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ORIGINAL ARTICLE

Amyotrophic lateral sclerosis and anesthesia: a case series and review of the literature

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Abstract

Purpose Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that leads to death due to respiratory failure. This report describes the perioperative characteristics of ALS patients who underwent procedures with anesthesia at our institution.

Methods We reviewed perioperative records of ALS patients who underwent procedures with anesthesia from January 1, 2014, through December 31, 2015.

Results Seventy-eight patients underwent 89 procedures (71 procedures with monitored anesthesia care and 18 with general anesthesia), including 45 gastrostomy tube placements and 18 bone marrow biopsies. Three patients had prolonged duration of postoperative intubation related to preexisting respiratory muscle weakness, and one patient with bilateral pneumothorax required tracheal reintubation for respiratory distress. Four patients had prolonged duration of hospitalization. Three patients were hospitalized for ALS-related complications, and one patient was hospitalized for respiratory distress when pneumoperitoneum developed after gastrostomy tube placement. Three of these patients died of complications attributable to ALS within 30 days of the procedure. Twenty-nine (32.6%) procedures required minimal sedation (e.g., bone marrow biopsy, cataract surgery) and were performed on an ambulatory basis.

Conclusion When caring for patients with ALS, the perioperative team must be prepared to treat potentially complex medical conditions that may not be directly related to the procedure and anesthetic management. However, minor procedures performed with minimal sedation may be safely performed on an ambulatory basis.

Keywords Amyotrophic lateral sclerosis · Anesthesia · Outcomes

Abbreviations

ALS	Amyotrophic lateral sclerosis
ALSFRS-R	Amyotrophic lateral sclerosis functional rating scale-revised
EMG	Electromyography
MAC	Monitored anesthesia care
PEG	Percutaneous endogastric gastrostomy

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects the upper and lower motor neurons. Upper motor neuron involvement (which results in dysfunction of the motor axons in the brain and spinal cord) causes weakness, spasticity, hyperreflexia, and Babinski signs, and the corticospinal tract may show increased T2-weighted signal intensity on brain magnetic resonance imaging (Fig. 1a, b). Lower motor neuron involvement (which results in dysfunction of the anterior horn cell and motor peripheral nerve) causes weakness, muscular atrophy, fasciculations, and cramps and can be assessed with electromyography (EMG) (Fig. 1c–e). Weakness typically begins in the limbs but eventually involves the bulbar and respiratory muscles. The pattern of degeneration is heterogenous with regard to its course and affected areas [1]. Because ALS is a progressive disease, the degree of functional impairment is often serially assessed with questionnaires,

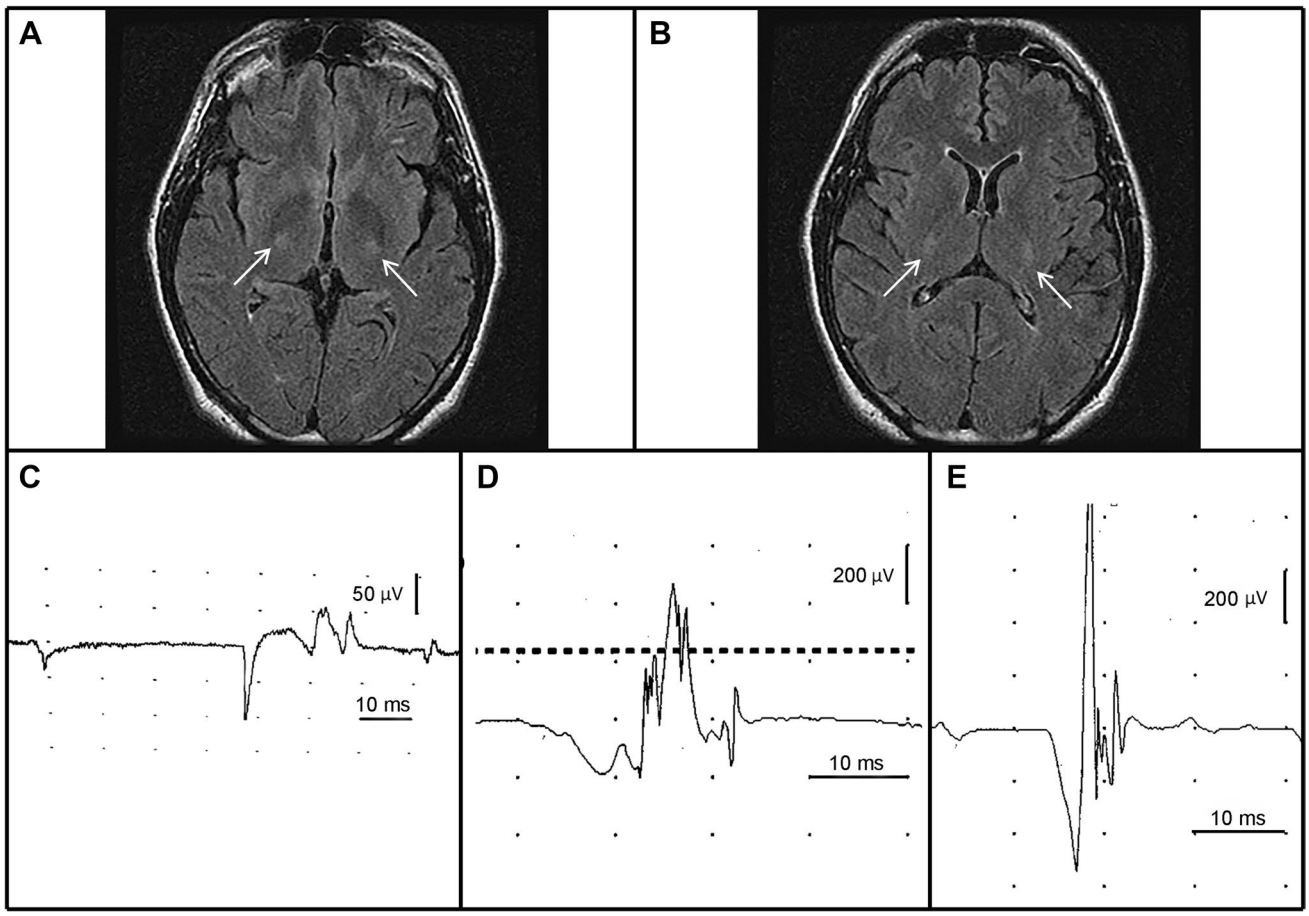

Fig. 1 Changes on magnetic resonance imaging and electromyography associated with amyotrophic lateral sclerosis. Axial magnetic resonance image (**a**) and fluid-attenuated inversion recovery sequence (**b**) showing increased bilateral signal intensity (arrows) through the corticospinal tract. **c** Electromyographic trace showing fibrillation potentials (upward deflections) and positive sharp waves (downward deflections), which represent spontaneous firing of denervated myofibers in a patient with amyotrophic lateral sclerosis. Presence of fibrillation potentials when the muscle should be electrically silent (i.e., flat baseline) indicates an active denervation process. Electromyographic traces showing long duration (**d, e**), high amplitude (**e**), and complex (**d, e**) voluntarily activated motor unit potentials, which are indicators of a neurogenic process with ongoing denervation and reinnervation

such as ALS Functional Rating Scale-Revised (ALSFRS-R) [2], serial pulmonary function tests, and overnight oximetry evaluations [3].

Regardless of the pattern of degeneration, death typically ensues within a few years of symptom onset and is attributable to worsening respiratory failure or complications such as dysphagia or immobility. Mean life expectancy after symptom onset is 3 years, but at least 14% of patients live 5 years or more [4]. ALS also affects the frontotemporal areas of the brain, leading to cognitive changes, especially in patients with a genetic component [5–7]. Incidence of ALS ranges from 1 to 2 cases per 100,000 patient-years [8].

Although ALS is fatal, various therapies may prolong or improve quality of life. Two medications, riluzole and edaravone, are approved for use in the United States for patients with ALS. Riluzole, a glutamate inhibitor, can modestly improve bulbar function and prolong life by a few months [9]. Edaravone, a free-radical scavenger, can slow disease progression in patients with early-stage ALS [10]. Transplant of mesenchymal stem cells, which secrete neurotrophic factors, is an experimental therapy that may delay motor neuron degeneration [11]. Because these patients have weak respiratory muscles in the later stages of disease, use of noninvasive ventilation, diaphragmatic pacing, or tracheotomy can improve quality of life. Additionally, they often have swallowing problems that require placement of a percutaneous endogastric gastrostomy (PEG) feeding tube.

Little information exists in the literature regarding the anesthetic care of these high-risk patients, but patients with ALS could be more susceptible to anesthesia-related complications than other patients [12]. As more therapies become available, more patients may undergo procedures that require anesthesia or sedation. Thus, anesthesiologists may encounter ALS more often. A better understanding of

anesthetic-related adverse outcomes in this unique population is needed to raise awareness and to develop clinical pathways and research questions for these patients. In this study, we describe the anesthetic outcomes of a contemporary cohort of surgical ALS patients from a single academic institution. In addition, to better delineate perioperative problems and complications that develop during management of this challenging condition, we reviewed the literature of ALS patients who underwent procedures with anesthesia.

Methods

This study was approved by the Mayo Clinic Institutional Review Board (No. 16-004555). Consistent with Minnesota Statute § 144.295, only patients who provided authorization for research use of their electronic health records were included.

This retrospective study was designed to evaluate perioperative outcomes of ALS patients who underwent procedures with anesthesia at Mayo Clinic in Rochester, Minnesota. Participants were identified by querying our institution's electronic health records from January 1, 2014, through December 31, 2015. Eligibility criteria included adult patients with actively treated or recently diagnosed (within 12 months) ALS who received monitored anesthesia care (MAC) or general anesthesia.

The electronic health records of identified patients were queried to identify preoperative ALS characteristics, including results of functional assessments (e.g., ALSFRS-R [2], pulmonary function tests, and overnight oximetry studies), and therapies for ALS management (e.g., noninvasive ventilation). The ALSFRS-R is a validated instrument used to assess functional impairment in four functional domains: bulbar function, fine motor skills, gross motor skills, and respiratory function. ALSFRS-R includes 12 questions that ask the physician to rate the patient's breathing and level of functional impairment when performing nine common tasks. Each task is rated on a 5-point scale (0, complete inability; 4, normal ability). Individual item scores are summed to produce an overall score from 0 (worst) to 48 (best).

We reviewed surgical and anesthetic records to identify perioperative management techniques and perioperative complications, particularly failure to extubate the trachea when extubation may have been expected, postoperative respiratory failure, and worsening ALS signs and symptoms. We also reviewed types of procedures and functional characteristics of patients who received MAC to assess whether functional status was associated with admission status.

The 12 patient functions were categorized as bulbar function (speech, salivation, swallowing), fine motor skills (handwriting, cutting food, dressing and hygiene), gross motor skills (walking, climbing stairs, turning in bed), and respiratory function (dyspnea, orthopnea, respiratory insufficiency). Severe impairment was defined as a subcomponent score less than 2.

We summarize demographic and epidemiologic characteristics and perioperative complications. Continuous variables are reported as mean (SD) or median (interquartile range). Categorical variables are reported as number and percentage.

We searched Embase and PubMed (January 2008 through April 2018) to determine current knowledge of anesthetic implications and considerations for patients with ALS. We searched for English-language articles using the terms "amyotrophic lateral sclerosis", "anesthesia complication", and "anesthetic agent".

Results

We identified 78 patients who underwent 89 procedures. Demographic and clinical characteristics are presented (Table 1), and notably, a high percentage of patients had severe functional impairment and abnormal pulmonary function. Surgical and anesthetic characteristics of these procedures, including medications used for MAC, are summarized (Table 2). Most procedures were related to PEG tube placement for nutritional support [$n=45$ (51%)]. MAC was administered during 71 procedures (79.8%) and general anesthesia during 18 (20.2%). Volatile anesthetics were administered to all patients who received general anesthesia. Succinylcholine was not administered to any patient, and a nondepolarizing neuromuscular blocking drug was administered to three patients (3.4%). No intraoperative complications were identified.

Intraoperative outcomes

Of 18 patients who received general anesthesia, four remained intubated and were transferred to the intensive care unit, and one of these patients underwent aortic valve replacement. The other three patients underwent PEG tube placement under general endotracheal anesthesia and remained intubated because of underlying respiratory weakness and aspiration concerns attributable to bulbar dysfunction. Two of these patients had severely decreased vital capacity (25% and 26% of predicted capacity, respectively). Although the third patient had relatively preserved vital capacity (74% of predicted capacity), her maximal inspiratory pressure was severely decreased (32% of predicted capacity). All three patients had their tracheas extubated within 1 h of admission to the intensive care unit. In addition, a 41-year-old man who underwent diaphragm pacemaker lead placement reported dyspnea after extubation

Table 1 Clinical characteristics of patients with ALS who underwent procedures with anesthesia

Characteristic	Value[a,b]
Age at diagnosis ($N=78$) (years)	60.8 (10.8)
Age at surgery (years)	61.8 (10.9)
Body mass index (kg/m^2)	25.7 (6.3)
Comorbid conditions	
Cardiovascular disease	4 (4.5)
Pulmonary disease	10 (11.2)
Neurologic disease	4 (4.5)
Diabetes mellitus	5 (5.6)
ALSFRS-R score ($n=55$)[c]	29 (22–39)
Severe impairment (ALSFRS-R subcomponent score < 2)	
Bulbar impairment	27 (49.1)
Speech	24 (43.6)
Salivation	11 (20.0)
Swallowing	11 (20.0)
Fine motor impairment	26 (47.2)
Handwriting	17 (30.9)
Cutting food	24 (43.6)
Dressing and hygiene	21 (38.2)
Gross motor impairment	33 (60.0)
Turning in bed	15 (27.3)
Walking	13 (23.6)
Climbing stairs	33 (60.0)
Respiratory impairment	8 (14.5)
Dyspnea	6 (10.9)
Orthopnea	6 (10.9)
Breathing insufficiency	2 (3.6)
Pulmonary function tests ($n=62$)[c]	
Vital capacity < 70% of predicted	37 (59.7)
Maximum inspiratory pressure greater than − 60 cm H_2O	53 (54.5)
Overnight oximetry ($n=29$)[c]	
Mean overnight oxygenation < 93%	14 (48.3)
ALS therapy	
Riluzole	32 (36.0)
Feeding tube	9 (10.1)
Noninvasive ventilation	25 (28.1)
Tracheostomy	2 (2.2)

ALS amyotrophic lateral sclerosis, *ALSFRS-R* Amyotrophic Lateral Sclerosis Functional Rating Scale-revised

[a]Categorical variables are shown as no. (%), and continuous variables are shown as mean (SD) or median (interquartile range)

[b]All values were calculated according to the no. of cases ($n=89$) unless indicated otherwise

[c]Determined within 6 months before surgery

in the operating room. Chest radiography showed bilateral pneumothorax. His trachea was reintubated, and he was mechanically ventilated until the following day. Five patients had noninvasive ventilatory devices (diaphragm pacemaker leads) placed immediately after extubation. Two patients underwent tracheostomy. Six patients had standard airway management after extubation at the end of the procedure.

Ambulatory vs hospital-based procedures

Twenty-nine (32.6%) procedures were performed on an ambulatory basis, 7 (7.9%) resulted in hospital admission to a standard inpatient ward, and 53 (59.6%) resulted in intensive care unit admission. All patients who had general anesthesia were admitted to the hospital after the procedure, except for a 50-year-old man who underwent magnetic resonance imaging with general anesthesia as an ambulatory procedure.

Among patients who received MAC, 28 (39.4%) underwent ambulatory procedures and 43 (60.6%) were admitted to the hospital. All patients who underwent PEG tube placement ($n=39$) were postoperatively admitted to the hospital, and all patients who underwent bone marrow aspiration ($n=18$) were treated on an ambulatory basis. In addition, patients who were hospitalized were older, had lower ALSFRS-R scores, and had decreased vital capacity and maximum inspiratory pressure (Supplemental Table).

Postanesthesia care unit admission

Thirty-eight patients [38 of 89 procedures (42.7%)] were admitted to the postanesthesia care unit. Anesthesia recovery was unremarkable, except for one patient who had hypoventilation attributable to opioid administration after spine surgery. All other patients were discharged directly from the operating room to the intensive care unit, including most patients who underwent PEG tube placement.

Postoperative course

Four patients had prolonged duration of hospitalization. Three of these patients were hospitalized for ALS symptoms and had a procedure with anesthesia: a 67-year-old woman had PEG tube placement, 21-day hospitalization, and ALSFRS-R score of 28 and severe gross motor domain impairment (scores of 0 for turning in bed, walking, and climbing stairs); an 81-year-old woman had PEG tube placement, 9-day hospitalization, and ALSFRS-R score of 20; and a 62-year-old man had tracheostomy, 65-day hospitalization, and ALSFRS-R score of 18. The fourth patient, a 72-year-old woman, had ALSFRS-R score of 33 and underwent PEG tube placement, which was complicated by the accumulation of a large volume of intraperitoneal air that led to atelectasis and respiratory distress. Her PEG tube was readjusted, pneumoperitoneum gradually resolved, and her respiratory status returned to baseline. She was discharged after 5 days.

Table 2 Characteristics of anesthetic procedures used to treat patients with ALS

Characteristic	Value ($N=89$)[a]
Procedure	
Percutaneous endoscopic gastrostomy tube placement	45 (50.6)
Bone marrow biopsy	18 (20.2)
Laparoscopic diaphragm pacemaker lead placement	7 (7.9)
Endoscopic examination	4 (4.5)
Bronchoscopy	2 (2.2)
Pacemaker implant	2 (2.2)
Orthopedic surgery	2 (2.2)
Tracheotomy	2 (2.2)
Other[b]	7 (7.9)
Surgical duration (min)	126 (72)
Anesthetic type	
Monitored anesthesia care	71 (79.8)
Propofol	64 (90.1)
Midazolam	19 (26.8)
Dose (mg)	1.5 (1–2)
Fentanyl	46 (64.8)
Dose (mcg)	75 (50–100)
General anesthesia	18 (20.2)
Endotracheal intubation	
Direct intubation	10 (11.2)
Video laryngoscope[c]	7 (7.9)
Laryngeal mask airway	1 (1.1)
Volatile anesthetic	18 (100)
Neuromuscular blocking drug[d]	3 (3.4)
Opioid dose, mg intravenous morphine equivalent	14.75 (8.75–22.13)
Vasoactive treatment of intraoperative hemodynamic instability (hypotension)	
Infusion[e]	3 (3.4)
Bolus[f]	19 (21.3)
PACU admission	38 (42.7)
PACU duration (min)	52 (38–78)
Postoperative disposition	
Ambulatory	29 (32.6)
Standard inpatient ward	7 (7.9)
Intensive care unit	53 (59.6)
Postoperative respiratory support	
No respiratory support	57 (64.0)
Noninvasive ventilation	10 (11.2)
Nasal cannula	13 (14.6)
Endotracheal tube	5 (5.6)
Tracheostomy[g]	4 (4.5)

ALS amyotrophic lateral sclerosis, *PACU* postanesthesia care unit

[a]Categorical variables are shown as no. (%), and continuous variables are shown as mean (SD) or median (interquartile range)

[b]Includes aortic valve replacement, burr hole placement, cataract extraction, computed tomography-guided biopsy, lymph node biopsy, magnetic resonance imaging, and closure of scalp laceration

[c]One intubation with a video laryngoscope required use of a fiberoptic scope as a flexible stylet, because the patient was swallowing and the glottis was anterior

[d]All neuromuscular blockers were nondepolarizing muscle relaxants

[e]Phenylephrine was administered to these three patients: two underwent diaphragm pacemaker lead placement; one, tracheostomy

[f]Ephedrine was administered to 14 patients; phenylephrine, 16; and vasopressin, 1. Some patients received more than one medication

[g]One patient with a previous tracheostomy had two procedures

An additional three patients died of ALS within 30 days of the procedure: a 67-year-old woman (ALSFRS-R score of 28) died 8 days after discharge (day 29 postoperation); an 81-year-old woman died 17 days after PEG tube placement (ALSFRS-R score not determined within 6 months of the procedure); and a 61-year-old man died 11 days after diaphragm pacemaker lead placement (ALSFRS-R score of 43).

Literature review

Our review identified 32 case reports or series, yielding a total of 503 patients with ALS who underwent procedures with sedation or anesthetic management. Anesthetic techniques were MAC (402 patients) [13–20], general anesthesia (83 patients) [21–35], and regional anesthesia (18 patients) [36–44]. Reported complications are summarized (Table 3). Twelve serious complications were reported after MAC, including 4 ALS-related deaths within 30 days [14], three cases of aspiration pneumonia during endoscopy

Table 3 Complications after anesthetic care among patients with ALS reported in the literature, 2008 through 2018

Source	Procedure (no. of patients)		Anesthetic complications and notable events (no. of events)
MAC			
Thompson et al. [14]	PEG tube placement ($n=107$)		Death within 30 days secondary to ALS ($n=4$)
Sato et al. [16]	PEG tube placement and ultrathin EGD without sedation ($n=14$)		No minor complications observed
	PEG tube placement and conventional EGD without sedation ($n=17$)		Aspiration pneumonia ($n=3$)
	PEG tube placement and conventional EGD and MAC ($n=14$)		Apnea and hypoventilation ($n=3$)
Liu et al. [17]	PEG tube placement ($n=9$)		Intensive care unit admission for poor respiratory effort ($n=1$)
Kak et al. [18]	Gastrostomy or PEG tube placement ($n=41$)		Respiratory distress requiring noninvasive ventilation ($n=1$)
General anesthesia			
You et al. [21]		Dental treatment ($n=1$)	Pulseless electrical activity after anesthesia induction; hypovolemia was the suspected cause ($n=1$)
Thourot et al. [24]		Magnetic resonance imaging ($n=1$)	Hyperkalemia (9.2 mmol/L) after succinylcholine administration ($n=1$)
Chang et al. [26]		Ureteroscopic ureterolithotomy ($n=1$)	Continued weakness after rocuronium reversal with sugammadex that required 4 h of postoperative ventilatory support ($n=1$)
Schmiesing et al. [32]		Laparoscopic diaphragm pacemaker lead placement ($n=3$)	Ventricular tachycardia and QT prolongation ($n=1$)

ALS amyotrophic lateral sclerosis, *EGD* esophagogastroduodenoscopy, *MAC* monitored anesthesia care, *PEG* percutaneous endoscopic gastrostomy

without sedation [16], and five cases of poor respiratory effort [16–18]. Four serious complications were reported for patients who received general anesthesia: pulseless electrical cardiac arrest attributable to hypovolemia [21]; hyperkalemia after succinylcholine administration [24]; residual muscle weakness after rocuronium reversal with sugammadex that required 4 h of mechanical ventilation [45]; and postoperative ventricular tachycardia in a patient with previously undiagnosed cardiomyopathy [32].

The patient who was administered succinylcholine (a 63-year-old man) was fiberoptically intubated to manage respiratory failure and to evaluate muscular weakness with magnetic resonance imaging [24]. His endotracheal tube became dislodged, and succinylcholine was administered to facilitate reintubation. After administration of succinylcholine, his electrocardiogram markedly changed and his potassium level was elevated (9.2 mmol/L). ALS was subsequently diagnosed. No complications were reported after he received regional anesthesia.

Discussion

Several interesting findings were observed in this cohort of ALS patients who underwent procedures with anesthetic management. First, minor procedures that require limited sedation (e.g., bone marrow biopsy, cataract extraction) can be performed safely on an ambulatory basis. Second, more extensive procedures can result in patients undergoing decompensation; we noted decompensation that resulted in respiratory failure for two patients. One patient had small pneumothorax after diaphragm pacemaker lead placement, and the other had pneumoperitoneum after PEG tube placement. Third, a patient with extremely poor respiration may require postoperative ventilation, even after minor procedures such as PEG tube placement. Lastly, the high acuity of ALS can result in prolonged duration of hospitalization or death. These complications were not attributable to the procedure per se; rather, they were sequelae of the underlying disease. Several patients with intraoperative hypotension required treatment, which was administered in accordance with our standard treatment of hypotension in general surgical patients.

Anesthesiologists are increasingly involved in the care of ALS patients because of the increasing number of therapeutic options designed to improve and prolong the lives of these patients. The medical literature indicates increasing experience in anesthetic management. We identified 31 studies published in the past decade that described a total of 503 ALS patients who underwent procedures that required sedation or anesthesia. Similar to the procedures described in our series, most reported procedures were performed with MAC. Postoperative respiratory failure is the major concern for these patients [12] and is the cited rationale for preferring regional anesthetic techniques in many published cases [36–44]. Indeed, no complications were reported among patients who underwent regional anesthetic techniques. The most serious reported complications occurred during the course of general anesthesia. Life-threatening hyperkalemia developed in 1 patient after succinylcholine administration [24], highlighting the importance of avoiding depolarizing muscle relaxants in patients with ALS. Another patient had residual muscle weakness that required postoperative mechanical ventilation despite reversal with sugammadex [45]. In our series, three patients were administered nondepolarizing muscle relaxants: two patients received neostigmine and glycopyrrolate for neuromuscular blockade reversal and were extubated without adverse sequelae; and one patient that underwent open heart surgery, was transferred to the intensive care unit, and received mechanical ventilation without neuromuscular blockade reversal. Of the two cardiac complications reported in the literature, one case of supraventricular tachycardia occurred in a patient with unrecognized heart disease, and ALS was probably not a contributing factor [32]. The case of pulseless electrical activity after induction of anesthesia was attributed to hypovolemia by the authors, and nutritional difficulties could have been a contributing factor [21].

In our series, three patients required postoperative mechanical ventilation after PEG tube placement, and all had severely diminished respiratory function. Patients with ALS often undergo serial pulmonary function tests, and the results of these tests should be reviewed preoperatively to determine whether these patients require postoperative mechanical ventilation [3]. Postoperative application of noninvasive ventilatory devices can facilitate successful extubation, and five of our patients underwent surgery for diaphragm pacemaker lead insertion. In addition to serial pulmonary function tests, other tests (e.g., ALSFRS-R) are used to assess functional status of ALS patients at regular intervals. All three patients who had prolonged hospital stays attributable to ALS symptoms had low ALSFRC-R scores (thereby indicating severe disease and functional impairment) [2].

This study has all the inherent limitations of a retrospective case series. Although this is the second largest case–cohort series published in the past decade [14], we evaluated a cohort that received various procedures. Furthermore, several patients did not have preoperative functional assessments. These shortcomings limited our ability to formally assess patient status and risk of perioperative complications. However, the characteristics of patients who required postoperative mechanical ventilation or prolonged hospital stay suggested that patients with preoperative evidence of greater functional impairment may require additional postoperative care resources.

In conclusion, surgical patients with ALS may have high-acuity disease status, and the perioperative team must be prepared to treat potentially complex medical conditions, which may not be directly related to the procedure and anesthetic management. Preoperative review of functional assessments, which are often obtained serially, may help guide decision-making for optimal anesthetic management and extubation. However, minor procedures that require minimal sedation may be performed on an ambulatory basis.

Compliance with ethical standards

Conflict of interest TNW currently serves as a consultant to Medtronic in the role as chairman of the Clinical Endpoint Committee for the Prodigy Trial; has received research support from Respiratory Motion (study equipment) and unrestricted investigator-initiated grants from Merck (active) and Baxter (completed).

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