Airway management and perioperative adverse events in children with mucopolysaccharidoses and mucolipidoses: A retrospective cohort study

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Abstract
Background: Children suffering from mucopolysaccharidoses (subtypes I, II, III, IV, VI, and VII) or mucolipidoses often require anesthesia, but are at high risk for perioperative adverse events. However, the impact of the disease subtype and the standard of care for airway management are still unclear.

Aims: This study aimed to assess independent risk factors for perioperative adverse events in individuals with mucopolysaccharidoses/mucolipidoses and to analyze the interaction with the primary airway technique implemented.

Methods: This retrospective study included individuals with mucopolysaccharidoses/mucolipidoses who underwent anesthesia at two high-volume centers from 2002 to 2016. The data were analyzed in a multivariate hierarchical model, accounting for repeated anesthesia procedures within the same patient and for multiple events within a single anesthesia.

Results: Of 141 identified inpatients, 67 (63 mucopolysaccharidoses and 4 mucolipidoses) underwent 269 anesthesia procedures (study cases) for 353 surgical or diagnostic interventions. At least one perioperative adverse event occurred in 25.6% of the cases. The risk for perioperative adverse events was higher in mucopolysaccharidoses type I (OR 8.0 [1.5-42.7]; P = .014) or type II (OR 8.8 [1.3-58.6]; P = .025) than in type III. Fiberoptic intubation through a supraglottic airway was associated with the lowest risk for perioperative adverse events and lowest conversion rate. Direct laryngoscopy was associated with a significantly higher risk for airway management problems than indirect techniques (estimated event rates 47.8% vs 10.1%, OR 24.05 [5.20-111.24]; P < .001). The risk for respiratory adverse events was significantly higher for supraglottic airway (22.6%; OR 31.53 [2.79-355.88]; P = .001) and direct laryngoscopy (14.8%; OR 14.70 [1.32-163.44]; P = .029) than for fiberoptic intubation through a supraglottic airway (2.1%).
1 | INTRODUCTION

Mucopolysaccharidoses (MPS) and mucolipidoses (ML) are rare progressive hereditary lysosomal storage diseases which cause an accumulation of substrates in various body tissues. The particular substrate stored and the predominant storage sites vary according to the genotype and determine the phenotype of the specific MPS subtype (I, II, III, IV, VI, and VII). MPS has an incidence of approximately 3.4-4.5 per 100,000 live births. Children suffering from MPS and related diseases often require anesthesia for surgical or diagnostic interventions. Registry data show that almost half of children with MPS I undergo two or more surgeries until the age of four. Many clinical manifestations of MPS/ML, especially progressive airway obstruction, restrictive lung disease, thorax deformity, adenotonsillar hypertrophy, obstructive and central sleep apnea, macroGLOSSIA, cervical spinal canal stenosis, dens hypoplasia, atlantoaxial instability, spinal cord compression, and skeletal dysplasia, have important implications for anesthesia.

The reported incidence of serious adverse events in pediatric anesthesia varies between 0.14% (North American registry data) and 5.2% (prospective European multicenter study). A 30-day inhospital mortality rate of 0.1% has been found in children undergoing anesthetic procedures. Respiratory complications are the most frequently reported adverse events. However, perioperative morbidity and mortality are dramatically higher among children with MPS/ML. In MPS type I, a perioperative morbidity of up to 30% and a 30-day risk of death per procedure of approximately 0.7% have been reported.

Airway management is challenging in children with MPS/ML. Fiberoptic intubation through a supraglottic airway and videolaryngoscopy are frequently used as indirect intubation techniques with high success rates in children with difficult airways. Although it is recognized that MPS/ML poses unique anesthesia-related challenges, the standard of care for airway management in these children still remains unclear, and the impact of the disease subtype and primary airway approach on perioperative adverse events is unknown.

This study aimed to assess independent risk factors for perioperative adverse events—such as airway management problems and respiratory and cardiocirculatory events—in individuals with MPS/ML and to analyze the interaction with the primary airway technique implemented.

2 | PATIENTS AND METHODS

This retrospective, two-center study was approved by the Ethical Committee of the Medical Board of Hamburg, Germany (reference number PV4832, October 28, 2014).

2.1 | Data acquisition

The electronic patient management system (SAP BW™; SAP SE & Co. KG) was systematically screened for pediatric or adult inpatients with a diagnosis of MPS or ML within the study period (April 2002-January 2016). Identified records were checked against records from the MPS outpatient clinic of the University Medical...
Center Hamburg-Eppendorf. The medical records of each identified patient were systematically reviewed for anesthesia procedures. Individuals with MPS or ML who underwent general anesthesia, regional anesthesia, or monitored anesthesia care at either of the study centers (University Medical Center Hamburg-Eppendorf or AKK Altona Children's Hospital, Hamburg) were included, thus comprising the study cohort. Patients' baseline characteristics, medical history, comorbidities, procedural and anesthesia-related data, and outcome data, were collected from electronic medical records (Soarian™ Health Archive, Release 3.04 SP12, Siemens Healthcare) and anesthesia charts.

### 2.2 Anesthesia procedures (study cases)

A standardized anesthesia protocol was not implemented during the study period, and management was left to the discretion of the supervising anesthesiologist.

The analysis was based on the following assumptions and definitions.

For general anesthesia, the primary airway technique implemented was either bag-mask ventilation, supraglottic airway, or tracheal intubation. Tracheal intubation was facilitated by direct laryngoscopy, indirect intubation techniques, or fiberoptic intubation through a supraglottic airway (FOI SGA). Indirect intubation techniques, such as conventional fiberoptic intubation techniques (FOI CON), video laryngoscopy, or rigid fiberscopes, were implemented in order to visualize laryngeal structures and to guide tracheal tube positioning. The category “FOI CON” subsumes any fiberoptic nasal or oral intubation prior to or after the anesthesia induction without routine use of a supraglottic conduit. A laryngeal mask was used as a supraglottic conduit to guide fiberoptic intubation during FOI SGA. Videolaryngoscopy was typically enabled by C-MAC™ (Karl Storz) in both centers. Cases of local anesthesia performed by a surgeon with solely “anesthesia standby” were excluded from the outcome analysis. Cases that did not necessitate a secured airway (eg, regional anesthesia, procedural sedation, and analgesia or solely bag-mask ventilation) were not included in the multivariate model.

### 2.3 Outcome measures

The primary outcome measure was perioperative adverse events, defined as follows.

- Airway management problems: clearly documented severe airway complications, difficult bag-mask ventilation, ≥3 attempts with the primary airway technique, Cormack-Lehane classification (C/L) III° or IV°, C/L II° with additional severe complications during airway management or high air leakage clearly documented over a long time period during ventilation, conversion to a different airway technique (rescue technique), or abandoned anesthesia.
- Respiratory adverse events: clearly documented, severe respiratory complication, hypoxia (drop of peripheral oxygen saturation <90% for >1 minute or any below 80%), hypercapnia (endtidal or arterial partial carbon dioxide pressure >50 mm Hg for >1 minute or any above 60 mm Hg), aspiration, reintubation, airway obstruction, or reduced lung compliance accompanied by low tidal volumes and/or differences between peak inspiratory and end-expiratory airway pressure ≥25 mbar, severe laryngospasm, or postextubation stridor requiring any therapeutic intervention.
- Cardiocirculatory adverse events: clearly documented, unstable hemodynamic conditions, resuscitation, requirement of multiple or high doses of drugs (eg, atropine, epinephrine, or norepinephrine) for severe bradycardia or unexpected severe hypotension not directly linked to a surgical complication (eg, bleeding episode).
- Secondary outcomes were as follows.
  - Conversion rate: frequency of the transition to a different (rescue) airway technique or abandoned anesthesia in relation to the total number of airway techniques.
  - Emergency tracheotomy.
  - Cardiac arrest requiring resuscitation.

Outcome measures were recorded during anesthesia and in the early postoperative period until discharge from the postanesthesia recovery unit or admission to an intensive care unit. Anesthesia charts were independently checked for perioperative adverse events by three assessors (TD, MAP, MP). Adverse events were designated based on a consensus decision.

### 2.4 Statistical analysis

The primary aim of the study was to identify independent risk factors for perioperative adverse events in individuals with MPS/ML. It was an exploratory study. Continuous data are presented as medians with interquartile ranges. Categorical data are presented as frequencies (percentage values in relation to the number of valid data).

### 2.5 Multivariate multilevel regression model

As a first step, potentially eligible factors and covariates for the multivariate analysis were identified through clinical considerations and literature research. The primary airway techniques were subcategorized as either supraglottic airway, direct laryngoscopy, indirect intubation techniques, or FOI SGA. MPS subtypes IV and VI and ML were clustered in order to create the category “very rare diseases.”

A multivariate three-level mixed-effects logistic regression model was fitted in order to identify risk factors for perioperative
adverse events. In order to account for repeated anesthesia procedures within the same patient and for multiple events within a single anesthesia episode, two nested random effects were added. Four factors (disease subtype, subcategory of primary airway technique, predicted difficult airway, and gender) and five covariates (age, American Society of Anesthesiologists physical status classification, emergency procedure, duration of anesthesia, and indication for anesthesia) were included in the model as fixed effects. Additionally, a variable identifying the type of adverse event and the interaction term between this variable and the predictor "primary airway technique" was included in the model. The final model results from a complete case analysis.

Results are presented as odds ratios (OR) with 95% confidence interval (CI). The reference category for calculation of the ORs for categorical variables was based on clinical considerations. The subgroup with the lowest rate of perioperative adverse events was favored. The interaction and subgroup contrast between event subcategories (airway management problems, cardiocirculatory, or respiratory events) and primary airway approaches were visualized by calculating the marginal predicted probability with the corresponding 95% CI. Differences were considered significant with an alpha error of less than 5% (P-value <.05). Nominal P-values were reported. Statistical analysis was performed using STATA version 15.0 (StataCorp).

3 | RESULTS

3.1 | Study cohort

A total of 141 inpatients suffering from either MPS or ML were identified during the study period. Within this group, we identified 67 patients (the "study cohort") who underwent 274 anesthesia procedures at the two medical centers, 63 with MPS, and four with ML. Five procedures had to be excluded, as anesthesia charts were unavailable. This left a total of 269 anesthesia procedures (the "study cases") for analysis. Overall, patients underwent 353 surgical or diagnostic interventions. Frequently, two or more procedures were combined within a single anesthesia episode (Table 1). Ten cases were excluded from the analysis of perioperative adverse events, as only a local anesthesia was implemented by a surgeon (eg, ophthalmological procedures).

The study cohort predominantly included individuals with MPS types I (35.8%), II (16.4%), III (28.3%), IV (4.5%), VI (6.0%), and some individuals with ML (6.0%). Table 1 shows the age range of our cohort. The types of procedure recorded were either surgical (63.7%), dental (6.5%), interventional (4.2%), or diagnostic (25.5%). Twenty children suffering from Hurler syndrome (MPS I H) underwent hematopoietic stem cell transplantation. Furthermore, three children with Hurler and two children with Scheie (MPS I S) syndrome solely received enzyme replacement therapy (ERT). Lastly, two children received ERT after graft failure.

| TABLE 1 Patient characteristics and procedures |
|-----------------------------------------------|
| Patients (n = 67)                             | n (%) | median [IQR] |
| Sex [male/ female]                           | 44/ 23 |
| Mucopolysaccharidoses (type: eponymous name) |       |
| I: Hurler syndrome (I H)                     | 24    |
| II: Hunter syndrome                          | 11    |
| III: Sanfilippo syndrome                     | 19    |
| IV: Morquio syndrome                         | 3     |
| VI: Maroteaux-Lamy syndrome                  | 4     |
| Mucolipidoses                                | 4     |
| Type II: I-cell disease                      | 2     |
| Type III: Pseudo-Hurler polydystrophy        | 1     |
| Intermediate type                            | 1     |
| Procedures (n = 353)                         |       |
| Diagnostics (most frequently MRI)            | 90    |
| Interventions (eg, arthrography, bone marrow biopsy, or bronchoscopy) | 15 |
| Dental surgeries/ interventions              | 23    |
| Surgery                                      | 225   |
| Ear, nose, and throat                        | 49    |
| Orthopedic and spine surgery                 | 88    |
| General, visceral, and thoracic surgery      | 20    |
| Ophthalmologic surgery                       | 22    |
| Neurosurgery                                 | 10    |
| Vascular surgery and catheter implantation   | 33    |
| Others                                       | 3     |

Note: Continuous variables are presented as median [interquartile range (IQR)]; categorical data are presented as frequencies (percentage values); MRI, magnetic resonance imaging; * multiple planned procedures within a single anesthesia episode; the dataset of this analysis is complete without any missing values. Of note, the study cohort includes 10 cases which involved only local anesthesia performed by a surgeon (eg, ophthalmological procedures), these cases were included in the descriptive analysis (Table 1 and 2) but not in the outcome analysis (Table 4, Figures 1 and 2).
3.2 Anesthesia and airway management

In most cases, general anesthesia was used (92.6%). A total of 280 airway approaches were documented; 244 primary airway techniques were used (Tables 2 and 3). Conversion to a rescue airway approach was required 36 times, as the primary or subsequent technique was regarded as insufficient. In two of these cases, anesthesia and surgery were abandoned due to failed airway attempts. Of note, FOISGA was not attempted in these two cases. The conversion rates and pathways, if the attempted airway technique was regarded as insufficient, are illustrated in Table 3. A conversion was not noted in any case of FOISGA. As FOISGA was not accompanied by airway management problems (Figure 2, middle panel); in any case, the rule of three was used to calculate the upper limit of the 95% confidence interval in that subcategory.16

### TABLE 2 Anesthesia in individuals with mucopolysaccharidoses/mucolipidoses

| Characteristics (n = 269) | n (%) | median [IQR] |
|---------------------------|-------|--------------|
| Duration of anesthesia [min] | 120 | [75-180] |
| Duration of procedures (cumulative) [min] | 45 | [25-100] |
| ASA physical status classification [grade] | | |
| II | 68 | (26.2%) |
| III | 174 | (66.9%) |
| IV | 18 | (6.9%) |
| Emergency procedure | 14 | (5.3%) |
| Predicted difficult airway | 181 | (67.3%) |
| Oral midazolam for premedication | 147 | (54.6%) |
| Type of anesthesia | | |
| Monitored anesthesia care | | |
| Anesthesia standby and local anesthesia | 10 | (3.7%) |
| Procedural sedation and analgesia | 6 | (2.2%) |
| Regional anesthesia | 4 | (1.5%) |
| General anesthesia | 249 | (92.6%) |
| Total intravenous | 160 | (59.5%) |
| Balanced anesthesia | 89 | (33.1%) |
| Primary airway technique | | |
| Airway not secured* | 25 | (9.3%) |
| Supraglottic airway | 69 | (25.7%) |
| Tracheal intubation: | | |
| Direct laryngoscopy | 73 | (27.1%) |
| Indirect intubation techniques: | | |
| Conventional fiberoptic intubation* | 23 | (8.6%) |
| Videolaryngoscopy | 19 | (7.1%) |
| Other approaches | 5 | (1.9%) |
| Fiberoptic intubation through a supraglottic airway** | 55 | (20.4%) |

Note: Continuous variables are presented as median [interquartile range (IQR)]; categorical data are presented as frequencies (percentage values);* eight missing values in this category;* the category “airway not secured” includes 5 cases in which solely bag-mask ventilation was used;* of note, the study cohort includes ten cases which involved only local anesthesia performed by a surgeon (eg, ophthalmological procedures); these cases were included in the descriptive analysis (Table 1 and 2) but not in the outcome analysis (Table 4, Figures 1 and 2).* conventional fiberoptic intubation includes cases of nasal or oral fiberoptic tracheal intubations prior to or after induction of anesthesia without routine use of a supraglottic conduit;** laryngeal masks were used as a supraglottic conduit to guide fiberoptic intubation.

3.3 Perioperative adverse events

In 25.6% of the cases studied, one or more perioperative adverse events were recorded (Table 4). Overall, 84 perioperative adverse events were observed (46 airway management problems, 30 respiratory and eight cardiocirculatory adverse events). Aspiration was not reported in any case of our cohort. Bag-mask ventilation was difficult in 4.3% of cases. One child, a 14-year-old boy with MPS Type II who received a FOICON in conscious sedation, developed hypoxic cardiac arrest due to a fulminant laryngo- and bronchospasms during fiberoptic intubation. Despite immediate cardiopulmonary resuscitation and emergency tracheotomy, the child died 8 hours later in the intensive care unit.

3.4 Multivariate analysis of risk factors for perioperative adverse events

Because missing data were not imputed (complete case analysis), cases with missing values in the dependent or independent variables were deleted listwise. This left 236 anesthesia procedures in 62 patients with 83 perioperative adverse events for the fitting of the multivariate multilevel regression model (Figure 1).

Age, indication for anesthesia (diagnostics, minor or major surgery), and duration of anesthesia did not significantly impact perioperative adverse events in our study cohort. Interestingly, a pooling of two or more procedures during a single anesthesia episode (combinations of one or more surgeries and/or diagnostic procedures) did not increase the predicted probability for perioperative adverse events in our cohort.

Male gender (OR 3.1 [1.1-9.2]; P = .038) and an anticipated difficult airway during preoperative assessment (OR 3.2 [1.2-8.3]; P = .019) were independent risk factors for perioperative adverse events.

The risk for perioperative adverse events was higher in MPS type I (OR 8.0 [1.5-42.7]; P = .014) or type II (OR 8.8 [1.3-58.6]; P = .025) than in type III. Very rare diseases (MPS types IV, VI and ML) tended to have a higher risk for perioperative adverse events (OR 5.1 [0.8-34.0]; P = .095) than MPS III.
The analysis of the interaction between the primary airway approach and event subcategory (airway management problems, cardiovascular and respiratory events) revealed the following:

- The adjusted event rates and 95% confidence intervals (CI) for cardiovascular events were 1.6 (0.4-4.8) % for direct laryngoscopy, 4.1 (0.9-9.3) % for supraglottic airway, 3.5 (0.7-6.5) % for indirect intubation, and 2.2 (0.6-6.2) % for FOI\textsubscript{SGA}. A significant association between primary airway techniques and cardiovascular events was not found (Figure 2, left panel).
- The adjusted event rates for airway management problems were 47.8 (35.9-59.8) % for direct laryngoscopy, 14.4 (5.6-23.2) % for supraglottic airway, 10.1 (2.7-17.5) % for indirect intubation, and 0 (0-5.6) % for FOI\textsubscript{SGA}. The risk for airway management problems was significantly higher for direct laryngoscopy than for supraglottic airway (OR 13.73 [3.66-51.48]; \( P < .001 \)) or indirect techniques (OR 24.05 [5.20-111.24]; \( P < .001 \)).
- The adjusted event rates for respiratory adverse events were 14.8 (6.0-23.6) % for direct laryngoscopy, 22.6 (12.2-32.9) % for supraglottic airway, 8.7 (1.9-15.5) % for indirect intubation, and 2.1 (0-6.0) % for FOI\textsubscript{SGA}. The risk for respiratory adverse events associated with direct laryngoscopy (OR 14.70 [1.32-163.44]; \( P = .029 \)) and associated with the supraglottic airway (OR 31.53 [2.79-355.88]; \( P = .001 \)) was significantly higher than for FOI\textsubscript{SGA} (Figure 2, right panel).

### Table 3 Conversion rates and rescue airway approaches

| Overall airway approaches | Conversion to rescue airway approach (n) | Conversion rate (%) |
|---------------------------|----------------------------------------|---------------------|
|                           | DL | SGA | FOI\textsubscript{SGA} | FOI\textsubscript{CON} | VL | Other* |       |
| Direct laryngoscopy [DL]  | -  | 4   | 2                       | 4                        | 7\( ^a \) |            | 24.4% [19/78] |
| Supraglottic airway [SGA]| 3  | -   | 1                       | 0                        | 2   |        | 10.7% [8/75] |
| FOI\textsubscript{SGA}   | 0  | 0   | -                       | 0                        | 0   | 0      | 0% [0/59]   |
| FOI\textsubscript{CON}   | 2  | 2   | 1                       | -                        | 0   | 0      | 17.2% [5/29] |
| Videolaryngoscopy [VL]   | 0  | 0   | 0                       | 2                        | -   | 1      | 12.5% [3/24] |
| Others* (n)              | 0  | 0   | 0                       | 1                        | -   |        | 6.7% [1/15]  |
| Sum Applied as rescue    | 5  | 6   | 4                       | 6                        | 5   | 10\( ^a \) | 12.9% [36/280] |

Note: Overall airway approaches (n = 280) include the primary airway techniques (n = 244) and subsequent rescue airway approaches (n = 36) which include 2 cases of abandoned anesthesia\( ^a \); conversion rate: frequency of the transition to a different (rescue) airway technique or abandoned anesthesia in relation to the total number of airway techniques; *the category "others" includes various techniques such as bag-mask ventilation, rigid optics, tracheostoma, or abandoned anesthesia.

Abbreviations: FOI\textsubscript{CON}, conventional fiberoptic intubation; FOI\textsubscript{SGA}, fiberoptic intubation through a supraglottic airway.

## Discussion

This study investigated independent risk factors for perioperative adverse events in a large MPS/ML cohort. The main and most important finding was that the disease subtype and primary airway technique were the most important independent risk factors for individuals with MPS/ML. FOI\textsubscript{SGA} was associated with the lowest risk for respiratory adverse events, while conversion to another technique was not required and other airway management problems were not observed. Direct laryngoscopy was associated with a much higher probability for airway management problems and respiratory adverse events compared to indirect intubation techniques.

Currently, evidence-based standard recommendations regarding the optimal first-line airway approaches in children suffering from MPS with an anticipated difficult airway are lacking. There is growing evidence that limiting the number of intubation attempts may avoid intubation-related adverse events in children.\(^9\) Thus, appropriate airway techniques should be chosen wisely; based on the anticipated first-pass success rate of the device, the individual experience of the anesthetist and the patient-specific risks linked with the disease subtype.

Our data highlight the important role of indirect intubation techniques in children with MPS or ML with a predicted difficult airway. Excessive direct laryngoscopy attempts should be avoided in these children. However, as institutional experiences and standards vary broadly, a specific type of indirect intubation technique cannot be emphasized in children with MPS.

In nonsyndromic children, the risk for perioperative critical events decreases with age.\(^8\) However, it has been proposed that due to disease progression during the natural history of MPS, the risk for intubation problems might paradoxically increase.\(^4,10,11\) Nevertheless, after adjustment for multiple confounders, we found that perioperative adverse events did not increase with age in our multivariate analysis. This finding could be attributed to the therapeutic effects of bone marrow transplantation or enzyme replacement therapy, which may slow down disease progression.\(^4,5,17\)

### 4.1 The disease subtype is an independent risk factor

MPS III was associated with the lowest rate of perioperative adverse events in our study. Airway management was usually
uneventful, which is consistent with previous findings. The risk for perioperative adverse events was significantly higher in MPS type I and II than in MPS type III. Previous case series reported high event rates in MPS types I and II, but did not provide a direct comparison between MPS subtypes with an adjustment for relevant, confounding factors. Although case numbers for very rare disease are too low to draw clear conclusions, we found a high rate of perioperative adverse events in children with ML. Current knowledge concerning anesthesia in ML is based on only very few reports.

Male gender was found to be an independent risk factor for perioperative adverse events. For the interpretation of this finding, the genetic pathway of MPS/ML should be taken into account. While most MPS subtypes are inherited autosomal recessive, MPS II is inherited in an X-linked recessive manner.

### 4.2 The primary airway technique is an independent risk factor

Previous case series addressed the issue of airway techniques in MPS, but did not provide direct comparative assessments taking essential confounding factors into account.

### 4.2.1 Supraglottic airway

We found the supraglottic airway to be associated with a lower risk for airway management problems than direct laryngoscopy. However, it was associated with a higher risk for respiratory adverse events as opposed to indirect intubation techniques and FOISGA. Thus, caution should be exercised should a supraglottic airway be implemented in

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**Table 4** Perioperative adverse events (PAE) in individuals with mucopolysaccharidoses/mucolipidoses (unadjusted event rates)

| Characteristics (n = 254) | Total number of PAE | Cases with at least one PAE | Event rate within subgroup |
|--------------------------|----------------------|-----------------------------|---------------------------|
| Perioperative adverse events (overall) | 84 | 65 | 25.6% |
| Airway management problems (primary technique) | 46 | | |
| Respiratory events | 30 | | |
| Cardiocirculatory events | 8 | | |
| Primary airway technique | | | |
| Airway not secured | 0 | 0 | 0% |
| Supraglottic airway | 23 | 19 | 27.5% |
| Direct laryngoscopy | 41 | 32 | 45.1% |
| Indirect intubation techniques | | | |
| Conventional fiberoptic intubation | 13 | 8 | 34.8% |
| Videolaryngoscopy | 4 | 3 | 15.8% |
| Other approaches | 1 | 1 | 20% |
| Fiberoptic intubation through a supraglottic airway | 2 | 2 | 3.6% |
| Disease type (n = number of anesthesia cases) | | | |
| Mucopolysaccharidoses type I (n = 135) | 53 | 43 | 31.9% |
| Mucopolysaccharidoses type II (n = 39) | 14 | 10 | 25.6% |
| Mucopolysaccharidoses type III (n = 44) | 6 | 4 | 9.1% |
| Mucopolysaccharidoses type IV + VI (n = 33) | 8 | 6 | 18.2% |
| Mucolipidoses (n = 10) | | | |
| Type II (n = 8) | 3 | 2 | 25% |
| Type III (n = 1) | 0 | 0 | 0% |
| Intermediate type (n = 1) | 0 | 0 | 0% |
| Indication for anesthesia (n = number of cases) | | | |
| Diagnostics (n = 56) | 15 | 13 | 23.2% |
| Minor surgery (n = 124) | 37 | 30 | 24.2% |
| Major surgery (n = 38) | 24 | 16 | 42.1% |
| Any combinations (n = 43) | 8 | 6 | 14.0% |

Note: Data are presented as frequencies (percentage values in relation to the number of valid data in the category); only 254 cases were included in the analysis of perioperative adverse events; *10 cases were excluded because they involved only local anesthesia performed by a surgeon (eg, ophthalmological procedures), and 5 cases were excluded due to missing values in the outcome parameter.
**FIGURE 1** Independent risk factors for perioperative adverse events in individuals with mucopolysaccharidoses/mucolipidoses (MPS/ML): multivariate multilevel regression model with two nested random effects accounting for repeated anesthesia procedures within the same patient and for multiple events within a single anesthesia episode; a forest plot illustrates the risk for perioperative adverse events on a logarithmic scale; the diamonds and lines indicate the odds ratio (OR) with the 95% confidence interval (95% CI); solid diamonds indicate statistically significant, open diamonds insignificant findings; n = 236 cases in 62 individuals with general anesthesia and secured airway were included in the complete case analysis. Abbreviations: ASA, American Society of Anesthesiologists; ref, reference for categorical variable.

| Disease type (ref: MPS type III) | OR (95%-CI) | P-value |
|---------------------------------|-------------|---------|
| MPS type I                      | 8.0 (1.5 - 42.7) | 0.014 |
| MPS type II                     | 8.8 (1.3 - 58.6) | 0.025 |
| MPS type IV, VI and ML          | 5.1 (0.8 - 34.0) | 0.095 |

| Age at Intervention [years]     | OR (95%-CI) | P-value |
|---------------------------------|-------------|---------|
| Male gender                     | 3.1 (1.1 - 9.2) | 0.038 |
| Predicted difficult airway      | 3.2 (1.2 - 8.3) | 0.019 |
| Emergency procedure             | 1.1 (0.2 - 4.9) | 0.908 |
| Duration of anesthesia [h]      | 1.3 (1.0 - 1.6) | 0.079 |

| ASA physical status (ref: class II) | OR (95%-CI) | P-value |
|-----------------------------------|-------------|---------|
| Class III / IV                    | 2.5 (0.8 - 7.8) | 0.111 |

**Indication for anesthesia (ref: diagnostics)**

- Minor surgery: 0.7 (0.2 - 2.1) | 0.503
- Major surgery: 0.9 (0.2 - 4.1) | 0.875
- Any combination: 0.3 (0.1 - 1.2) | 0.086

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**FIGURE 2** Interaction between the primary airway techniques and subcategories of perioperative adverse events in individuals with mucopolysaccharidoses/mucolipidoses: distribution of estimated marginal means with 95% confidence intervals for the predicted probability of perioperative adverse events. Of note, because fiberoptic intubation through a supraglottic airway was not accompanied by airway management problems in any case, the rule of three was used for approximation of the upper limit of the 95% confidence interval in that subcategory, even though this calculation does not take the interaction between dependent variables and repeated measures into account.16
individuals suffering from MPS/ML who present with progressive respiratory dysfunction or a narrowed upper airway. There is growing evidence that the laryngeal mask airway is associated with lower postoperative complication rates, as opposed to tracheal intubation in pediatric cohorts.27,28 Our data indicate that these findings should not be extrapolated without critical consideration to children with MPS/ML.

4.2.2 | Indirect tracheal intubation techniques

A previous study has suggested that limiting the number of direct laryngoscopy attempts and quickly transitioning to indirect techniques might improve safety in children with a difficult tracheal intubation.9 The initial choice of an indirect tracheal intubation technique was associated with a lower risk for airway management problems and respiratory adverse events than with direct laryngoscopy in our study cohort. Of note, in our study, fiberoptic intubation was the predominant indirect intubation technique, while videolaryngoscopy was rarely implemented.

4.2.3 | Fiberoptic intubation through a supraglottic airway (FOISGA)

As awake FOI CON is often poorly tolerated by children, FOISGA is a very popular approach in children with difficult airways. In a large multicenter trial, FOISGA was associated with a higher overall success rate than videolaryngoscopy in children with difficult airways.15 FOISGA is gaining widespread popularity in children at risk for spinal cord compression, as an extension of the head can be avoided and the cervical spine remains aligned.29 This is an extremely important issue for children with MPS/ML, who frequently exhibit a cervical spinal canal stenosis or dens hypoplasia with atlantoaxial instability. Although FOISGA has been established for more than two decades, data concerning its implementation in children with MPS/ML are still very limited.14,30 Our analysis is based on data stemming from two high-volume centers. Our study cohort included the largest ever case series focused on FOISGA in MPS. During the study period, FOISGA was typically enabled by a stepwise approach, which was finalized by the insertion of a tracheal tube railroaded straight via a bronchoscope through a disposable laryngeal mask. However, impossible laryngeal mask placement, which is a limitation for FOISGA, has not been observed with FOISGA in our study.

The retrospective nature of this study is a well-recognized limitation and a potential source for selection bias. Moreover, our data only reflect experiences from two centers, and caution should be exercised should our results be generalized. Appropriate caution should also be exercised if conclusions are drawn from unadjusted data.

In conclusion, our study demonstrated that the disease subtype and the primary airway technique were the most important independent risk factors for perioperative adverse events in children with MPS or ML. Our findings indicate that indirect techniques, such as FOISGA, should be favored for the initial tracheal intubation attempt in children with MPS/ML with a predicted difficult airway. FOISGA might further be beneficial for children with MPS/ML with an increased risk for spinal cord compression. However, it should be noted that difficult laryngeal mask placement is a technical limitation for FOISGA.

CONFLICT OF INTEREST

NMM has received travel and/or research grants as well as speakers’ honoraria from Biomarin, Genzyme, and Shire. NMM has been involved in clinical studies conducted by Biomarin, Genzyme, PTC Therapeutics, and Shire. SB has received reimbursements of travel cost from Biomarin. AFK has received reimbursements of travel cost and speakers’ honoraria from Biomarin, Genzyme, and Shire. KU has received reimbursements of travel cost from Shire and Nutricia Metabolics. All other authors declare that they have no competing interests in the subject discussed in this manuscript.

ETHICAL APPROVAL

This study was approved by the Ethical Committee of the Medical Board of Hamburg, Germany (reference number PV4832, October 28, 2014).

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