PERIOPERATIVE MANAGEMENT OF CHILDREN WITH NEUROMUSCULAR DISORDERS: PROSPECTIVE STUDY

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Running head: Perioperative management in neuromuscular patients

ABSTRACT

Background: Children with neuromuscular diseases (NMDs) often display altered vital functions mainly respiratory muscle weakness which increase the risk of postoperative pulmonary complications after general anesthesia or sedation. Non-invasive ventilation (NIV) associated with cough assistance can successfully reduce these complications. The aim of this study was to report our experience with a peri-operative protocol that consists in using NIV combined with mechanical insufflation-exsufflation (MI-E) to improve the postoperative outcome of children with NMD.

Methods: To this end, we conducted a multicenter, observational study on consecutive pediatric patients with NMDs undergoing anesthesia or sedation for surgical and diagnostic procedures from December 2015 to December 2018 in 13 Italian hospitals.

Results: We found that 89% of the 167 children included in the study (mean age 8 y), were at risk of respiratory complications, due to the presence of at least one respiratory risk factor. In particular, 51% of them had preoperative technology dependence, while 25% displayed severe dysphagia. Average hospital length of stay (LOS) was 12 (±17) days. Despite the complexity of these children, only 26 patients developed intraoperative surgical complications, whereas 14 developed postoperative respiratory complications. No patient needed tracheostomy. The occurrence of long-term mechanical ventilation (MV), severe scoliosis or dysphagia in the preoperative period and the use of cough assistance or invasive MV (IMV) longer than 24 h in the postoperative period were all associated with prolonged hospital LOS.

Conclusion: A carefully planned, multidisciplinary approach for the perioperative management of pediatric NMD patients can help prevent and resolve postoperative complications.

1. INTRODUCTION

Recent advances in the management of children with neuromuscular diseases (NMDs) have improved patient overall survival.[1,2] This has however led to a concomitant increase in the frequency of corrective surgical procedures (e.g., orthopedic surgery and feeding tube placement) needed to improve these children's quality of life[3-8]. To make matters worse, these children may present with altered vital functions, such as respiratory muscle weakness, dysphagia, scoliosis and cardiac involvement, which increase the risk of surgical procedures, requiring general anesthesia or sedation. In particular, in the postoperative period, prolonged impairment of neuromuscular functions and suppression of the central respiratory drive can compromise the already limited pulmonary reserve of these patients, leading to acute respiratory failure (ARF)[9-13]. Moreover, some anesthetic agents can trigger life-threatening reactions, such as malignant hyperthermia (MH) and rhabdomyolysis[14-17].

Even though childhood NMDs comprise a diverse group of illnesses, such as anterior horn cell diseases, motor neuropathies and myopathies, they all require a similar perioperative management.[11] In this regard, recommendations for anesthesia and perioperative management of these patients have been recently issued[9-13,18]. In particular, non-invasive ventilation (NIV) combined with mechanical insufflation-exsufflation (MI-E) (Figure 1) can successfully resolve upper airway obstruction, hypoventilation and airway secretion retention, thereby avoiding prolonged intubation, postoperative respiratory complications (PPCs) and tracheostomy[9-13,18,19]. However, these recommendations are mainly consensus statements derived from expert opinion rather than evidence based guideline.

The primary aim of this study was to assess the post-operative outcome of pediatric patients affected by NMDs which require anesthesia for surgical or radiological procedures. In particular, we studied the incidence of perioperative complications and the hospital and ICU LOS. In addition, because there is a low number of patients described in scientific literature that use NIV and airway clearance techniques (i.e., manual assisted cough and MI-E) in the postoperative period the secondary aim of this study is to strengthen the scientific evidence of this perioperative management.

2. METHODS

2.1 Patients and data collection

By conducting a multicenter, observational study, we aimed to describe the effect of a perioperative standardized protocol on the postoperative outcome of children with NMDs. For this purpose, 167 consecutive pediatric patients with NMDs undergoing anesthesia or sedation for surgical and diagnostic procedures were enrolled in the study. Data were collected from December 2015 to December 2018 in 13 Italian hospitals and uploaded on a password-protected web database. All collected variables are available as online supporting information.

NMD was defined as a range of conditions that impair the functioning of the muscles, either directly, being pathologies of the voluntary muscle, or indirectly, being pathologies of spinal cord, peripheral nervous system or neuromuscular junctions. Brain diseases (e.g., cerebral palsy) are not considered “neuromuscular” diseases. Unknown neuromuscular disease was defined as neuromuscular disorders of unknown etiology.

The institutional protocol of the coordinating center (protocol No. 473, November 4th, 2015), also adopted by the other collaborating centers, was reviewed and approved by the Ethics Committee on Clinical Investigations. The local ethics committees in all contributing centres approved our protocol. The study was performed in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. We enrolled in the study only those patients whose parents or legal guardian provided written authorization for the use of their medical records for research. This study was supported by the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI), the Italian Pediatric and Neonatal Society of Anesthesia and Resuscitation (SARNePI) and the Italian Duchenne Parent Project.

2.1 Protocol

All patients were treated pre- and postoperatively according to a standardized protocol aimed to identify patients at risk of PPCs through respiratory assessment. The preoperative respiratory tests measured gas exchange, lung volume and cough effectiveness. Furthermore, swallowing and scoliosis were evaluated by Gilardeau dysphagia score[19] and Cobb angle, respectively.

Patients with NMDs were considered at high risk of PPCs if at least one of the following preoperative findings was present: *i)* hemoglobin saturation in room air (SpO_2) < 95%; *ii)* diurnal or nocturnal hypercapnia; *iii)* history of weak cough; *iv)* prolonged respiratory illnesses or recurrent pneumonia; *v)* long-term MV; *vi*) manual and/or MI-E use at home; *vii*) forced vital capacity (FVC) < 50% of the predicted; *viii)* preoperative

peak cough flow (PCF) < 270 L/min; *ix)* Gilardeau dysphagia score > 1; *x)* Cobb angle ≥ 50°.

Patients identified at risk of PPCs were trained in NIV and airway clearance techniques before intervention, if they were naïve to these techniques. All high-risk patients were extubated to NIV and MI-E. An Intensive Care Unit (ICU) was always accessible for the management of the postoperative course.

The preoperative evaluation also included discussions with patients and relatives regarding their attitudes toward prolonged MV dependency, tracheostomy and advance directives. In addition, patients with myopathies underwent careful assessment of heart function as well as optimization of cardiac therapies before anesthesia or sedation. In particular, an electrocardiogram and echocardiogram were performed before anesthesia, if they had not already been done in the previous 12 months.

The choice of anesthetic drugs, opioids and non-depolarazing muscle relaxants as well as the type of postoperative pain management were left to the anesthesiologist's discretion.

Statistical Analysis

Data analysis was performed using R software version 3.6.1. Continuous variables were expressed as mean ± standard deviation (SD), while dichotomous variables were represented as absolute number and percentage. Multiple regressions were performed to estimate the relationship between the length of stay (LOS) (dependent variable) and some relevant pre-, intra- and postoperative predictive independent clinical variables. Since LOS can be measured as number of days spent in a hospital, we chose a

Poisson-like model as the correct approach for multiple regression analysis. As we expected data to be over-dispersed, we opted for a negative binomial model. Appropriateness of negative binomial regression over Poisson regression was calculated by likelihood ratio (LR) tests, which were also used for global tests of model fit using the null model (i.e., regression model without independent variables) as reference.

The incidence rate ratio (IRR), which estimates the effect of a certain exposure or its relative risk or odds ratio if such occurrence is rare, was calculated as the incidence rate of the exposed proportion of the population divided by the incidence rate of that of the non-exposed proportion. *P* values of < 0.05 were considered statistically significant.

2. RESULTS

3.1 Patient characteristics

A total of 202 neuromuscular pediatric patients undergoing anesthesia or sedation for surgical or diagnostic procedures were screened. Thirty-five of them were excluded due to incompleteness of the data. Thus, the final number of children enrolled in the study was 167.

Preoperative NMD diagnoses are shown in the online supplement (Table S1). Myopathies were present in 40% of patients. Spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) were the most frequently found illnesses (22% and 11%, respectively). Of note, it is important to highlight that only three patients with DMD are younger than 12 years old. For 35% children, diagnosis was still unknown at hospital discharge. The high number of unknow diagnosis can be explained by fact that

in 35 cases out of 59 patients underwent muscle biopsy to clarify the diagnosis and the diagnostic process usually requires a long time.

Demographic data are summarized in Table 1. Half of the patients (51%) had at least one preexisting medical technology support at home (Table 1). Of them, 80 were dependent on long-term MV or cough assistance. More than one-third of the study participants reported using an MI-E device, which was the most frequently employed device for airway clearance. Fifty-seven children were dependent on MV, while 75% of them were non-invasively ventilated. Thirty-one patients received MV at night only, while 17 children underwent MV at night plus a few hours during the day (less than 20 h per day). In 9 cases, MV was administered for more than 20 h per day. Among mechanically ventilated children, 47 (82%) were also using MI-E device. Only 4 children requiring MI-E device were tracheostomized.

3.2 Anesthesia/sedation requirement and pre-anesthetic management

All surgical and diagnostic procedures are described in Table S2. In particular, our cohort of patients required anesthesia or sedation mainly for orthopedic surgery, muscle biopsies and surgical interventions increasing the need for technology support (e.g., gastrostomy placement and tracheostomy). Almost one-third of patients underwent orthopedic procedures. Gastrostomy and muscle biopsies were performed in 23% and 21% of cases, respectively. Surgery time lasted more than 1 h in 51% of patients, while in 24% was longer than 3 h.

According to pre-operative evaluation, 149 (89%) patients had increased risk of PPCs due to the presence of at least one respiratory risk factor and 62 (37%) patients had 3 or more of them. Among them, 48% were dependent on long-term MV and/or cough assistance, 27% were hypercapnic, and 25% had severe dysphagia (Table 2). Forty-eight percent of children had a history of weak cough or prolonged respiratory illnesses. Most children were not able to perform spirometry or peak cough flow measurement.

After preoperative evaluation, 12 patients, who were completely naïve to NIV and cough assistance, were trained in these techniques, while other 36 children were retrained. In all cases, the caregivers (in most cases the parents) were also included in the training program. Finally, 47 patients were admitted to ICU or High Dependency Unit before the procedures.

3.3 Anesthetic technique and airway management

Difficult intravenous cannulation was reported in 48 cases. The majority of children underwent total intravenous anesthesia (TIVA) (Table 3). Neuromuscular blockade was performed only in 22% of cases. In 10 children, sedation was associated with regional anesthesia.

Difficult endotracheal intubation was reported in 37% of 82 intubated patients, with difficult direct laryngoscopy observed in 9 children—i.e., Cormack classification III in 7 cases and Cormack classification IV in 2 cases. Moreover, 14 patients were

intubated by bronchoscopy, 6 through a video laryngoscope and 1 by inserting a Frova catheter.

Postoperative pain management included opioid-based analgesia in 38% of patients. Finally, 86% received acetaminophen or ibuprofen, while opioids were never used following gastrostomy, muscle biopsy, MRI and bronchoscopy (Table 3).

3.4 Perioperative complications, postoperative care and hospital length of stay

No lethal intraoperative complications related to anesthesia were described. Relevant intraoperative bleeding occurred in 26 patients, who were transfused. Among them, massive bleeding was reported in three patients, and intraoperative blood recovery was performed in 10 cases.

After surgery, 100 (60%) patients were admitted to ICU, 41 of whom have been admitted to ICU before the surgery.

NIV and MI-E were administered to 92 children at risk of PPC following tracheal extubation (Table 4).

Only 27 (16%) children had postoperative complications, which included 14 cases with illnesses of the respiratory system (Table 4). ARF, secretion retention and atelectasis were the most frequently reported complications. In the group of patients with PPCs, 13 underwent non-invasive respiratory assistance post-operatively (7 MI-E, 4 NIV and 2 NIV associated with MIE), whereas 8 of them were also subjected to invasive mechanical ventilation (IMV). Eight of these patients were preoperatively

trained in using NIV and/or MI–E. Among children with PPCs, 12 were admitted to ICU. None of them was tracheostomized or died in the postoperative period.

Only three patients died during hospitalization, all of them more than 30 days after surgery. The cause of death was ARF in two cases, while one patient died of septic shock. Two of them had a treatment escalation limitation plan (TELP) in the preoperative period. All of them were ventilated at home more than 20 h/day, with a Gilardeau dysphagia score of 4. One of them had already been tracheostomized.

As we observed prolonged ICU (8 ±14 days) and hospital (12 ± 17 days) LOS in the course of our study, we performed multiple regression to characterize the relationship between hospital LOS and some of the most relevant preoperative, intraoperative and postoperative predictive independent clinical variables. The preoperative determinants “long-term MV”, “Cobb angle higher than 50°” and “presence of dysphagia” were found to be associated with hospital LOS, while no significant relationship with the variable “presence of cough assistance” was detected (Table 5). Hospital LOS was significantly associated with general anesthesia, major spine surgery and urgent surgery (Table 5). Patients with cough assistance in the postoperative period were 38 percent more likely to stay in the hospital time than those who did not require cough assistance. The locations where patients were hospitalized after the procedure were also statistically related to patients’ hospital LOS (i.e., surgical ward and ICU compared to Day Surgery Unit). Lastly, as expected, IMV longer than 24 h was also significantly associated with increased hospital LOS. Of note, in our model, PPCs were not significantly associated with hospital LOS (Table 5).

4. DISCUSSION

Children with NMDs can sometimes present with respiratory muscle weakness, which increases the risk of PPCs13. In the preoperative evaluation of these patients, it is therefore very important to identify children requiring NIV and airway clearance techniques following extubation to prevent respiratory complications.9,10,11,12 In the adult population, the respiratory assessment mainly consists of spirometry and peak flow measurement. However, these tests are particularly difficult to perform in preschool children, a population where careful assessment of pulmonary complications along with recording history of previous respiratory events is highly recommended 12. Vital capacity and peak flow measurement should be measured in all patients with NMDs who are capable to perform them, generally from six years of age [12]. As a consequence, clinical history is fundamental in the preoperative evaluation of a children population. Indeed, only a minority of our patients were able to complete spirometry and peak flow measurement. On the other hand, half of them had a history of weak cough or multiple respiratory illnesses. Moreover, half of the children had medical device dependence at home. Lastly, over a quarter of our patients were trained or retrained in NIV or MI-E preoperatively, and more than half of the study population used these devices in the postoperative period.

The clinical outcomes of our cohort are very encouraging. PPCs were observed in 14 patients, and none of them were tracheostomized or died postoperatively. Despite the complexity of these children, the positive outcomes may be due to the peculiarities of the medical centers where they were treated, particularly to the presence of trained teams skilled in the use of pediatric NIV and airway clearance techniques13. Another

important aspect to consider was the availability of a pediatric ICU to manage a potentially prolonged postoperative course.9,6 In fact, sixty percent of our patients were admitted to ICU after surgery.

Our results confirm the findings of previous studies describing the postoperative use of NIV and MI-E in NMD patients. 4,6,21, 19Bach et al. illustrated five children with flaccid scoliosis secondary to muscular dystrophy or SMA who had very high pulmonary risk, who were preoperatively trained in the use of NIV and MI-E prior to spinal fusion. All patients were extubated by the third postoperative day to NIV despite continuous ventilator dependence. No patient developed any postoperative pulmonary complications or required a tracheotomy19. Khirani et al. revealed the absence of PPCs in 13 NMD children with severe spinal deformities first trained in NIV and MI-E preoperatively and then using these devices after tracheal extubation.6 Birnkrant et al. described the postoperative use of NIV in two patients with severe DMD after PEG tube placement, preventing PPC from occurring.4 Finally, Marchant et al. reported a case of a child with SMA undergoing single-stage posterior spinal fusion successfully treated with MI-E and nasal NIV, avoiding sputum retention and tracheostomy.21

Despite the severe degree of baseline disability among our study cohort, documentation of resuscitation status or care limitation was only present in 3 cases—one do-not-resuscitate order and two refusals to perform tracheostomy. This finding is similar to what previously reported by Graham et al., who found that this documentation was present only in 4% of cases in a population of 25 children with spinal muscular atrophy (SMA) (10 type I, 8 type II, 7 type III), accounting for 56 general and regional anesthesia cases.5 This may reflect poor documentation practice or, more likely, a barrier

surrounding the discussion of advanced decision-making between medical providers and their families.22

Although acute heart failure has been described during major surgical procedures in patients with myopathies,23 no cardiac complications were documented in our series. Similar data were reported by Muenster et al. in a review of 232 cases of patients with DMD undergoing orthopedic surgery.7

The prolonged hospital LOS observed in our study may be ascribed to the extremely high-risk population analyzed. Protracted LOS was also reported in a study describing anesthesia and perioperative management of 56 cases of children with SMA, showing a mean LOS of 29 (±29) days for SMA type 1 patients and, respectively, of 8 (±5) and 6 (±6) days for SMA type 2 and type 3 patients.5

Our multiple regression analysis, aimed to determine a possible relationship between hospital LOS and some other relevant independent clinical variables, indicates that prolonged hospital LOS is more likely to occur in the presence of long-term MV, severe scoliosis or dysphagia preoperatively or when patients undergo cough assistance or IMV longer than 24 h postoperatively. These findings are in line with previously published data.9-14

Of note, the postoperative use of morphine was not associated with variations in hospital LOS. This observation may be explained by the well-established role of continuous NIV / MI-E in avoiding suppression of cough and ventilation caused by postoperative narcotics.10,11,12 Even though some authors have expressed concern that a compromised ventilation reserve may limit the use of morphine for relief of

postoperative pain,13 in our study, despite the frequent use of morphine for postoperative pain relief, none of our patients required reintubation due to opioid respiratory depression, in good agreement with previous publications.5,6 Thus, our data suggest that if no other therapeutic option is available for the relief of postoperative pain —i.e, wound infiltration with local anesthetics, transverse abdominis plane (TAP) block, peripheral nerve block or epidural analgesia—NIV and MI-E may be used in combination with morphine to avoid PPCs. Moreover, concerns regarding wound dehiscence should not obviate the use of cough assist technology, as MI-E only causes a relatively mild increase in abdominal pressure.23 Fittingly, none of our patients experienced wound dehiscence after the use of cough assist technology.

As expected, spine surgery25,26 and urgent surgery27 prolonged the hospital length of stay. General anesthesia was also associated with increased hospital LOS confirming that in NMD patients with decreased pulmonary function regional anesthesia should be preferred whenever possible.9,10,12,13 Indeed, general anesthesia in these patients may exacerbate respiratory failure due to marked sensitivity to anesthetic agents, opioids and neuromuscular blocking drugs.,13,28

With regard to anesthetic strategies in patients with NMDs it is recommended that non-depolarazing muscle relaxants should only be used in selected cases and at low doses. Treated patients should then be subjected to continuous monitoring of neuromuscular function, and there should be complete antagonism at the recovery from anesthesia.13,29,30 Our data show that neuromuscular blockade was only employed when strictly required, as suggested by the literature.13 Indeed, it was performed in just 40% of cases undergoing general anesthesia. Moreover, all cases underwent short-

acting neuromuscular blockade with rocuronium administration, which was antagonized before extubation, even though continuous neuromuscular function monitoring was only reported in 18% of patients receiving neuromuscular-blocking drugs.

Another important concern is related to life-threatening reactions triggered by the anesthetic agents. In particular, succinylcholine must be avoided in all categories of NMDs. Furthermore, the use of inhaled anesthetics is generally regarded as at high risk of malignant MH or acute rhabdomyolysis in myopathic patients.15,13,16,17,31 In our study, TIVA was given to the majority (77%) of cases performing general anesthesia, and no lethal intraoperative complications related to anesthesia were described.

In good agreement with the literature, we recorded difficult intubation in 37% of our intubated children highlighting that direct laryngeal intubation may be difficult in NMD patients. This may due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine.5,10,24,32. According to our findings two others retrospective studies on SMA5 and DMD7 patients undergoing general anesthesia showed difficulty in performing direct laryngoscopy and reported the frequent use of fiberoptic-assisted endotracheal intubation.

Our study has some limitations. The first limitation is the absence of a control group. However, NIV and MI-E are used on a routine basis in our hospitals as a first-line treatment in the extubation process for all children with NMDs. Thus, a prospective randomized controlled trial would be difficult to realize due to ethical reasons. Secondly, we enrolled a limited number of children in this study, which is, however justified by the fact that NMDs are rare diseases.12. Finally, we included in the study patients with a

very heterogenous group of NMDs which undertaken different surgical or radiological procedures. Consequently, it may be difficult to generalize the efficacy of our peri-operative protocol.

In conclusion, the present study shows that our perioperative protocol may allow preventing and successfully treating PPCs in NMD pediatric patients requiring anesthesia or sedation, even when their level of baseline complexity is quite high. In particular, when patients with severe respiratory muscle weakness were trained preoperatively in the use of NIV and mucus clearance techniques and were extubated directly to NIV, we found that PPCs only occurred in 8% of patients and that post-procedure tracheostomy could be avoided. In addition, we found that 1) the presence of long-term MV, severe scoliosis or dysphagia in the pre-operative period, 2) the presence of spine surgery, urgent surgery and general anesthesia, and 3) the use cough assist technology or IMV longer than 24 h postoperatively were all associated with prolonged hospital LOS. Finally, our findings confirm that perioperative management of NMD patients should be carefully planned and based on a multidisciplinary approach.

Further and larger prospective studies are needed to strengthen the scientific evidence of the efficacy of this peri-operative protocol evaluating single cohort of NMD patients which undertake surgical procedures of similar nature.

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