RESEARCH REPORT

Perioperative management of children with glycogen storage disease type II—Pompe disease

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Summary

Background: Pompe disease is a rare metabolic disorder caused by a deficiency of the lysosomal enzyme acid α -glucosidase. Glycogen accumulation damages skeletal, cardiac, and smooth muscles, causing a progressive and debilitating muscle weakness and cardiomyopathy. As life expectancy has much improved since the introduction of enzyme replacement therapy an increasing number of patients are referred for surgical procedures. Due to the potential cardiopulmonary complications, these patients form a high-risk group for the anesthesiologist.

Aims: In this study, we investigated the incidence of perioperative complications in children with Pompe disease treated in our hospital since the introduction of enzyme replacement therapy.

Methods: Anesthetic and perioperative data of children with Pompe disease treated between 1999 and 2015 in the Erasmus MC—Sophia Children's Hospital, University Medical Centre, Rotterdam, The Netherlands, were collected, retrospectively.

Results: Of the 65 children with Pompe disease, 34 patients underwent in total 77, mostly low-risk, surgical procedures. Twenty-one children had the classic infantile form and 13 had a nonclassic presentation of Pompe disease. In 13 (16.8%) procedures, 1 or more perioperative complications occurred. Perioperative desaturation was the main complication (12.9%), followed by arrhythmia (3.8%) and heart failure requiring diuretic treatment (2.6%). One child died 2 days postoperatively, but this was considered unrelated to the procedure.

Conclusion: Despite the potentially high anesthetic risk for children with Pompe disease under enzyme replacement therapy, the incidence of perioperative complications in our study was relatively low. Our data suggest that with proper precautionary measures and a critical choice of timing of the operation, general anesthesia in children with Pompe disease could be relatively safe nowadays.

KEYWORDS

adverse events, child, congenital anomalies and syndromes, infant, muscle disorders

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1 | INTRODUCTION

Pompe disease is a metabolic myopathy or lysosomal storage disorder caused by an inheritable deficiency of the lysosomal enzyme acid α glucosidase. Glycogen accumulates progressively in the lysosomes and causes damage to myocytes. Pompe disease presents as a clinical spectrum with a predicted frequency of 1:40 000. The classic infantile form of Pompe disease (1:138 000), represents the most severe end of the spectrum with generalized hypotonia, cardiomyopathy, and respiratory insufficiency as characteristic features. Without enzyme replacement therapy (ERT), these children rarely survive beyond 1 year of age due to cardiorespiratory failure. Patients with nonclassic presentations (1:57 000) may present at any age from early infancy to late adulthood and the course may vary widely. 1-3 Symptoms relate to skeletal and respiratory muscle weakness and most of the patients become wheelchair bound or dependent on a respirator at some time in life. Since the diaphragm is also involved pulmonary function in supine position is mostly lower than in upright position. In these patients, the heart is rarely involved.⁴

The worldwide introduction of ERT with recombinant human acid α-glucosidase in 2006 has altered life expectancy substantially, providing a therapeutic option for this previously untreatable disease.^{5,6} One of the consequences is that these patients are increasingly eligible for surgical procedures, not only procedures related to the disease (insertion of a Port-a-Cath [PAC] for ERT or muscle biopsy) but also common elective surgical and diagnostic procedures. However, its implications for perioperative and anesthesia practice are largely unknown. To date, the anesthetic literature on Pompe disease is limited and knowledge is mainly based on small case series and case reports.⁷⁻¹⁰ In children with the classic infantile form of Pompe disease, fatal perioperative cardiac complications, related to cardiomyopathy, have been described.⁷⁻⁹ The heart is rarely affected in children with nonclassic presentations. 11 In addition, serious pulmonary complications due to respiratory muscle weakness, such as repeated (silent) aspiration and prolonged ventilation, are mentioned for both forms of Pompe disease. 12-14 Bulbar weakness leading to dysphagia as described in both children and adults may also contribute. According to a long-term study in children with classic infantile form of disease receiving ERT, these children suffer from facial muscle weakness, reduced pharyngeal and laryngeal sensibility, and dysphagia, making them more vulnerable for postoperative aspiration. 15,16

Enzyme replacement therapy was introduced in the Erasmus MC—Sophia Children's Hospital, University Medical Centre, Rotterdam, The Netherlands, already in 1999 as part of the first clinical trial performed, applying recombinant human α -glucosidase produced in milk of transgenic rabbits.⁵

In this article, we provide an overview of our anesthetic experience in children with Pompe disease since the introduction of ERT in our hospital. We investigated the incidence of perioperative complications and risk factors making a separation between patients with classic and nonclassic presentations, and attempted to make a

What is already known

• Children with Pompe disease are nowadays treated with recombinant human acid α -glucosidase, which has improved life expectancy substantially, making these patients increasingly eligible for surgical procedures under general anesthesia. However, implications for perioperative practice are largely unknown.

What this study adds

 With adequate ERT by peripheral infusion to reduce left ventricular mass, before undergoing an elective procedure under general anesthesia, and with a thorough preoperative evaluation of the child's cardiac and pulmonary status by a multidisciplinary team, anesthesia in children with Pompe disease can be performed relatively safe nowadays.

recommendation regarding the anesthetic and perioperative management of children with Pompe disease.

2 | MATERIALS AND METHODS

This retrospective cohort study investigated all children diagnosed and/ or treated with Pompe disease in the Erasmus MC—Sophia Children's Hospital, University Medical Centre, Rotterdam, The Netherlands, between 1999 (introduction of ERT in our hospital) and 2015. The medical charts of all Pompe patients who underwent a surgical or diagnostic procedure under anesthesia in this period were screened for general parameters, cardiac status, respiratory status, motor function tests, perioperative parameters, and adverse events. As some patients underwent more than 1 procedure, the analysis has been done on procedure level, with the patient status at the time of every procedure.

General parameters like age at diagnosis, age at time of the procedure, comorbidity, form of disease (classic infantile or nonclassic presentation), and gender were collected. Also age of starting ERT and length of treatment with ERT by the time of the first procedure were collected, as a short duration of ERT and consequently a potential high left ventricular mass index are related to severe cardiomyopathy and hypothetically a higher incidence of cardiac complications during anesthesia. 7,17

Cardiac status included parameters from cardiac history, physical examination, and echocardiography to record the severity of patients' cardiomyopathy. Systolic function was categorized in normal, moderate, or severely affected as described in the echocardiographic report. Ventricular hypertrophy was divided into 4 categories: normal, mild, moderate, or severely affected. Left ventricular mass index was measured in Boston z score and BSA/Haycock according to local standards. For all parameters, time from investigation to surgical procedure was documented.

Respiratory status included reports of a polysomnography, if available. Important parameters were number of desaturations per hour, desaturation index, apnea index, mean oxygen saturation level, and highest carbon dioxide level (normal <52 mm Hg). Spirometry parameters, in sitting and supine position, were included in the database if available. It was documented if patients were dependent on permanent or intermittent home ventilation or additional oxygen supply.¹⁸

Motor function tests included Alberta Infant Motor Score, Bayley Scales of Infant Development second edition, and Quick Motor Function Scale Test (QMFS%).¹⁹

Perioperative parameters included the anesthetic technique used (local or general), medication for induction and maintenance of anesthesia (intravenous or inhalational), duration of induction, procedure and recovery, type of monitoring, and postoperative destination (ward or intensive care unit, ICU).

Adverse events were divided into 3 groups: cardiac complications related to the cardiomyopathy (cardiac arrest, ECG ST changes, arrhythmias, signs of heart failure), respiratory complications related to respiratory muscle weakness (desaturation <90%, prolonged ventilation, prolonged neuromuscular blockade, aspiration), and general complications (anaphylaxis, difficult airway management). If applicable, the time of occurrence in the perioperative process (preoperative, perioperative, postoperative) was categorized, as were unexpected ICU admissions postoperatively.

2.1 Statistics

Categorical data are described as counts and percentages. Continuous variables are described as medians and interquartile ranges. The relation of influencing factors and occurrence of perioperative complications were analyzed using the Mann-Whitney *U* and chi-square test. Data were collected and analyzed using IBM SPSS Statistics 22 (IBM Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | General parameters

Sixty-five patients with Pompe disease were diagnosed and/or treated in the Erasmus MC—Sophia Children's Hospital, Rotterdam, the Netherlands, between February 1999 until January 2015. During this period, 31 patients had no indication to undergo a procedure requiring anesthesia and were therefore excluded. Our final study sample consisted of 34 children who underwent 1 or more surgical or diagnostic procedures, mostly low risk (Table 1). Twenty-one (61.7%) of these children had the infantile form and 13 (38.3%) were children with nonclassic presentations. These 34 children underwent in total 77 procedures: 48 (62.3%) in children with infantile form and 29 (37.7%) in the others. All except 1 child, started to receive ERT at some point during the study period. Six patients with the classic infantile form of disease and 10 children with nonclassic presentations underwent the first procedure before starting ERT (Table 2).

3.2 | Perioperative parameters

Of the 77 procedures, 71 were performed under general anesthesia. Six were performed with a local anesthesia technique: 5 diagnostic muscle biopsies with awake caudal anesthesia (2 of these procedures were combined with a local anesthesia for a PAC insertion) and 1 single PAC insertion under local anesthesia. One patient with non-classic presentation of disease had a tendon release of the foot under general anesthesia, unfortunately exact intraoperative information was missing.

In both forms of Pompe disease, intravenous (IV) induction of anesthesia with propofol was most common. Three children with classic infantile type of disease (6.3%) and 1 child with nonclassic presentation (3.4%) had an induction with ketamine. For maintenance of anesthesia, IV anesthesia with propofol (dose range 3-15 mg/kg/h) was used more commonly in both forms of Pompe disease (Table 3).

Over the years we found a change in the anesthesia technique used. All procedures under local anesthesia took place during the first years (1999-2004) after introduction of ERT. During this period, IV induction of anesthesia was the most used technique in children with both forms of disease.

This gradually shifted to an increased use of inhalational anesthesia in the period from 2010 to 2015 (Figure 1A). This trend was seen as well for maintenance of anesthesia in both forms of Pompe disease (Figure 1B). There was no difference in incidence of adverse events with the change in anesthetic technique. In 17 of 77 procedures, muscle relaxants were used (22.1%). None of the children had a prolonged duration of neuromuscular block or delayed extubation.

TABLE 1 Type of surgical procedures

Type of procedure	N (%)
Insertion/Revision PAC	43 (55.8)
Insertion PAC & Muscle biopsy	9 (11.7)
Muscle biopsy	7 (9.1)
Insertion PEG	5 (6.5)
Tendon release extremity (foot)	4 (5.2)
Tracheostomy	3 (3.9)
Insertion tympanic membrane tubes	1 (1.3)
Correction eye lid	1 (1.3)
Nissen fundoplication	1 (1.3)
MRI	1 (1.3)
Laryngoscopy	1 (1.3)
Scoliosis correction	1 (1.3)
Total	77 (100)

MRI, magnetic resonance imaging; PAC, Port-a-Cath; PEG, percutaneous endoscopic gastrostomy.

TABLE 2 Key parameters of the patients with both types of Pompe disease (patient level)

	Classic infantile disease (N = 21)	Nonclassic presentation of disease (N = 13)
Number procedures per patient	2 (1-4)	2 (1-3)
Sex (M/F, %)	10/11 (47.6/52.4%)	7/6 (53.8/46.2%)
Age 1st procedure (mo)	7 (4.5-8.0)	132 (28.5- 157.5)
ERT (%) ^a	21 (100%)	12 (92%)
Age start ERT (mo)	4 (1-7)	143 (44-152)
Start ERT—1st procedure (mo)	3 (0-6.5) ^b	7 (1-35) ^c
Cardiac status		
LV mass index/BSA/(g/m²) during first procedure ^d	56.9 (37.6-106.5)	64 (49-81) ^e

Data are represented as median with 25th and 75th percentile for continuous variables.

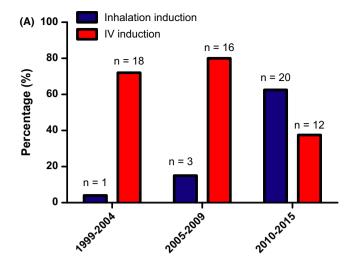
TABLE 3 Anesthetic technique (procedure level)

	Total (N = 77)	Classic infantile disease (N = 48)	Nonclassic presentation of disease (N = 29)
Local anesthesia, n (%)	6 (8)	5 (10)	1 (3.5)
General anesthesia, n (%)	71 (92) ^a	43 (90)	28 (96.5)
Induction of anesthesia ^a			
Inhalation induction, n (%)	24 (34)	19 (44)	5 (19)
Intravenous induction, n (%)	46 (66)	24 (56)	22 (81)
Maintenance of anesthesia ^a			
Inhalation, n (%)	25 (36)	17 (40)	8 (30)
Intravenous, n (%)	40 (57)	22 (51)	18 (67)
Combination inhalation/IV, n (%)	5 (7)	4 (9)	1 (3)

^aMissing data for 1 procedure for a patient with nonclassic presentation of disease, who had general anesthesia. The exact choice of anesthetic agents is missing.

3.3 | Adverse events

Table 4 shows the adverse events that occurred perioperatively. One or more adverse events occurred in 13 procedures (16.8%): in 9 (18.8%) procedures in children with the classic infantile form, and in 4 (13.8%) children with nonclassic presentation of disease. Desaturation <90% was the most frequent adverse event in both groups (12.9%), occurring both during anesthesia



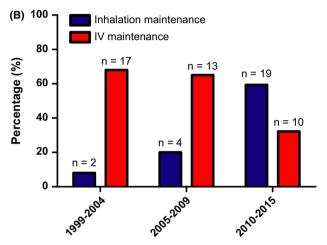


FIGURE 1 A, Technique used for induction of general anesthesia, 5-y interval (procedure level). Missing data for 1 procedure for a patient with nonclassic presentation of disease, who had general anesthesia in 2009. The exact choice of anesthetic agents is missing. B, Technique used for maintenance of general anesthesia, 5-y interval (procedure level). Missing data for 1 procedure for a patient with nonclassic presentation of disease, who had general anesthesia in 2009. The exact choice of anesthetic agents is missing. Five procedures are not included in this figure, because a combination of inhalation and IV maintenance was used (2 procedures in 2005-2009 and 3 procedures in 2010-2015) [Colour figure can be viewed at wileyonlinelibrary.com]

and postoperatively. Also cardiac arrhythmias occurred in both groups (3.8%). In 2 cases, the occurrence of atrial extra systoles was related to insertion of a PAC and was self-limiting by withdrawal of the mechanical stimulus. One child suffered from a bradycardia of 20 beats per minute intraoperatively, with an adequate reaction to atropine. Exact duration of hemodynamic instability could not be retrieved from written anesthetic recordings. Diuretic treatment because of signs of perioperative heart failure was needed in 2 children with classic infantile form of disease (2.6%). One child with classic infantile form presented in the hospital, at the age of 7 months, with a very severe

^aNumber (%) of patients starting ERT during study period.

^bSix patients did not start ERT by the time of the 1st procedure.

^cTen patients did not start ERT by the time of the 1st procedure.

^dNormal value <95 g/m² female, <115 g/m² male.

^eMissing data in 2 patients.

TABLE 4 Perioperative complications (procedure level)

	Classic infantile d (N = 48)	Classic infantile disease (N = 48)		Nonclassic presentation of disease (N = 29)	
Complication	Yes	No	Yes	No	
Number of procedures	9	39	4	25	
Age of start ERT (mo)	3 (2-6.5)	4 (1-7)	16 (12-31.2)	147.5 (126-153)	
ERT not started during procedure	1	5	1	9	
ERT ≤3 mo during procedure	3	6	1	1	
ERT > 3 mo during procedure	5	28	2	15	
Total length of ERT	4 (2-69)	7 (3-28)	17 (1-93.8)	15.5 (0-58.8)	
Intermittent or permanent home ventilation (n)	2	13	0	6	
Moderate or severe systolic dysfunction (n) ^a	1	2	0	0	
Moderate or severe LV hypertrophy (n) ^b	6	21	0	0	
Enzyme replacement therapy	ERT+	EI	RT- ERT+	ERT-	
Total number of complications	12	2	4	0	
Number of procedures with one or more complications	8	1	4	0	
Cardiac complications	3	1	1	0	
Arrhythmia ^c	2	0	1	0	
Signs of heart failure requiring diuretic treatment	1	1	0	0	
Maintenance of anesthesia	0	1	0	0	
<24 h postoperatively (on ICU or PACU)	1	0	0	0	
Respiratory complications	9	0	3	0	
Desaturation >90%	9	0	0	0	
Induction of anesthesia	1	0	0	0	
Maintenance of anesthesia	2	0	1	0	
<24 h postoperatively (on ICU or PACU)	6	0	2	0	
Other complications					
Death (<30 d after operation)	0	1	0	0	

Data are represented as median with 25th and 75th percentile for continuous variables.

cardiomyopathy, too advanced for a positive response on ERT, due to the late diagnosis. This child had general anesthesia with induction with ketamine and maintenance with sevoflurane to perform a diagnostic muscle biopsy. Two days after the operation the child died of respiratory failure. Because of the poor condition of the child, it was chosen not to initiate artificial ventilation. For this reason, the outcome is considered to be unrelated to the operation or perioperative management.

We compared for both forms of disease the groups with and without perioperative complications for several relevant parameters, (such as age at start of ERT, cardiac and respiratory status, anesthesia technique used) to determine a possible risk factor for perioperative adverse events (Table 4). However, we could not demonstrate any relationship between these parameters and the occurrence of adverse events in both groups. The study sample was too small for a reliable and definite statistical analysis.

4 | DISCUSSION

The purpose of this study was to determine the incidence and severity of perioperative complications for children with Pompe disease, undergoing anesthesia for surgical or diagnostic procedures and to identify possible predictive factors for poor outcome. This retrospective investigation demonstrated that in 18.8% of procedures in children with the classic infantile form of disease, 1 or more adverse events occurred. For children with nonclassic presentations, this was the case in 13.8% of procedures.

Given the respiratory muscle weakness in children with Pompe and the severe cardiomyopathy in children with classic infantile type of disease, we expected to find more complications. Literature about Pompe disease and anesthesia is limited, but the case series and reports available show serious anesthetic complications. The fact that during the first years of our study (1999-2004), the anesthetic record was still written manually, instead of

^aIn 1 patient with nonclassic presentation of disease, data are missing or investigation not performed.

^bIn 1 patient with nonclassic presentation of disease, data are missing or investigation not performed.

^cAll arrhythmias occurred intraoperatively.

parameters being automatically processed on the computer, may have caused underreporting of adverse events. Also, most surgical procedures were low-risk procedures such as PAC insertion or muscle biopsies. Only a few patients underwent more extensive surgery, such as scoliosis correction or Nissen fundoplication. This may explain the lower incidence of perioperative complications as well.

The most common complication was a period of perioperative desaturation <90%. In Pompe disease, there is a disproportionate involvement of the diaphragm, which causes a reduced forced vital capacity especially in the supine position. For this reason, it is extremely important to perform spirometry in both sitting and supine position in older children (above 6 years of age) and/or perform a preoperative polysomnography in the younger ones. Children with classic infantile form of disease with severe cardiomyopathy may also have lung lobar collapse from cardiac compression of the airway. Many patients, both with classic and nonclassic presentations, become (partly) dependent on mechanical ventilator support as disease progresses. Respiratory failure is a major cause of death. Bulbar weakness may also occur in all children with Pompe disease, but particularly in children with classic infantile form of disease, this may cause an increased risk of aspiration. Therefore, desaturation could indeed be expected perioperatively, and also other respiratory complications, such as prolonged postoperative ventilation or respiratory insufficiency after extubation. 14,17 We advocate to focus on these aspects prior to the initiation of an anesthetic procedure.

Also in healthy children, respiratory complications are the most common adverse events during general anesthesia. A study in 9297 children undergoing surgery, showed an incidence of 15% respiratory adverse events perioperatively.²⁰ In 10% of the children, a period of desaturation <95% was described. The incidence of perioperative desaturation for children with Pompe disease in this study is higher than in the general pediatric population, even when a different definition of desaturation is taken into account (<90% vs 95%). In our study, the period of desaturation had no further implications for treatment.

Excessive accumulation of glycogen within the lysosomes of many tissues, including cardiac muscle cells, leads to a progressive cardiomyopathy in children with the classic infantile form of Pompe disease.^{3,4} At the time of diagnosis, a severe cardiomyopathy and cardiac failure is present in most children, generating a high risk on the occurrence of anesthetic complications. In children with nonclassic presentations, the heart is sporadically affected.¹³ A noncompliant left ventricle predisposes a patient to diastolic heart failure, an elevated left ventricular end diastolic pressure and common development of systolic heart failure.⁷⁻⁹ Glycogen accumulation can also be situated in the cardiac conduction system, leading to abnormal conduction velocities.²¹ The combination of factors makes children with the classic infantile form of disease especially vulnerable to develop a ventricular and supraventricular tachycardia. This fragile balance represents a challenge for a safe anesthetic procedure. In the current

study, we found cardiac arrhythmias in 2 children with classic infantile form of disease and in 1 child with nonclassic form of disease. In 2 cases, the arrhythmia was probably related to the insertion of a PAC. Ing et al described a case series of 5 children with the classic infantile form, undergoing a total of 13 anesthetics. During one of these procedures, a cardiac arrest occurred, followed by a successful defibrillation procedure. In 2 cases, ST-segment depression occurred, normalizing after administration of phenylephrine. Wang et al screened 139 patients with Pompe disease for adverse events during anesthesia. They describe 9 patients experiencing serious cardiac arrhythmia or arrest soon after induction of anesthesia. This article suggests an association between LV mass indices and mortality risk, as a LV mass index >350 g/m² was associated with death in children with classic infantile form of disease. In our study none of the children had LV mass indices in this range when undergoing anesthesia.

In the study of Ing et al, ⁹ all complications occurred in the group of children who were not on ERT. The exact duration of ERT at the time of the anesthesia was not mentioned in the article of Wang et al. ⁷ In our study, the median time of ERT before the first anesthesia in children with classic infantile type of disease was 3 months, as most of the children were given ERT by peripheral infusion before undergoing a PAC insertion under anesthesia. One of the most important reasons to start ERT first on a peripheral infusion and to insert a PAC later was to increase the stability of the child first, prior to any (elective) intervention requiring general anesthesia. During the first 3 months of treatment, we monitor cardiac hypertrophy and function on a monthly basis and every 3 months thereafter. ¹⁴⁻²² Once the risk of cardiac and respiratory failure seems reduced, general anesthesia is considered.

Other factors that may have contributed to a better outcome is that we focus on potential signs and symptoms of bulbar muscle weakness, respiratory difficulties, and infections which may increase the risk of aspiration. Preoperative polysomnography is performed when there are doubts. In older children, spirometry in sitting and supine position is performed. All of these measures probably provide an important explanation of our relatively low percentage of complications. Also the fact that children receive a higher dose of ERT in our hospital may have contributed to a better preoperative stability.

We did not find a relation with anesthetic technique used and complication rate. From the sparse available literature on anesthesia in children with classic infantile form of disease, the common sense is that additional care in maximizing coronary perfusion pressure and minimizing arrhythmia risk must be given. For these reasons, it was recommended to avoid propofol or high concentrations of sevoflurane. In other studies, agents such as ketamine and etomidate were advised as the cornerstone for induction in order to better support coronary perfusion pressure and to avoid decreasing diastolic blood pressure with vasodilatory agents.⁷⁻⁹ However, since the introduction of ERT and with children in a physically better condition, propofol and sevoflurane

were used in our hospital to anesthetize children with Pompe disease. The results of our study suggest that these anesthetic agents can be used safely in children with Pompe on ERT provided that a careful preoperative workup has taken place. Ketamine and etomidate, or the use of a local anesthetic technique still should be considered in children with severe cardiomyopathy. ^{24,25}

5 | CONCLUSIONS

The purpose of this study was to determine the incidence and severity of perioperative complications for children with Pompe disease, and to identify predictive factors for poor anesthetic outcome. One child with classic infantile form of disease who had a fatal clinical condition on admission, died 2 days postoperatively, but this was probably unrelated to the general anesthesia. The other perioperative respiratory and cardiac complications found in this study were generally mild. Based on the experience of our hospital and the results of this study, a multidisciplinary approach is strongly advised, with a close cooperation between pediatric anesthesiologists and pediatricians with experience in treating children with Pompe disease. Any elective procedure under general anesthesia should be postponed until the child has received adequate ERT by peripheral infusion and cardiac hypertrophy is reduced to an acceptable level and consequently arrhythmic risk. With this standard of treatment with ERT, and a thorough preoperative cardiac analysis in children with classic infantile form of disease (ultrasound, ECG) and pulmonary workup in both forms of disease (polysomnography, and if possible sitting and supine spirometry) to assess respiratory risk, anesthesia may be relatively safe. A multidisciplinary approach and close cooperation between pediatricians, pediatric surgeons, and pediatric anesthesiologists is essential for timing of the surgical procedure, deciding on the best anesthesiologic treatment and perioperative care for the individual patient.

ETHICAL APPROVAL

This study has been performed according to the World Medical Association Declaration of Helsinki. The local Medical Ethics Committee waived the need for informed consent, because of the retrospective study design and patients were not subjected to investigational actions.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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