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CHARCOT MARIE TOOTH DISEASE
AND THE USE OF NEUROMUSCULAR BLOCKERS

by

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Bachelor of Arts in Nursing, Concordia College, 2010

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

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PERMISSION

Title Charcot Marie Tooth Disease and Neuromuscular Blockers
Department Nursing
Degree Master of Science

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Abstract

Title: Charcot Marie Tooth Disease and the Use of Neuromuscular Blockers

Background: Charcot Marie Tooth disease (CMTD) is a chronic and progressive neurological disease affecting both motor and sensory nerves. Clinical presentation includes numbness and weakness to the lower extremities, with disease progression to the upper extremities, and in some cases, the diaphragm (Szigeti & Lupski, 2009).

Purpose: The purpose of this independent study is to determine if the omission of neuromuscular blockers (NMBs) results in fewer post-operative problems, such as muscle weakness, respiratory depression, re-intubation, etc., in patients with CMTD who are undergoing general anesthesia.

Process: A comprehensive review of the literature was completed using PubMed and Medical Subject Headings (MeSH) databases, through the Harley E. French Library at the University of North Dakota.

Results: Research studies indicate NMBs have been used safely in both children and adults with CMTD. Anesthesia providers have reported situations in which omitting the use of a NMB altogether was the safest route for their patients with CMTD in order to avoid any potential respiratory complications.

Implications: The use of NMBs in patient's with CMTD should be determined individually based on, the severity of their symptoms and the disease progression rate. More research is needed regarding documenting the use of NMBs in patients with CMTD, and more specifically careful documentation of any complications that may arise throughout the patient's intraoperative and postoperative period.

Keywords: Charcot Marie Tooth disease (CMTD), anesthesia implications, neuromuscular blocker (NMB), general anesthesia and respiratory distress, Charcot Marie Tooth disease type 1A (CMT1A)

Introduction

Charcot Marie Tooth disease (CMTD), also referred to as a hereditary motor and sensory neuropathy, is one of the most prevalent neurogenetic conditions with an estimated prevalence of 4 in every 10,000 people (Schmitt & Munster, 2006). Neurologists Charcot and Marie of France and Tooth from England first described CMTD in 1886 (Smith, Minkin, Lindsey & Bovino, 2015). Classic symptoms include peripheral muscle weakness and sensory loss of extremities due to demyelination of the peripheral nerve fibers (Schmitt & Munster, 2006). This disease is complex because over 25 genes have been identified to be associated with this disorder, resulting in several different types of CMTD with varying degrees of symptom onset, presentation and rate of progression (Pareyson & Marchesi, 2009). Genetic testing supports the diagnosis, with the most common gene affected being identified as peripheral myelin protein 22 (Kulkarni, Sayed, Garg & Patil, 2015). Over 50% of all inherited peripheral neuropathies are caused by various mutations of this gene (Kulkarni, Sayed, Garg & Patil, 2015). Furthermore, 70% of CMTD type 1 cases involve duplication of this gene (Szigeti & Lupski, 2009).

As an anesthesia provider, one must be fully aware of the patient presenting with this particular neuromuscular disorder and develop the most appropriate anesthesia plan. Some of the chief concerns regarding general anesthesia in a patient with a neuromuscular disease relates to the decision of whether to use NMBs and the ability to fully reverse their paralytic effects, all while planning a timely emergence and extubation from anesthesia. These concerns are applicable to all patients with CMTD, and even more so as the patient's disease severity worsens. It is also important to keep in mind the variability of symptoms and the possibility of atypical symptom presentation. For example, "several rare types of CMTD have phrenic nerve involvement which may cause diaphragmatic weakness, even in early stages of the disease"

(Schmitt & Munster, 2006, p. 987). Questions regarding patient safety arise due to a variety of concerns with the use of a NMB. The following concerns can be avoided by omitting the use of a muscle relaxant: (a) the concern for adequately reversing the patient; (b) the patient being too weak to spontaneously breathe or unable to obtain adequate tidal volumes needed to meet extubation criteria; (c) a potentially prolonged intubation period and/or a prolonged post-anesthesia care unit (PACU) stay due to respiratory issues; and (d) the risk of recurarization. Therefore, the purpose of this independent study is to determine whether the omission of NMBs results in fewer post-operative problems, such as muscle weakness, respiratory depression, reintubation, etc., in CMTD patients who are undergoing general anesthesia.

Case Report

A 38-year-old, 58 kilogram (kg), 165 centimeter (cm) tall Caucasian male, with a body mass index (BMI) of 21.3, presented for left extracorporeal shock wave lithotripsy. The patient had an allergy to Percodan. Medical history included hypertension, melanoma, decreased lung capacity, osteopenia, leukocytopenia, poorly controlled gastroesophageal reflux disease (GERD), Charcot Marie Tooth disease type 1A (CMT1A), migraine headaches without aura, nonischemic cardiomyopathy, sleep-related hypoventilation due to neuromuscular disorder, sleep apnea controlled with the use of bi-level positive airway pressure (BIPAP) at night, kidney disease and nephrolithiasis. Surgical history included a spinal fusion, extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy with stone manipulation and retrograde. Current medications included oxycodone-acetaminophen (Percocet), ciprofloxacin, butalbital-acetaminophen-caffeine (Fioricet), metoprolol succinate (Toprol XL) and cholecalciferol (vitamin D). The patient had no history of anesthetic complications with previous general anesthesia.

Prior to the patient's arrival, the anesthesiologist (MDA), certified registered nurse anesthetist (CRNA) and student registered nurse anesthetist (SRNA) discussed the patient's case and decided to use an endotracheal tube (ETT) due to the patient's poorly-controlled GERD. The anesthesia team made a collaborative decision to avoid the use of a NMB due to the patient's advanced CMTD. Evidence of the patient's advanced disease included the following: the patient had been wheelchair-dependent for several years, presented with numbness and weakness in his upper and lower extremities, and had extensive upper and lower limb deformities. Potential risks for giving a muscle relaxant to a patient with such advanced CMTD include the potential for weakness upon emergence, the possibility of being unable to obtain/maintain adequate tidal volumes, and the risk for a prolonged intubation (Smith, Minkin, Lindsey & Bovino, 2015). Other concerning past medical history included his decreased lung capacity, a spinal fusion, and sleep-related hypoventilation due to CMTD, requiring the use of BIPAP at night. Another apprehension regarding the patient's care was the location of the facility. The patient was having the procedure at a same day surgery center. This facility is limited in resources for handling high-acuity cases, such as patients that would require post-operative ventilation. If the patient should require post-operative ventilation, he would require transport via ambulance to the local hospital.

According to the American Society of Anesthesiologists, the patient was given a level 3 physical status due to his health conditions; his airway was assessed as a Mallampati class II. Preoperative vital signs were as follows: blood pressure 125/87 mm Hg, heart rate 94/min, respiratory rate 16/min, pulse oximetry 98% on room air, and temperature 98.4 degrees Fahrenheit. Upon auscultation, lung sounds were clear and equal bilaterally with regular S1 and S2 heart sounds.

The patient received 1 milligram (mg) midazolam intravenously (IV) and 50 micrograms (mcg) of fentanyl IV in the pre-op holding room due to pain and anxiety. An hour later, the patient was transported to the operating room, where he was carefully assisted and positioned onto the lithotripsy table per patient comfort. Upon confirmation of proper positioning, with particular attention paid to the patient's head and neck, the SRNA attached the electrocardiogram, non-invasive blood pressure cuff and finger pulse oximetry monitors, and pre-oxygenated the patient via facemask at 10 liters per minute (LPM). The induction medications were administered intravenously for a rapid sequence intubation (RSI) which included the following: 2 mg versed, 100 mcg fentanyl, 40 mg of 2% lidocaine and 200 mg propofol. As indicated earlier, it was decided by this anesthesia team to avoid the use of a NMB, to prevent any potential respiratory complications from occurring. During intubation, the MDA applied manual in-line stabilization (MILS), due to the patient's history of a spinal fusion and cricoid pressure was applied by the CRNA due to the patient's history of poorly controlled GERD. Once MILS was applied, the SRNA used a GlideScope size 4 blade to visualize the patient's vocal cords. With the GlideScope, only the left arytenoid was visualized. A 8.0 mm stiletted ETT did not easily pass through the patient's vocal cords and the patient's oxygen saturation rate quickly dropped to the 70s. The SRNA removed the GlideScope and ETT and manually bagged the patient, which brought his oxygen saturation level back up to the 90s. The patient was then given another bolus of 200 mg propofol IV, and a second attempt was made, this time using a size 3 GlideScope blade. The SRNA obtained a grade 2 Cormack and Lehane view and successfully intubated the patient with an 8.0 mm ETT. Bilateral breath sounds were auscultated and the patient was placed on the mechanical ventilator in a volume mode with a respiratory rate of 12 and a tidal volume of 550 milliliters (mL). The ETT was secured in place

and sevoflurane was started with end-titration concentrations of 1.2 – 2.1 throughout the case. The patient's oxygen level was decreased to 50% fraction of inspired oxygen (FiO₂) and 50% air. Two grams of cefazolin IV was administered for the preoperative antibiotic.

After the second bolus of propofol and a successful intubation, the patient's non-invasive blood pressure cuff had the following readings over a ten-minute period: 80/60 mm Hg, 72/51 mm Hg, 83/52 mm Hg, 70/45 mm Hg, 90/57 mm Hg, 81/48 mm Hg, 83/45 mm Hg all before returning to ideal blood pressures with mean arterial pressures (MAP) greater than 60 throughout the remainder of the case. The above, less-than-ideal blood pressure readings were treated accordingly and at the appropriate time with a total of 300 mcg phenylephrine IV, given as 3 doses of 100 mcg IV each, and 10 mg ephedrine IV.

Nearing the end of the procedure, the SRNA made appropriate ventilation adjustments and the patient began to spontaneously breathe. The SRNA discontinued sevoflurane and placed the patient on 100% FiO₂. Total procedure time was 167 minutes. The patient quickly met extubation criteria, evidenced by taking spontaneous breaths with a regular respiratory rate, achieving tidal volumes greater than 400 ml and moving all extremities to command. The patient was suctioned and extubated without complication. Oxygen was applied at four LPM of oxygen via nasal cannula for transport. The OR staff carefully assisted the patient off the lithotripsy table onto his bed and he was transferred to the PACU for further monitoring.

Upon arrival to the PACU, the patient was still drowsy from the anesthesia. However, he was able to answer all questions appropriately and denied having any pain or nausea. Later in the PACU, the patient did complain of pain and was treated accordingly, with two tablets of oxycodone-acetaminophen (Percocet) 5-325 mg which the patient took orally. The patient's same-day surgery PACU stay was complicated only by anxiety about being discharged. He

remained in the PACU for over four hours and was discharged later that day with no further complaints.

Literature Search Strategies

The author conducted an online literature search to address the PICO question of concern, which started by logging into UND's Harley E. French Library of the Health Sciences website. The author first accessed PubMed and selected the "full text articles" link. The first search term used was "Charcot-Marie-Tooth disease." This was very generic and produced over 3,000 articles. The author then utilized the Medical Subject Headings (MeSH) database in pursuit of search terms most applicable to the results desired for the PICO question. Further searches used Charcot-Marie-Tooth disease, with the following additional terms: anesthesia implications, anesthesia management, neuromuscular blockers, neuromuscular blockade, recurarization, general anesthesia and respiratory distress. The search terms Charcot-Marie-Tooth disease and neuromuscular blockers yielded the most relevant results to the PICO question, yielding 19 results. Of the 19 articles, 16 were in full text and only 14 were in English. Of the 14 articles, 8 were pertinent to the topic. A further investigation included a review of the reference sections of the 8 pertinent articles. This yielded 3 additional articles, for a total of 11 articles.

Review of Literature

CMTD and its subtypes continue to be investigated. CMT1A, an autosomal dominant disease, is the most commonly occurring subtype (de Carvalho Alcantara, et al., 2015). Other clinical subtypes with varying symptom presentations include CMTD type 2, Dejerine-Sottas neuropathy, congenital hypomyelinating neuropathy and Roussy-Levy syndrome (Szigeti & Lupski, 2009). This study focuses on CMTD and, when appropriate, CMT1A.

The primary objective of this independent project is to determine if patients with CMTD can be safely given a NMB without the risk of respiratory complications, or if the safer alternative would be to avoid the use of NMBs altogether. The following specific topics will be discussed: (a) diagnosis of CMTD; (b) pathophysiology of CMTD; (c) management of CMTD; (d) predicting respiratory muscle weakness; (e) concern regarding the use of NMBs in patients with CMTD; (f) cases where NMBs were used; (g) prolonged neuromuscular blockade; and (h) cases where NMBs were avoided or reduced doses were given.

Diagnosis of CMTD

Genetic testing confirms the diagnosis of CMTD. The most common gene affected is known as peripheral myelin protein 22 (Kulkarni, Sayed, Garg & Patil, 2015). Authors Szigeti and Lupski (2009) found that this particular gene is duplicated in over 70% of CMTD type 1 cases. CMTD has several potential inheritance patterns, with the most common being the autosomal dominant demyelinating form. Other less common inheritance patterns include: autosomal dominant, autosomal recessive or X-linked (Szigeti & Lupski, 2009).

Two major classifications of CMTD exist. The first involves demyelination and is characterized by slower-than-normal nerve conduction velocity (NCV), defined as nerve conduction speed less than 38 meters per second (m/s). The second major classification affects axons, resulting in reduced muscle action potentials with either normal or subnormal NCV. More invasive diagnostic tests such as nerve biopsies may be utilized if results from genetic testing do not lead to a molecular diagnosis. For example, sural nerve biopsies can identify both CMTD classifications, with results exposing: (a) demyelinating biopsies that show segmental demyelination; or (b) axonal biopsies that show axonal loss. (Szigeti & Lupski, 2009). Signs of slowed nerve conduction velocity is seen as early as two years of age, is established in most

patients between three and five years of age and does not continue to change after childhood (Kulkarni, Sayed, Garg, & Patil, 2015). Furthermore, the degree of slowed nerve conduction velocity does not correlate with overall disease severity (Kulkarni, Sayed, Garg, & Patil, 2015).

Pathophysiology of CMTD

The pathophysiology of CMTD is complex, with various degrees of severity and symptom presentation. Pareyson and Marchesi (2009) found the following:

CMTD is caused by mutations in genes that encode proteins with different locations, including compact and non-compact myelin, Schwann cells, and axons, and that are involved in very different functions, ranging from compaction and maintenance of myelin to cytoskeleton formation, axonal transport and mitochondrial metabolism. (p. 654)

Regardless of the specific defect affecting the myelin or axon, the result is an “axonal degenerative process that, in most cases, mainly involves the largest and longest fibers” (Pareyson & Marchesi, 2009, p. 654). Molecular genetic research has identified over 25 genes associated with CMTD, resulting in multiple different subtypes and various degrees of symptom onset, presentation and rate of progression (Pareyson & Marchesi, 2009). The onset of symptoms for both CMTD type 1 and type 2 occur within the first or second decade of life. Cardinal features of CMTD include motor deficits and sensory signs and symptoms. The first noticeable motor symptoms involve muscle weakness, wasting in the feet, and bone deformities such as high-arched feet and hammertoes. Both motor and sensory symptoms start distally in the feet, with disease progression in an ascending pattern. Once the disease has progressed proximally to the lower 1/3 of the thigh, the hands start to become affected, with natural progression to the forearms and further up (Pareyson & Marchesi, 2009). Common complaints include muscle weakness, numbness and tingling in the feet with signs of advancement involving

the same symptoms of weakness, numbness and tingling in the patient's hands. Other sensory symptoms include "loss of vibration and joint position sense followed by decreased pain and temperature sensation in a stocking and glove distribution" (Szigeti & Lupski, 2009, p. 704). Further symptoms indicative of CMTD include restless leg syndrome, difficulty walking and running, complaints of tripping and/or twisting of the ankle, foot drop, hand tremors, cold feet and frequent muscle cramping in the feet or legs (Pareyson & Marchesi, 2009). Asymmetrical involvement of symptoms correlates with advanced age and severity of neuropathy and is seen in CMT1A (Kulkarni, Sayed, Garg & Patil, 2015).

Although CMTD predominantly presents with peripheral neuropathies, the following features are also consistent with the disease: sensorineuronal hearing loss, adie's pupil, ophthalmoparesis, facial weakness, vocal cord paralysis, bulbar signs, hyperkeratosis and juvenile glaucoma. In addition, 20% of patients with CMTD also have scoliosis. Overall, only a few patients experience difficulty walking and become wheelchair-bound, but all patients with CMTD will present with some noticeable symptoms by the age of 60. (Pareyson & Marchesi, 2009; Szigeti & Lupski, 2009).

Management of CMTD

Although there is no cure for CMTD, physical therapy and occupational therapy may help patients maintain their range of motion and functional level. These patients will likely end up requiring orthotic devices, assistive equipment and multiple surgeries to correct skeletal deformities. Common surgical procedures include soft-tissue surgery, such as plantar fasciotomy, tendon transfers and tendon releases, or osteotomies on the calcaneal, metatarsal and tarsal bones as well as various types of joint fusions (Pareyson & Marchesi, 2009).

Pain is another feature of CMTD. The most common areas of pain include the feet, lower extremities and lumbar region of the spine (Pareyson & Marchesi, 2009). Symptomatic inflammatory pain typically responds to nonsteroidal anti-inflammatory drugs (NSAIDs), while neuropathic pain can be treated with gabapentin, pregabalin or a tricyclic antidepressant such as amitriptyline (Szigeti & Lupski, 2009). Caffeine and nicotine use is discouraged, as they can aggravate fine tremors. (Szigeti & Lupski, 2009).

Predicting Respiratory Muscle Weakness

Upon completion of a field study involving 40 participants with CMTD, authors Nathanson, Yu, and Chan (1989) concluded that proximal upper limb involvement may predict whether patients will develop respiratory dysfunction in the future. Their study showed that 8 of the 15 participants positive for respiratory muscle weakness also had proximal upper limb muscle weakness. On the contrary, only 3 of the 25 participants with normal respiratory muscular function had proximal upper limb muscular weakness. These authors also determined that the measurements of functional vital capacity (FVC), postural change in FVC and maximal inspiratory pressure (MIP) while sitting up are all useful in evaluating respiratory muscle weakness (Nathanson, Yu & Chan, 1989).

In a more recent research study, 16 adult patients with CMT1A were randomly selected from an outpatient CMTD clinic and compared against two control groups with the purpose of evaluating respiratory function (de Carvalho Alcantara, et al., 2015). Each patient was assessed with the Charcot-Marie-Tooth neuropathy score (CMTNS), a tool consisting of nine assessments related to signs, symptoms and neurophysiology. Each assessment is scored 0 – 4 points, with a total score ranging from 0 – 36 points. Patients with a CMTNS score of 10 or less are classified as mild, those with a score 11 – 20 are moderate and those with a score greater than 20 are

classified as severe (Murphy, et al., 2011). For a better understanding of disease severity in the 16 patients, 12 were able to walk by themselves, 3 had a history of foot or ankle surgery and required the use of orthotics or walking devices, and 1 patient, with a known CMTNS score of 34, was wheelchair-bound (de Carvalho Alcantara, et al., 2015).

During this study a spirometry exam found restrictive respiratory dysfunction only in the wheelchair-bound patient, who had the greatest symptom severity. The most consistent abnormality was related to respiratory pressures; maximal expiratory pressure (MEP) was reduced in 12 patients while maximal inspiratory pressure (MIP) was reduced in 5 patients. The authors found that MEP was the most consistently decreased value among the 16 patients, indicating compromise of the abdominal and internal intercostal expiratory musculature. In comparison, the diaphragmatic and external intercostal inspiratory musculature was less affected, as evidenced by fewer patients with decreased MIP. (de Carvalho Alcantara, et al., 2015).

As stated previously, the main underlying cause of neurological dysfunction in CMTD patients is related to axonal degeneration of nerve fibers (Pareyson & Marchesi, 2009). De Carvalho Alcantara, et al. (2015) concluded that “axonal degeneration of intercostal and phrenic nerves is responsible for the abnormalities detected in respiratory function of CMT1A patients” (p. 1168). Another predictor of respiratory function is the measurement of vital capacity in the supine and upright positions and comparison of these values. For example, a vital capacity decrease of greater than 25% in the supine position is suggestive of significant diaphragmatic dysfunction in patients with a neuromuscular disorder (Fromageot, et al., 2001).

Neurological disability measured by CMTNS demonstrates a significant correlation to the degree of respiratory compromise. However, de Carvalho Alcantara et al. (2015) were unable to determine which specific CMTNS scores are indicative of respiratory insufficiency.

Concern Regarding the Use of NMBs in Patients with CMTD

Neuromuscular blockers should be used with caution in patients with neuromuscular disorders (Nagelhout, 2014). Similar to other neuromuscular diseases, the use of succinylcholine for induction in patients with CMTD may result in severe hyperkalemia, as these patients may have an “up-regulation of extrajunctional acetylcholine receptors, which render them more likely to have an exaggerated release of potassium upon exposure to succinylcholine” (Heller & Marn, 2015, p. 2). Antognini (1992) reasoned that because “denervation is one of the most potent predisposing factors for release of potassium after exposure to succinylcholine” (p. 399), the use of succinylcholine in CMTD patients is typically avoided. In situations – such as in an emergency – in which the use of succinylcholine cannot be avoided, using a “small defasciculating dose of a non-depolarizing muscle relaxant may lessen the potassium release from diseased muscle” (Antognini, 1992, p. 399). If hyperkalemic reactions do occur, effects can range from subtle EKG changes or peaked T waves to malignant arrhythmias and even cardiovascular collapse (Antognini, 1992).

Due to classical symptoms of generalized muscle weakness in patients with CMTD, the concern for respiratory dysfunction is present and may be enhanced with the use of non-depolarizing NMBs, resulting in prolonged muscle weakness (Heller & Marn, 2015). Additionally, the use of volatile anesthetics can further potentiate the effects of a non-depolarizing NMB (Schmitt & Munster, 2006). Reports from the early 1980’s also mention paradoxical worsening of a patient’s neuromuscular blockade when reversal agents were given, which further complicates the use of non-depolarizing NMBs (Greenberg & Parker, 1992).

Cases Where NMBs Were Used

Several case studies have been reported in which succinylcholine and non-depolarizing NMBs were safely used in the CMTD patient population. In two separate studies, the first involving five children and the second involving five adult patients with CMTD, 0.2 mg/kg of mivacurium IV was used for intubation without redosing, and all ten patients were found to have a near-normal response and recovery from mivacurium (Schmitt, Wick & Munster, 2006; Schmitt & Munster, 2006).

In a left foot tendon transfer involving a 16-year-old female, 0.1 mg/kg vecuronium IV was used for intubation and redosed several times, for a total of 13 mg (0.26 mg/kg IV) vecuronium IV. Atropine and neostigmine were used to reverse the NMBs, and resulted in a normal, or even faster-than-normal recovery (Baraka, 1997).

In a case report of a six-year-old male who presented to a rural facility for emergent repair of a left humerus fracture, the anesthesiologist was “concerned about the underlying disease and the potential for requiring postoperative ventilatory support” (Greenberg & Parker, 1992, p. 305). The facility was unable to provide such services, therefore the patient was transferred to a nearby facility with adequate resources. The patient received vecuronium for an RSI. Glycopyrrolate and neostigmine were given intravenously at the end of the procedure to reverse the NMB. After showing signs of “adequate strength (i.e., sustained tetanus, TOF, head lift) and appropriate alertness (i.e., eyes open, responds to commands)” (Greenberg & Parker, 1992, p. 305), the patient was extubated and discharged the next day without complications. Greenberg and Parker (1992) also did a retrospective review of children under 16 years with CMTD who underwent surgery in the previous 10 years. Seven patients underwent nine

procedures; both depolarizing and non-depolarizing NMBs were used with no indication of a prolonged block or respiratory complications (Greenberg & Parker, 1992).

In Antognini's chart review (1992) of 86 patients who underwent 139 procedures requiring general anesthesia, succinylcholine was used in 56 surgeries while a non-depolarizing agent was used in 50 surgeries. Twenty-six out of 50 patients that were administered a non-depolarizing agent were also given a NMB reversal agent. In regards to symptom severity, almost 80% of the patients had disease involvement of all four extremities. Antognini (1992) reported 19 patients complained of postoperative weakness, but stated "no complications occurred as a result of muscle relaxants, i.e., objective weakness, prolonged intubation or reintubation" (p.400). Antognini (1992) concluded, "although succinylcholine has been considered to be contraindicated in this disease, no complications occurred from its use in these patients who had chronic symptoms" (p. 400).

Prolonged Neuromuscular Blockade

One case report found a patient with CMTD received a NMB and experienced a prolonged neuromuscular block. Pogson, Telfer, & Wimbush (2000) published the case report of a 59-year-old male who presented to a hospital for surgical correction of a fractured fibula and tibia. The patient's previous surgical history included an L5-S1 discectomy and insertion of a hip screw into the left femur with no complications noted in either case. Induction medications consisted of 10 mg morphine, 350 mg thiopental and 0.11 mg/kg vecuronium, all administered IV. Maintenance anesthesia consisted of a mixture of 1% isoflurane with a 2:1 ratio of nitrous oxide and oxygen. A peripheral nerve stimulator was not used throughout the case. The surgery lasted 115 minutes; emergence was initiated by placing the patient on 1.0 FiO₂ and administering 2.5 mg neostigmine IV with 0.5 mg glycopyrrolate IV for the reversal of

neuromuscular blockade. “Spontaneous diaphragmatic breathing with an adequate tidal volume followed and the tracheal tube was removed uneventfully although the patient was not fully conscious” (Pogson, Telfer, & Wimbush, 2000, p. 915). The patient was placed on oxygen via facemask and taken to recovery, where he became “anxious and distressed, with signs of incomplete reversal of neuromuscular block, including twitching of the limbs and uncoordinated movements. Oxygenation and ventilation remained normal” (Pogson, Telfer, & Wimbush, 2000, p. 915). At this time, a peripheral nerve stimulator was used. Train-of-four stimuli to the right ulnar nerve revealed one palpable twitch. The patient had obvious muscle wasting of his forearm, therefore TOF was applied to his right facial nerve, where one twitch was visible. The patient was given 2.5 mg neostigmine IV and within two minutes of its administration, the patient had four visible twitches in his facial muscles. The patient remained in the hospital for overnight observation; his condition improved and required no further interventions (Pogson, Telfer, & Wimbush, 2000).

Cases Where NMBs Were Avoided or Reduced Doses Were Given

Heller and Marn (2015) report a case in which the surgical and anesthesia team avoided the use of a NMB in a CMTD patient. The patient, a 15-year-old male with acute appendicitis, presented for emergent laparoscopic appendectomy. Upon learning of his medical history, the surgical and anesthesia team thoroughly discussed how to provide optimal surgical conditions. Succinylcholine presented concern for hyperkalemia, and use of a non-depolarizing NMB was concerning for the possibility of prolonged weakness. The team chose a total intravenous anesthetic (TIVA) due to the increased risk of malignant hyperthermia in a CMTD patient. Ultimately, an RSI was completed with the following medications given intravenously, 0.2 mg glycopyrrolate, 3 mg/kg propofol and 5 mcg/kg remifentanyl for a smooth induction and

intubation. Anesthesia was maintained with a propofol infusion at 175 mcg/kg/min and a remifentanyl infusion at 0.2 – 0.4 mcg/kg/min. At the end of the surgery, the maintenance infusions were stopped, the patient met extubation criteria and was extubated without complications. Post-operative analgesia was obtained with fentanyl, ketorolac and acetaminophen, all given intravenously. The surgeon reported “laparoscopic surgical conditions were identical to standard management with neuromuscular blockade” (Heller and Marn, 2015, p. 2). Although Heller and Marn’s case report provides documentation of a successful TIVA without the use of NMBs in an emergent laparoscopic appendectomy, the authors recommend more research be done before generalizations in this patient population can be made (Heller and Marn, 2015).

Another case report involved a 74-year-old male who was first diagnosed with CMTD as a child. The patient had fallen and hit his chin on the bathroom sink; he presented to the emergency room with a bilateral mandibular fracture requiring surgical repair. “Because the patient had serious motor and sensory neuropathy associated with his disease, special anesthetic and surgical recommendations had to be considered before he underwent general anesthesia” (Smith, Minkin, Lindsey & Bovino, 2015, p. 1). The surgical and anesthesia team carefully considered the use of muscle relaxants as well as the most effective surgical approach. In patients with CMTD, who already suffer from extensive muscle weakness, an ideal surgical plan should be “minimally invasive and avoid prolonged periods of immobility,” as it is “difficult to rehabilitate muscles already damaged or atrophied” (Smith, Minkin, Lindsey & Bovino, 2015, p. 2). Induction drugs given for the 65 kg male included 2 mg midazolam IV, 200 mg propofol IV, 200 mcg fentanyl IV and a one-time dose of 20 mg of rocuronium IV. A GlideScope facilitated placement of a 7.0 nasal RAE in the patient’s right nostril, without complications. A standard

weight-based induction dose of rocuronium is 0.6 – 1.2 mg/kg IV, so a standard induction dose for this 65 kg patient is 39 – 78 mg IV. Therefore, the 20 mg of rocuronium IV the patient received may be considered a sub-therapeutic dose of muscle relaxant (Nagelhout, 2014). After 30 minutes, the patient had 4 strong twitches when assessed with the train-of-four (TOF) monitor; no neuromuscular reversal agent was given to the patient at the end of the case, with a surgical time of 150 minutes. Once he was able to achieve adequate tidal volumes (>550 ml), have a regular respiratory rate (>10 breaths/minute), and able to follow verbal commands, including lifting his head for more than 5 seconds, the patient was extubated. The patient was discharged home the next day with no reported complications. (Smith, Minkin, Lindsey & Bovino, 2015).

Smith, Minkin, Lindsey & Bovino (2015) additionally noted “because of the progressive nature of the morbidities associated with CMTD, these patients undergo general anesthesia at a higher frequency than that of the general population” (p. 2). A review of the patient’s recent surgical history revealed right and left hip replacements, in 2002 and 2010, under general anesthesia. The authors reported no complications with the surgery, although they did not identify whether NMBs were used in the case. Symptoms of CMTD place these patients at a higher risk for falling, which is a major contributing factor for requiring general anesthesia. This patient was no exception, as a “serious gait disturbance secondary to a lack of lower extremity muscle tone, pes caves, and claw toes predisposed him to frequent falls” (Smith, Minkin, Lindsey & Bovino, 2015, p. 1917.e2). The patient’s mandibular fracture was his third serious traumatic event directly related to a fall, with the first and second events being hip fractures requiring replacement (Smith, Minkin, Lindsey & Bovino, 2015).

Discussion

Although research regarding the anesthetic management of patients with CMTD is limited – and occasionally conflicting – it appears patients with CMTD can safely receive succinylcholine and non-depolarizing NMBs. Hyperkalemia is well-reported in patients with nerve injuries and other polyneuropathy diseases similar to CMTD, so although there is some evidence of safe administration of succinylcholine, avoidance is recommended due to this risk (Pogson, Telfer, & Wimbush, 2000). Limited research on this matter exists, which may in itself be supportive of the use of NMBs in this patient population, and likely “suggests that anesthetic complications are rare” (Smith, Minkin, Lindsey & Bovino, 2015). One potential reason for conflicting results among this patient population is the variation in symptom presentation, disease progression and severity; patients present for surgery all along the continuum (Pogson, Telfer, & Wimbush, 2000). This variability also makes it extremely difficult, if not impossible, to make generalizations for patients with CMTD.

One should take into account several considerations when caring for a patient with CMTD. The patient should receive a thorough pre-op examination, with careful attention paid to the respiratory and cardiovascular systems. The patient’s baseline deficits should be carefully documented. The incidence of respiratory dysfunction ranges from 0 – 30 % and is usually restrictive in nature, due to weakness of the intercostal and diaphragmatic musculature (Smith, Minkin, Lindsey & Bovino, 2015). CMTD is a slowly progressive disease, therefore one should carefully review previous anesthesia records and dates, keeping in mind the patient’s disease may have progressed considerably since his/her previous surgery. Development of a safe anesthetic plan may require deviations from previous plans.

Train-of-four monitoring of the facial nerve may be the most beneficial monitoring medium with utilization of NMBs in CMTD patients. Pogson, Telfer, & Wimbush (2000) report “conduction velocity in the facial nerve is usually less affected than the ulnar or peroneal nerve in CMTD patients” (p. 916). Therefore, the facial nerve may be the most useful for monitoring, titrating a patient’s neuromuscular block, and assessing for adequate reversal of NMB agents. Schmitt, Wick & Munster (2006) stated the two main reasons to use the facial nerve are “(i) cranial nerves are normally spared in CMTD; and (ii) relaxation of eye muscles corresponds well to the diaphragm” (p. 186).

When intubated, CMTD patients should be extubated awake and only after meeting extubation criteria. Standard extubation criteria includes the following parameters: hemodynamically stable, normothermia, patient’s ability to maintain a patent airway as evidenced by intact cough and gag reflex and appropriate level of consciousness, ability to follow commands, adequate muscular strength as evidenced by a firm hand grip, strong head lift sustained for more than 5 seconds, sustained oxygen saturation levels above 90%, regular respiratory rate and adequate tidal volumes, approximately 5 – 7 ml/kg (Nagelhout & Plaus, 2014). Post-anesthesia care unit (PACU) nurses should have specific education regarding the patient’s medical history and needs, with special emphasis on the importance of vigilant monitoring of the patient’s respiratory status (Greenberg & Parker, 1992).

Other factors to keep in mind, as seen in the case report of the 74-year-old male with a mandible fracture: not only are CMTD patients more likely than the general population to present for surgery, but they are also at a higher risk for falling, due to lower extremity and foot abnormalities which further increase their likelihood of requiring surgery to repair trauma from falls (Smith, Minkin, Lindsey & Bovino, 2015). Lastly, patient positioning is extremely

important. Their limbs may be deformed and may require extra time for padding and optimal positioning, and any degree of nerve compression may exacerbate their current level of neuropathy (Smith, Minkin, Lindsey & Bovino, 2015).

Application of the Literature Review to the Case at Hand

Research supports the actions and decisions made in the presenting case. Concern regarding the use of a NMB was the most significant issue at hand and was thoroughly addressed by the anesthesia team and surgeon. The team completed a thorough preoperative evaluation, reviewed the patient's past medical history, and determined the current stage of disease to be fairly advanced. One significant difference between this case and results of the literature search is the grave severity of disease with which this patient presented. Only one other patient mentioned in the literature reviewed was wheelchair-bound. The team made the most appropriate and safest decision after considering: (a) the type of procedure – an extra-corporeal shock wave lithotripsy (ESWL); and (b) the setting – a same-day surgery facility which lacks the resources to provide postoperative ventilatory support. The ESWL procedure in itself does not necessitate the patient to be paralyzed; however, the patient had a history of poorly-controlled GERD which required the use of an ETT. The up-regulation of acetylcholine receptors and potential response of hyperkalemia precluded the use of succinylcholine, as seen in the literature. The two remaining options were to use a non-depolarizing NMB or to administer increased doses of induction agents to avoiding the use of a NMB altogether. The team determined the latter option to be more appropriate, due to the patient's extensive disease and concern for a prolonged neuromuscular block without adequate resources to provide prolonged postoperative ventilation. Administration of higher doses of induction agents provided enough relaxation to safely secure

the patient's airway, without requiring a NMB. No respiratory or other complications occurred during the procedure itself or in the post-operative period.

The case report of a 15-year-old male who presented with acute appendicitis was most similar to the presenting case. The anesthesia and surgical teams discussed the use of muscle relaxants and collectively made the decision to proceed with laparoscopic appendectomy without the use of neuromuscular blockade (Heller & Marn, 2015). One of the two most recent case studies reportedly avoided the use of a muscle relaxant (Heller & Marn, 2015) while the other used a reduced intubating dose of rocuronium (Smith, Minkin, Lindsey & Bovino, 2015) due to the same concerns that are expressed with this present case. Overall, research supports the anesthesia and surgical teams' decisions in the case presented here.

Limitations and Assumptions

One must consider the limitations and assumptions of the evidence supporting or contesting the use of NMBs in CMTD patients. One of the main limitations of the present study is that the literature review yielded studies with relatively low-level evidence. The evidence presented originated from controlled trials without randomization, case-control studies, cohort studies, or systematic reviews. In effect, most of the evidence found in the literature search was either level III or level IV evidence, with systematic reviews ranked even lower, as level V evidence (Melnik & Fineout-Overholt, 2005).

The variability in onset, age of diagnosis, and rate of disease progression in CMTD also presents a limitation, as the patients in each study do not all display the same disease severity, but rather represent multiple points along the CMTD continuum. The variability in number of disease subtypes and potential genes affected further complicates this matter, making it extremely difficult to establish generalizations for this patient population.

There is also a great deal of variation in how studies were conducted and results measured. Most of the studies reported small sample sizes, ranging from 40 – 86 participants on the higher end to only 5 participants on the lower end. Some studies used volatile anesthetics, which are known to potentiate the effects of non-depolarizing NMBs (Schmitt & Munster, 2006), while other studies omitted the use of volatile anesthetics. In addition, one cohort study used surveys, which may present biased information since surveys are only returned from those who are willing and able to respond. It is possible that complications and deaths may be under-reported and that data may be incomplete (Antognini, 1992). Lastly, studies varied as to which nerve was used for TOF neuromuscular monitoring and how the neuromuscular block was measured.

Conclusion

In conclusion, the use of NMBs must be evaluated on a case-by-case basis, taking into consideration the extent of the patient's disease and type of surgery performed. Instances may occur where a CMTD patient may be better off without a neuromuscular blocking agent. Discussion between the anesthesia team and surgeon is important in determining optimal surgical conditions and the safest route of anesthetic administration. There are few descriptions in the literature regarding the anesthetic management of CMTD patients and more research must be done to safely and accurately make generalizations for the anesthetic management of patients with CMTD (Pogson, Telfer & Wimbush, 2000).

Research has shown that children and adults with CMTD who undergo general anesthesia for surgery recover within the normal, expected time frame when given a standard intubating dose of a NMB (either depolarizing or non-depolarizing), as compared to normal, healthy patients without CMTD. Furthermore, the possibility of pulmonary complications should be

considered in all CMTD patients, and their anesthetic management should be adjusted according to the needs of the individual patient. Increased awareness of CMTD, its anesthesia implications and practice recommendations will only benefit anesthesia providers and CMTD patients while minimizing risk, mortality and morbidity.

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Charcot Marie Tooth Disease and the use of Neuromuscular Blockers

Madalyn Muldoon, SRNA




Introduction— What is Charcot Marie Tooth disease?

- Charcot Marie Tooth disease (CMTD)
 - Chronic and progressive neurological disease
 - Affects both motor and sensory nerves
 - Prevalence: 1 in 2,500 people (0.04%)
 - Diagnosis: genetic testing
 - Over 25 genes associated with CMTD
 - Most common gene affected
 - Peripheral myelin protein 22
 - Autosomal dominant is most common
 - Onset: first or second decade



Wang et al. (2011)


(Furber, 2007; Gell, 2011; Furber & Mathew, 2009); (Shen, & Moxley, 2009); & Dign & Luyck, 2009)



Two major classifications of CMTD


- 1. Axonal degeneration of peripheral nerve fibers
 - Reduced muscle action potentials
 - Normal or subnormal nerve conduction velocity (NCV)
 - Type 1A: Can affect intercostal and phrenic nerves
 - Respiratory function abnormalities
- 2. Segmental demyelination of peripheral nerve fibers
 - Slower-than-normal nerve conduction velocity (NCV)
 - Nerve conduction speed < 38 meters/second

(deCaesteke, Atarbas, et al., 2011); (Furber & Mathew, 2009), p. 86




Symptoms of CMTD

- **Peripheral muscle weakness**
 - Hands, feet and diaphragm
- **Motor deficits**
 - Wasting of the feet
 - Bone deformities
 - high-arched feet, hammertoes
- **Sensory loss of extremities**
 - Numbness & tingling in the hand and feet
 - Loss of vibration and joint position
 - Decreased pain and temperature sensation



Furber & Mathew, (2009)

(Furber & Mathew, 2009); (Shen & Moxley, 2009); & Dign & Luyck, 2009)



Charcot Marie Tooth Disease

- Muscle wasting of legs & lower third of the thigh
- Foot deformities






(Furber & Mathew, 2009)

(Furber & Mathew, 2009); (Dign & Luyck, 2009)




Case Information

- 38 year old
- 58 kg
- 165 cm
- Male
- BMI: 21.3
- NKDA
- Procedure
 - Extracorporeal shock wave lithotripsy (ESWL)
- Location
 - Same-day surgery facility



Case Information cont'd

<p>Past Medical History</p> <ul style="list-style-type: none"> - CMTD type 1A - HTN - Melanoma - Decreased lung capacity - Osteopenia - Leukocytopenia - GERD - Migraine headaches - Nonischemic cardiomyopathy - Sleep-related hypoventilation - Sleep apnea - Kidney disease - Nephrolithiasis 	<p>Surgical History</p> <ul style="list-style-type: none"> • Spinal fusion • ESWL • Ureteroscopy • Wheel-chair dependent • No previous anesthetic complications with GA
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Pre-operative Evaluation

- **ASA: 3**
- Mallampati Class II
- BP: 125/87
- HR: 94
- RR: 16
- O2 Sats: 98% on RA
- Temp: 98.4 degrees F
- Lungs clear, bilaterally
- Heart: RRR

- **Current Medications**
 - Percocet
 - Ciprofloxacin
 - Fioricet
 - Metoprolol Succinate
 - Vitamin D






Photo © A. (2013)




Anesthetic Course

<p>Holding Room:</p> <ul style="list-style-type: none"> - 1 mg Midazolam IV - 50 mcg Fentanyl IV <p>Induction: RSI</p> <ul style="list-style-type: none"> - 2 mg Midazolam IV - 100 mcg Fentanyl IV - 40 mg Lidocaine IV - 200 mg Propofol IV - MILS - Cricoid pressure - GlideScope 4 	<p>2nd Attempt:</p> <ul style="list-style-type: none"> - 200 mg Propofol IV - MILS - Cricoid pressure - GlideScope 3 - 8.0 cuffed ETT - Sevoflurane 1.2-2.1 <p>Additional Drugs:</p> <ul style="list-style-type: none"> - 2 g Ancef IV - 4 mg Dexamethasone IV - 4 mg Zofran IV - 300 mcg Phenylephrine IV - 10 mg Ephedrine IV - 1200 mL R
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Emergence & PACU


- **Emergence**
 - Sevoflurane discontinued
 - 100% FIO2
 - Quickly met extubation criteria
 - 4 LPM O2 via nasal cannula
- **PACU**
 - Denied pain, n/v
 - No complications
 - Discharged home later that day



Discussion— Risks with Administering Neuromuscular Blockers

- CMTD neurological dysfunction: **Degeneration of nerve fibers**
- Depolarizing NMB: Succinylcholine
 - Up-regulation of acetylcholine receptors
 - Hyperkalemia
- Non-depolarizing NMB
 - Concern for respiratory dysfunction is present
 - Prolonged muscle weakness
 - Weakness upon emergence
 - Poor tidal volumes
 - Risk for a prolonged intubation
 - Recurarization


[Anisimich, 1992][Shimizu & Paine, 1992][Jain & Mar, 2005, p. 2][Shih & Mui-oh, 2005]



Cases Where NMB Safely Used

- 5 children: 0.2 mg/kg mivacurium IV
 - Normal recovery
- 5 adults: 0.2 mg/kg mivacurium IV
 - Normal recovery
- 16 yr female: 0.1 mg/kg vecuronium IV
 - Redosed several times, total of 13 mg vecuronium IV
 - Reversed with atropine and neostigmine
 - Normal recovery
- 6 yr male: vecuronium for an RSI
 - Reversed with glycopyrrolate and neostigmine
 - Normal recovery


[Shimizu & Paine, 1992, p. 303][Shih & Mui-oh, 2005][Shih & Mui-oh, 2005]



Cases Where NMB Safely Used

- Retrospective review
 - 7 pts under the age of 16 had 9 procedures
 - Both depolarizing and non-depolarizing NMB were used
 - No complications
- Chart review
 - 86 pts underwent 139 procedures
 - Succinylcholine was used in 56 cases
 - Non-depolarizing agents were used in 50 pts
 - 26/50 pts were reversed
 - 19 pts complained of weakness
 - “No complications occurred as a result of muscle relaxants, i.e. objective weakness, prolonged intubation or reintubation”


[Angeles et al., 1992, p. 400; [Dantony & Pater, 1992, p. 305.]



Prolonged Neuromuscular Blockade

- 59 yr old male
- Fractured fibula and tibia
- Induction
 - 10 mg morphine IV
 - 350 mg thiopental IV
 - 0.11 mg/kg vecuronium IV
- Peripheral nerve stimulator was not used
- 115 min. case
- Reversal
 - 2.5 mg neostigmine & 0.5 mg glycopyrrolate
- PACU
 - Twitching of his limbs, uncoordinated movements
 - 1 twitch, 2.5 mg neostigmine, 4 twitches


[Pogor, Wic, & Winkler, 2009.]



Case Where NMB Avoided

- 15 yr old male
- Emergent laparoscopic appendectomy
- RSI
 - 0.2 mg glycopyrrolate IV
 - 3 mg/kg propofol IV
 - 5 mcg/kg remifentanyl IV
- TIVA
 - Propofol infusion: 175 mcg/kg/min
 - Remifentanyl infusion: 0.2–0.4 mcg/kg/min
- “Laparoscopic surgical conditions were identical to standard management with neuromuscular blockade”


[Dellor and Mann, 2011.]



Research Findings

- The use of succinylcholine and non-depolarizing NMB can be safely used in patients with CMTD
- Suggested to avoid succinylcholine
 - Risk of hyperkalemia
- If need to use succinylcholine, use a defasciculating dose
 - May lessen the release of K from diseased muscle
- Limited research: anesthetic complications are rare


[Angeles et al., 1992, p. 398; [Pogor, Wic, & Winkler, 2009; [Dent, Mink, Under & Soane, 2005.]



Recommendations for Patients with CMTD

- Thorough pre-op exam
 - Respiratory dysfunction: 0 – 30%
- Document patient’s baseline deficits
- Review previous anesthesia records and dates
- TOF monitoring of the facial nerve
- Undergo GA at a higher frequency
- Higher risk of falling
 - Lower extremity and foot abnormalities
- Avoid nerve compression with positioning


[Pogor, Wic, & Winkler, 2009, p. 302,303, 304, 305; Under & Soane, 2005.]



Recommendations Cont’d

- Minimally invasive surgical plan
- Avoid prolonged periods of immobility
 - Difficult to rehabilitate damaged/atrophied muscles
- Extubation awake with extubation criteria met
 - Hemodynamically stable
 - 4 strong twitches with sustained tetany
 - Achieve adequate tidal volumes
 - Sustained head lift
 - Follow verbal commands
- Educate PACU: monitor respiratory status


[Daghrain & Pines, 2014; [Dent, Mink, Under & Soane, 2005.]



Conclusion

- More research must be done regarding the anesthetic management of CMTD patients
- Children & adults with CMTD recover within the normal, expected time frame when given a standard intubating dose of a NMB
- Use caution with patients of advanced disease
- Evaluate the use of a NMB on a case-by case basis

(Pogson, Telfer & Wimbush, 2000)



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Thank You!

Are there any questions?

