg /kg/minute. Anesthesia is deepened with an

inhalational agent such as sevoflurane, which has low lipid solubility allowing rapid on and off capabilities. Maintenance of anesthesia during the case is done with the inhalational agent and remifentanyl. Small doses of morphine or hydromorphone, nonsteroidal anti-inflammatory agents, and generous local anesthetic injection help with postoperative pain. At the end of each procedure, the DPS system is also used to increase the respiratory system compliance by decreasing posterior lobe atelectasis by maximally stimulating the diaphragm. Since ALS patients have little respiratory reserve, increasing respiratory compliance decreases their work of breathing, which helps in the immediate postoperative period. Extubation is routinely planned in the operating room and diaphragm function is improved by having the patient sitting up during this time.

Postoperative management

Patients who were on NPPV preoperatively are placed on it in the recovery room. It is important that the perioperative nursing staff is familiar with the patient's own NPPV system and mask. Many times this process is facilitated by having the patient's primary caregiver come to the postanesthesia care unit to help with the patient's machine. This also helps in communicating with the patient, especially if the patient has significant bulbar symptoms that make communication difficult. Some patients can only communicate with eye blinks and the caregiver/family member is invaluable in facilitating communication with the patient. Patients are routinely monitored overnight because of their weakness and proneness to apneas.¹⁴ Routine postoperative use of oxygen should be limited because ALS patients have an instability of respiratory control and their drive for respirations when sleeping is based on oxygen saturation. If a patient becomes confused, an arterial blood gas reading should be obtained to ensure the patient is not becoming hypercarbic. To decrease this risk, NPPV is used with a back-up respiratory rate. Excessive sedation is also avoided in the postoperative period. Patients routinely using cough assist devices/airway clearance devices are encouraged to bring their own machine and resume their usual routine.

Results

For the initial pilot trial, 16 patients were implanted at UHCMC from March 2005 to March 2007 with an average age of 50 years (range 32 to 70 years); 13 of the patients were males. The average predicted FVC at surgery was 56% (range 45% to 89%) with 5 patients having values below 50%. Two patients had hypercarbia before implantation. Six patients underwent simultaneous gastrostomy tube placements. The average time for the operation was 98 minutes (range 60 to 134 minutes).

In September 2007, 2 patients at UHCMC with FVC of 26% and 28% predicted were implanted under compassion-

ate use. Both patients had a simultaneous gastrostomy placed. One patient was dependent on NPPV for over 12 hours per day.

From March 2007 to March 2008, 33 patients at UHCMC and HFHS were implanted. The average age was 55 years (range 41 to 72 years) with 67% males. The average predicted FVC at implantation was 60 (range 45 to 87) with 7 patients below 50% predicted. Six patients had evidence of hypercarbia before implantation with 1 patient having a carbon dioxide level of 60 mmHg.

It was identified early in the study that ALS patients were being extubated more easily than expected. During the course of this study, 4 of these ALS patients were analyzed and previously reported by measuring the respiratory system compliance at the end of the procedure.¹⁵ DPS was synchronized with the anesthesiology ventilator and the change of respiratory compliance was measured before and after the use of DPS. There was a 19% increase of respiratory compliance when DPS was used. DPS was done routinely at the end of the procedure to help with extubation and improve respiratory compliance.

Using this management strategy there were no failures to extubate or 30-day mortalities. There were no perioperative respiratory infections. There were no prolonged hospitalizations, with most patients being discharged in less than 1 day. Three patients returned for second operations: 2 gastrostomies and 1 colon resection for colon cancer with no morbidity. The DPS system was used during the second operation not only to monitor diaphragm respirations but also to stimulate respirations in the now identified central sleep apnea these patients develop. In several cases DPS was used to stimulate respirations immediately postoperatively and in the 1 patient with significantly elevated P_{CO_2} continuous use of DPS postoperatively was able to drive down the P_{CO_2} .

Comments

This is the largest reported series of ALS patients undergoing general anesthesia safely for a laparoscopic procedure. General anesthesia consisting of remifentanyl, sevoflurane, and propofol was effective in facilitating neuromuscular evaluation and laparoscopic surgery in ALS patients without adverse perioperative effects. This strategy may be useful and facilitate other surgery on patients with ALS. The limiting factor in concluding that all surgery in ALS patients can be done safely is that the DPS system was implanted in all of the patients. Stimulating the diaphragm at the end of each case causes increased respiratory compliance, most likely by expanding the posterior lobes. This may be the reason that there were no perioperative pneumonias or any other respiratory problems. Use of the DPS system to start conditioning the diaphragm in 1 week may also be the reason that the 30-day mortality rate is much lower than the rate reported with gastrostomy placement alone. Patients with ALS may require surgical procedures during the course of

their disease (eg, appendicitis, cholecystitis) and an understanding that general anesthesia can be safely given to patients will increase their quality of life. Consideration should be given for implantation of the DPS system at the time of any surgery for patients with ALS for perioperative management and increasing perioperative respiratory compliance.

References

1. Bach JR. Amyotrophic lateral sclerosis: prolongation of life by non-invasive respiratory AIDS. *Chest* 2002;122:92–8.
2. Moser B, Lirk P, Lechner M, et al. General anaesthesia in a patient with motor neuron disease. *Eur J Anaesthesiol* 2004;21:921–3.
3. Chen LK, Chang Y, Liu CC, et al. Epidural anesthesia combined with propofol sedation for abdominal hysterectomy in a patient with amyotrophic lateral sclerosis—a case report. *Acta Anaesthesiol Sin* 1998;36:103–6.
4. Sanchez Castilla M, Rodriguez Tato P, Garcia Escobar M, et al. Anesthesia in two patients with motor neuron disease. *Rev Esp Anesthesiol Reanim* 1990;37:297–9.
5. Forbes RB, Colville S, Swingler RJ. Frequency, timing and outcome of gastrostomy tubes for amyotrophic lateral sclerosis/motor neurone disease: a record linkage study from the Scottish Motor Neurone Disease Register. *J Neurol* 2004;251:813–7.
6. Onders RP, Aiyar H, Mortimer JT. Characterization of the human diaphragm muscle with respect to the phrenic nerve Motor Points for diaphragmatic pacing. *Am Surg* 2004;70:241–7.
7. Onders RP, Ignagni AI, Aiyar H, et al. Mapping the phrenic nerve motor point: the key to a successful laparoscopic diaphragm pacing system in the first human series. *Surgery* 2004;136:819–26.
8. DiMarco AF, Onders RP, Ignagni AI, et al. Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. *Chest* 2005;127:671–7.
9. Onders RP, Ignagni AI, DiMarco AF, et al. The learning curve of investigational surgery: lessons learned from the first series of laparoscopic diaphragm pacing for chronic ventilator dependence. *Surg Endosc* 2005;19:633–7.
10. Onders RP, Elmo MJ, Ignagni AR. Diaphragm pacing stimulation system for tetraplegia in individuals injured during childhood or adolescence. *J Spinal Cord Med* 2007;30:25–9.
11. Onders R, Katirji B, Schilz R, et al. Diaphragm pacing in patients with MND/ALS: long term follow-up of completed safety and feasibility study. *Amyotroph Lateral Scler* 2007;5(suppl 1):82.
12. Miller RG, Rosenberg JA, Gelina DF, et al. Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review) report of the Quality Standard Subcommittee of the American Academy of Neurology. *Neurology* 1999;52:1311–23.
13. Brambrink AM, Kirsch JR. Perioperative care of patients with neuromuscular disease and dysfunction. *Anesthesiol Clin* 2007;25:483–509.
14. Bertorini TE. Perisurgical management of patients with neuromuscular disorders. *Neurol Clin. N Am* 2004;22:293–313.
15. Onders R, Schilz R, Sivashankara S, et al. Diaphragm pacing as a short-term assist to positive pressure mechanical ventilation in critical care patients. *Chest* 2007;132:571.

Discussion

Dr. Donald W. Moorman (Boston, MA): This work represents a further extension of the ongoing work of Dr. Onders and his group and the use of diaphragmatic pacing

technology in neurotrauma and neurodegenerative diseases. The report focuses on the general anesthesia techniques utilized for the patients and the current ALS trial. I have several questions.

First, you describe in the manuscript the concept of diaphragmatic conditioning. I would like you to help me understand the value in patients with neurodegenerative diseases. How much improvement will you see in pulmonary function with conditioning, or is this is even a consideration?

Second, the anesthesia technique described in the paper appears logical, but I could find no control data. Is this is a technique validated elsewhere, or is this a practice by consensus?

And third, while all of us are called upon to provide surgical care to patients with neurodegenerative or neuromuscular diseases, can this mapping and implantation be done in the acute setting? So, could we utilize the technique in a patient we would have to operate on acutely for an abdominal catastrophe?

Dr. Raymond P. Onders (Cleveland, OH): My thanks to Dr. Moorman, who was one of my mentors. I was going into family practice before he took me aside as a senior medical student and convinced me to go into surgery. I thank him for that.

Regarding your first question on diaphragmatic conditioning, we had an unexpected finding. Many ALS patients had conversion of their type 1 muscle fibers to type 2B, that is slow twitch to fast twitch. The diaphragm should normally have about 70% of the muscle as slow twitch fibers. Because of their upper motor neuron involvement, ALS patients have predominantly type 2B fibers. So, they benefit significantly from conditioning, just like a spinal cord-injured patient. So during that 30-day time period that we did this, we were converting them to a much stronger type 1 muscle fiber. That was an unexpected and key finding. In an elegant *New England Journal of Medicine* article from 3

months ago, it was shown that within 1 night on a ventilator, 50% of the diaphragm muscle is converted to the type 2B, or fast-twitch muscle fibers.

As for your third question, could this be utilized in an acute setting? We have done it in 2 patients with acute transverse myelitis, putting them on a ventilator to allow reconversion of diaphragm muscle fibers. We are presently in conversations with the FDA for a trial where we can perioperatively pace the diaphragm for another operation, just as you described.

As to your second question regarding anesthetic technique, this is truly a practice by consensus, as there are no data about general anesthesia in ALS patients. There was no alternative technique or control group. We have been utilizing this technique at 11 worldwide sites, and it has been successful and reproducible.

Dr. Douglas F. Naylor, Jr (Cleveland, OH): Do you have any information comparing your technique of diaphragmatic pacing versus rapidly evolving techniques, specifically noninvasive ventilation with varying levels of bilevel positive airway pressure (BIPAP)?

Dr. Onders: It's very interesting. One of the other aspects that we presented last year is that we implanted electrodes into the diaphragm to create EMG capability. We discovered, confirmed in that *New England Journal* article, the following: when we put patients on a ventilator or use noninvasive positive pressure ventilation techniques, most stop utilizing their own diaphragm, as we have identified in our ALS patients. The data demonstrate that if you do not use your diaphragm in 12 hours, you will convert to type 2B muscle fibers, which is very detrimental. The weaning from a ventilator in the intensive care unit is essentially an attempt to reconvert to type 1 slow twitch muscle fibers. And we have shown that pacing just 30 minutes a day will maintain the diaphragm as primarily type 1 fibers. We should consider earlier utilization of pacing for normal patients on a ventilator.