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Novel Treatment Using Intravenous Dantrolene Sodium for Postoperative Exacerbated Spasticity in Multiple Sclerosis: A Case Report

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Patients with upper motor neuron disease, such as multiple sclerosis, can present with severe spasticity in the perioperative period. In most cases, this can be managed with a combination of preoperative oral medications, regional or neuraxial anesthetic techniques, and intravenous muscle relaxants. We describe the clinical presentation of a patient with multiple sclerosis and the successful use of intravenous dantrolene sodium postoperatively for the treatment of exacerbated spasticity refractory to traditional management. (A&A Practice. 2018;11:25–7.)

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system characterized by the destruction of myelin and myelin-forming oligodendrocytes resulting in axonal demyelination, inflammation, and plaque formation. This results in impaired nerve impulse transmission, which manifests as muscle weakness, fatigue, imbalance, paresthesia, visual disturbance, and urinary incontinence. The presence of 2 or more areas of plaque formation on magnetic resonance imaging is diagnostic for MS.[1] Infectious exposure, genetic susceptibility, and environmental factors are thought to be causative factors of MS.[2] Perioperative risk factors for acute exacerbation are thought to include hyperpyrexia, spinal anesthesia, pain, and physiologic stress. There are no specific associations between anesthetic medications and acute exacerbation. Preexisting respiratory compromise or denervated muscle tissue from immobility or paresis may predispose to postoperative respiratory complications and hyperkalemia with administration of succinylcholine.

Treatment of MS is aimed at decreasing spasticity, minimizing medical complications, and improving quality of life. First-line treatment for spasticity is oral baclofen. Baclofen is a γ-aminobutyric acid (GABA)-B agonist postulated to hyperpolarize polysynaptic and monosynaptic afferent synaptic nerve terminals at the level of the spinal cord, restricting the release of endogenous excitatory neurotransmitters, glutamate, and aspartic acid. Clonidine, also a centrally acting oral agent, is an α-2 agonist, which inhibits sympathetic outflow and tone. Other oral treatment options include benzodiazepines, gabapentin, and dantrolene sodium. Benzodiazepines depress excitatory neurotransmitter release via postsynaptic GABA-A hyperpolarization. Diazepam is most commonly used for spasticity due to its superior muscle relaxant activity in addition to its hypnotic and antiepileptic properties. Gabapentin, developed as a GABA analog, appears to interact with cortical neurons at auxiliary subunits of voltage-dependent calcium channels. Dantrolene sodium is Food and Drug Administration approved to decrease muscle spasticity by direct uncoupling of excitation and contraction peripherally. Adverse effects of dantrolene include muscle weakness and a black box warning for fatal hepatotoxicity with chronic therapy. Before the black box warning, oral dantrolene was a first-line therapy for spasticity. Interventional treatments include an intrathecal baclofen pump or intramuscular botulinum toxin injections. An intrathecal baclofen pump delivers a high concentration of baclofen directly at the site of the spinal cord with the benefit of titrating the infusion rate and reducing the risk of systemic toxicity. Botulinum toxin injections reduce muscle spasticity by inhibiting the release of vesicular acetylcholine from presynaptic nerve terminals at the neuromuscular junction providing relief for up to 3–4 months.[3]

Intravenous (IV) dantrolene sodium is a peripherally acting ryanodine receptor-1 antagonist, which inhibits calcium release from the sarcoplasmic reticulum of the skeletal muscle resulting in muscle relaxation. It is indicated for the treatment of malignant hyperthermia by administration of 2.5 mg/kg with a maximum cumulative dose of 10 mg/kg. Dantrolene has been associated with skeletal muscle weakness, dyspnea, respiratory muscle weakness, and decreased inspiratory capacity. The concomitant administration of calcium channel blockers and dantrolene is associated with marked hyperkalemia and cardiovascular collapse. Other drug interactions include potentiated effects of neuromuscular-blocking agents, antipsychotics, and antianxiety agents.[4]

This case report presents the novel treatment using IV dantrolene for known refractory postoperative exacerbated spasticity in a patient with MS who underwent general anesthesia for oblique lumbar interbody fusion of L3–L5. The patient has provided written Health Insurance Portability and Accountability Act authorization to publish this case report.

CASE DESCRIPTION

A 63-year-old woman (80 kg) with a history of MS was scheduled for an oblique lumbar interbody fusion of L3–L5.

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The patient's history revealed severe postoperative exacerbated spasticity refractory to maximal doses of diazepam in each of her 6 previous procedures under general anesthesia, regional anesthesia, or monitored anesthesia care. These events lasted between 2 and 6 hours and caused significant emotional and physical distress as reported by the patient and her husband. A review of the patient's maintenance medications and a discussion with her neurologist was performed (Table). Per the patient's neurologist, the only medication that could be safely titrated upward was clonazepam, and he performed her next series of botulinum toxin injections the week before surgery. Her clonazepam was increased from 0.5 mg to 1.5 mg twice a day 5 days before surgery. She was instructed to increase to 2 mg twice a day 2 days before surgery if the prior increase did not cause oversedation. The patient was able to tolerate this increase. Neither of these interventions had been tried previously in the preoperative period. Both the patient and her neurosurgeon declined the option of adding neuraxial anesthesia for postoperative pain control. The patient had received neuraxial and regional anesthesia for prior surgeries and presented with acute bilateral lower extremity (BLE) spasticity postoperatively. In addition, she has a spinal cord stimulator in place that she desired to have removed in the future and did not want additional intervention on her back. The neurosurgeon reported the need for an oblique surgical approach and therefore would not be able to place an epidural catheter under direct visualization. An extensive discussion was held with the patient, her husband, neurologist, neurosurgeon, and these authors regarding the risks, benefits, and potential complications of using IV dantrolene for symptomatic management of her refractory postoperative exacerbated spasticity. Informed consent was obtained from the patient.

Preoperative evaluation was significant for diplopia, left facial nerve palsy, hypoglossal nerve palsy, decreased neck range of motion, 4/5 strength in bilateral upper extremities, and 4/5 strength in BLE with clonus. Before proceeding to the operating room, she was administered 10 mg of diazepam IV in 5-mg doses 5 minutes apart. Anesthetic induction was achieved with the IV administration of 100 µg of fentanyl, 40 mg of lidocaine, 150 mg of propofol, and 50 mg of rocuronium. Intubation was performed with video laryngoscopy. After induction, an infusion of dexmedetomidine was initiated at 0.4 µg/kg/h and continued for 1 hour postoperatively for postoperative pain control and anxiolysis. Anesthesia was maintained with O_2-air-sevoflurane (2%). Her bispectral index initially was 27.2, likely secondary to the preoperative administration of diazepam, induction of anesthesia, and starting the dexmedetomidine infusion. For the remainder of the case, the patient's bispectral index was approximately 39 with the goal of maintaining a deep anesthetic plane. The initial core temperature reading was 36°C and was maintained between 35.5°C and 36.7°C. The patient received 1 g of acetaminophen and 2 mg of hydromorphone IV intraoperatively for postoperative pain management. A total of 130 mg of rocuronium was used in 10- to 20-mg increments over the 5-hour case. Although the patient had recovered to 4/4 twitches on the train-of-four monitor, the 2 mg/kg dose of sugammadex was given at the conclusion of the case to avoid residual neuromuscular blockade. The patient was extubated and transported to the postanesthesia care unit (PACU). The onset of mild BLE spasticity occurred 26 minutes after arrival to the PACU, which subsided after 4 minutes without intervention. One minute after resolution, her spasticity reoccurred, and 25 mg of IV dantrolene was given after 6 minutes of sustained contracture. Within 1 minute after injection, the author was able to palpate release of the contraction. Over the next 17 minutes, her spastic diplegia continued intermittently, and another 5 doses of IV dantrolene in 25-mg increments were given at 2- to 3-minute intervals for a total of 150 mg with complete resolution of her spasticity. During each subsequent event, the release of contracture occurred within 1–2 minutes after dantrolene administration with no other intervention. The

Table. Preoperative Medication List of a Multiple Sclerosis Patient

Drug	Mechanism of Action[a]	Dose[b]	Maximum Dose
Baclofen	GABA-B agonist may block polysynaptic and monosynaptic afferent pathways inhibiting the release of glutamate and aspartic acid	20 mg QID	80 mg per day[c]
Botulinum toxin	Inhibits acetylcholine release at the motor nerve terminal	300 units injected every 3 mo	400 units injected every 3 mo[d]
Carbamazepine extended release	Anticonvulsant; inhibits use dependent Na channels, muscle relaxant, sedative properties	300 mg twice a day	1200 mg per day
Celecoxib	Nonsteroidal anti-inflammatory agent specific for inhibition of COX-II enzyme	200 mg QD	800 mg per day
Clonazepam	Benzodiazepine receptor agonist, allosterically interacts with GABA, increasing inhibition of the ascending reticular activating system	0.5 mg twice a day	20 mg per day
Clonidine	Presynaptic α-2 receptor agonist	0.1 mg TID	2.4 mg per day
Dalfampridine	K channel blocker	10 mg twice a day	20 mg per day
Gabapentin	GABA analog	900 mg TID	3600 mg per day
Glatiramer acetate	Immunomodulating agent proposed to act as decoy to locally generated autoantibodies	40 mg SQ MWF	40 mg 3 times weekly
Modafinil	Possible central α-1 adrenergic agonist, may inhibit excitatory glutaminergic transmission	100 mg twice a day	400 mg per day

Abbreviations: COX, cyclooxygenase; GABA, γ-aminobutyric acid; MWF, Monday Wednesday Friday; QD, daily; QID, four times a day; SQ, subcutaneous; TID, three times a day.

[a]National Institutes of Health, National Library of Medicine. DailyMed. Available at: https://dailymed.nlm.nih.gov/dailymed/. Accessed March 8, 2018.

[b]All medication doses administered orally unless otherwise stated.

[c]Maximum dose suggested is 80 mg per day; however, up to 150 mg per day has been given safely in some patients.

[d]Not well defined although recommendation is for a maximum dose of 400 units every 3 months.

patient was closely monitored in the PACU for an additional 2 hours when a brief, self-limiting episode of spasticity occurred. No additional therapy was given, and she was admitted to the intensive care unit overnight for observation. Twelve hours after administration of IV dantrolene, the patient's neuromuscular strength was 3/5 bilateral upper extremities and 3/5 BLE with clonus. The patient denied dyspnea throughout her postoperative course and did not have a significant oxygen requirement. She was transferred to the ward on postoperative day 1 and was discharged to a skilled nursing facility on postoperative day 3 where her neuro strength was 4 of 5 in all extremities. The patient and her husband endorsed a radical reduction in postoperative spasticity, anxiety, pain, and overall myalgia compared to her previous 6 surgical procedures.

DISCUSSION

Perioperative stress in patients with MS can result in an unpredictable and varying level of symptom severity. The anesthetic management of patients with MS should be aimed at preventing postoperative exacerbations. A variety of intraoperative anesthetic techniques have been successfully reported with particular attention to maintaining normothermia and aggressive postoperative pain control to minimize the risk of MS exacerbations. Preoperative and postoperative neurologic and respiratory physical examination findings should be documented, and a review of current medical management was performed. While no anesthetic technique is considered superior in patients with MS, emphasis should be placed on preventing hyperpyrexia as an increase in body temperature by 1°C can trigger an exacerbation. This is thought to be caused by a complete block of saltatory conduction in demyelinated nerves.[1] Efficacy and safety of neuraxial anesthesia in MS is inconclusive. Subarachnoid anesthesia has been postulated to exacerbate MS attacks due to the toxic effects of local anesthetics on demyelinated neurons. However, in a systematic review of neuraxial anesthesia in obstetric patients with MS, Bornemann-Cimenti et al[5] suggest that this mechanism of action is hypothetical and evidence is based on only a few case reports without a clear correlation between subarachnoid anesthesia and MS exacerbations. In addition, they report multiple incidences of spinal and epidural anesthesia in obstetric patients with MS with no negative outcomes. General anesthesia and the use of volatile anesthetics have been reported to be safe for patients with MS.[1] Dexmedetomidine is a selective α-2 agonist at low to medium doses (10–300 μg/kg) and may reduce spasticity by increasing presynaptic inhibition of motor neurons.[6] Anand et al[7] report successful use of dexmedetomidine as the sole sedative agent in patients with MS for monitored anesthesia care undergoing balloon angioplasty of the internal jugular and azygos veins, also known as the "Liberation Procedure." This has been theorized to improve chronic cerebrospinal venous insufficiency and therefore has been used in an attempt to decrease MS symptoms. Liberation therapy is not scientifically validated nor is it widely utilized. Benzodiazepines, specifically diazepam, are the standard therapy for controlling acute muscle spasms in MS.[3] There have been successful reports of alternative modalities for refractory spasticity using phenol nerve block,[8] magnesium sulfate infusion,[9] acupuncture,[10] and extracorporeal shock wave therapy.[11] These authors found no literature reporting the use of IV dantrolene for the treatment of acute exacerbated spasticity in the perioperative setting despite its historical oral use for spasticity. This case report highlights the unique anesthetic management of a patient with MS. The anesthetic plan included optimizing medication management, botulinum toxin injections 1 week before surgery, diazepam for preoperative anxiolysis and perioperative muscle relaxation, and dexmedetomidine infusion for postoperative anxiolysis and possible antispasticity effect. IV dantrolene was used in the treatment of postoperative exacerbated spasticity that occurred despite all aforementioned interventions. We conclude that our preoperative and intraoperative interventions lessened the duration and extent of the spasticity, and IV dantrolene was not the sole reason for the improved outcome. The patient's husband supported that overall this was the least severe occurrence and most rapid resolution.

DISCLOSURES

Name: Emily L. Sturgill, MD.
Contribution: This author helped care for the patient, and write and edit the manuscript.
Name: Robert L. Wittwer, BSN, SRNA.
Contribution: This author helped care for the patient, and write and edit the manuscript.
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REFERENCES

1. Hines RL, Marschall KE. *Stoelting's Anesthesia and Co-Existing Disease*. 6th ed. Philadelphia, PA: Elsevier; 2012.
2. Agamanolis DP. Demyelinative diseases. Neuropathology: an illustrated interactive course for medical students and residents. Available at: Http://neuropathology-web.org/chapter6/chapter6aMs.html. Accessed November 5, 2017.
3. Chang E, Ghosh N, Yanni D, Lee S, Alexandru D, Mozaffar T. A review of spasticity treatments: pharmacological and interventional approaches. *Crit Rev Phys Rehabil Med*. 2013;25:11–22.
4. *Ryanodex [package insert]*. Woodcliff Lake, NJ: Eagle Pharmaceuticals, Inc; 2016.
5. Bornemann-Cimenti H, Sivro N, Toft F, Halb L, Sandner-Kiesling A. [Neuraxial anesthesia in patients with multiple sclerosis—a systematic review]. *Rev Bras Anestesiol*. 2017;67:404–410.
6. *Dexmedetomidine [package insert]*. Lake Forest, IL: Hospira, Inc; 2010.
7. Anand S, Bhatia A, Rajkumar, Sapra H, Gupta V, Mehta Y. Dexmedetomidine for monitored anesthesia care in patients undergoing liberation procedure for multiple sclerosis: an observational study. *Saudi J Anaesth*. 2012;6:358–362.
8. Gaid M. Phenol nerve block for the management of lower limb spasticity. *ACNR*. 2012;12:23–25.
9. Rodrigo C, Fernando D, Rajapakse S. Pharmacological management of tetanus: an evidence-based review. *Crit Care*. 2014;18:217.
10. Lim SM, Yoo J, Lee E, et al. Acupuncture for spasticity after stroke: a systematic review and meta-analysis of randomized controlled trials. *Evid Base Compl Alternative Med*. 2015:1–12.
11. Lee JY, Kim SN, Lee IS, Jung H, Lee KS, Koh SE. Effects of extracorporeal shock wave therapy on spasticity in patients after brain injury: a meta-analysis. *J Phys Ther Sci*. 2014;26:1641–1647.