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Complications of anesthesia for children with malignant infantile osteopetrosis before and after hematopoietic stem cell transplantation

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Abstract

Objectives and Aims—The primary aim was to determine the frequency of anesthetic-related complications for patients with malignant infantile osteopetrosis (MIOP) before and after hematopoietic stem cell transplant (HSCT). The secondary aims were to describe the types of complications that occurred, to determine whether the risk of anesthetic complications was altered by HSCT, and to determine the frequency of difficult intubation.

Background—Patients with MIOP undergo HSCT, often in infancy, and anesthesia is frequently required for investigations and procedures associated with transplantation. Although MIOP has adverse implications for anesthetic management, the literature describing anesthetic management of MIOP patients is limited.

Methods/Materials—A retrospective review of medical and anesthetic records was undertaken between November 2000 and March 2008.

Results—Eleven patients underwent 127 anesthetics. The overall complication rate was 11%. Before HSCT, there were 12 complications in 62 anesthetics (19.3%). After HSCT, there were 2 complications in 65 anesthetics (3.2%). This difference was not statistically significant. All of the complications were airway or respiratory events. Of the 26 intubations associated with anesthesia, 23 (88.5%) were easy, 1 (3.8%) was moderately difficult, and 2 (7.7%) were difficult.

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Conclusion—Complications associated with anesthesia for infants and children with MIOP having HSCT are fairly common and are usually airway or respiratory related. Difficult endotracheal intubation is also common.

Introduction

Osteopetrosis is a group of rare heritable disorders caused by defects in osteoclasts, the large multinucleated cells that line the endosteal surface of the bone and are principally responsible for bone resorption. Dysfunctional osteoclasts cause the process of resorption and remodeling of immature bone to be impaired, which leads to numerous anatomic and physiologic abnormalities related to skeletal tissue (1).

Several variants of the disease have been identified, but clinical experience at St. Jude Children's Research Hospital has primarily been with the autosomal recessive malignant infantile osteopetrosis (MIOP), which is the most severe subtype of the disease (2). The exact incidence of MIOP is unknown, but it has been estimated to be 1:200,000 (1). Osteoclast dysfunction, in addition to normal osteoblast function, results in a disproportionate increase in mineralized bone and abnormal hematopoiesis. Consequently, bones are homogeneously dense, sclerotic, and radiopaque (3). Additionally, there is excess bone and mineralized cartilage leading to encroachment of medullary cavities and a subsequent decrease in medullary spaces (4). There are many serious clinical manifestations of the disease, and their variability may reflect different underlying genetic abnormalities (5).

Patients present to St. Jude, usually in infancy, for hematopoietic stem cell transplantation (HSCT), because it is the only treatment that can alter the mortality rate of approximately 70% before 6 years of age (1). Several researchers have reported potential reversal of the adverse manifestations of MIOP upon HSCT treatment, including noticeable weight gain, growth, and resolution of abnormal facial appearance (6,7). If the grafts are from human leukocyte antigen-identical siblings, the patients have a 5-year disease-free survival rate of 73%, and grafts from unrelated or mismatched donors result in a disease-free survival rate of up to 45% (8).

Before HSCT, patients receive anesthesia for procedures such as permanent central venous catheter placement, bone marrow aspiration, tracheostomy, and total body irradiation. Afterward, there are bone marrow biopsies to determine the success of HSCT and monitor for the development of graft-versus-host disease, radiological studies, and treatment of any surgical complications that arise (9). Although MIOP has adverse implications for anesthetic management (10), the literature describing anesthetic management of MIOP patients is limited. Furthermore, there has been no report in the medical literature regarding how HSCT changes anesthesia risk.

The primary aim of this study was to describe our recent experience with anesthesia for patients with MIOP before and after HSCT and determine the frequency of anesthetic-related complications. Secondary aims were to describe the types of complications that occurred, to determine whether the risk of anesthetic complications was altered by HSCT, and to determine the frequency of difficult intubation.

Materials and Methods

This retrospective study was approved by the institutional review board of St. Jude Children's Research Hospital. Patients with MIOP who had undergone HSCT between November 2000 and March 2008 were identified from the hospital database. Medical

records of these patients were reviewed to obtain patient age, sex, weight, age at diagnosis, comorbid conditions, physical examination findings, and results of laboratory and radiological studies. All anesthesia records for these patients were examined to determine the procedures performed under anesthesia before and after HSCT. Details of the anesthetic technique and any anesthesia-related complications were recorded. The anesthetic record has a section in which the practitioner notes the ease of intubation. This section was examined in cases where intubation took place.

The complication rate was defined as the number of anesthesia-related complications divided by the number of procedures performed for each patient before and after HSCT. The pre- and post-HSCT complication rates were compared using an exact Wilcoxon signed rank test.

Results

Eleven patients were identified in the database and included in the study. There were 8 boys and 3 girls. Most patients were diagnosed at birth (N=7); the other patients ranged in age at diagnosis from 1.7 to 8.1 months. Comorbid conditions present before HSCT are listed in Table 1. The median age at first HSCT was 8.4 months (range, 5.2–63.4 months). One patient (#3) had 2 HSCTs, and another patient (#11) had 4. Only data from anesthetics conducted before a second HSCT were included in the analysis. Post HSCT anesthetics included in the study occurred between 1 and 42 months after HSCT (mean, 10.5 months; median, 4 months).

Of the 127 procedures requiring anesthesia, 62 were done before HSCT, and 65 were done afterward. Airway management for the 62 pre-HSCT procedures included face mask (FM; n=22; 35.5%), tracheostomy (n=16; 25.8%), endotracheal tube (ETT; n=18; 29%), and laryngeal mask airway (LMA; n=6; 9.7%). Airway management for the 65 post-HSCT procedures included FM (n=27; 41.5%), tracheostomy (n=26; 40%), ETT (n=11; 16.9%), and LMA (n=1; 1.5%).

There were 26 oral endotracheal intubations (20.5%) out of 127 procedures. For another 3 procedures, the patient had already been intubated in the intensive care unit. Of the intubations associated with anesthesia, 23 (88.5%) were easy, 1 (3.8%) was moderately difficult, and 2 (7.7%) were difficult. All 11 patients were intubated at least once. Eight patients were intubated one or more times and were easy every time. One patient was intubated once and was moderately difficult, and another patient was intubated once and was difficult. One final patient was intubated 7 times and was noted to be difficult on one occasion but easy the other 6 times.

A total of 14 anesthetic complications in 8 patients were observed. The overall rate of anesthetic complications was 11%. Ten of 11 patients had at least one procedure both before and after HSCT. The other patient (#3) had procedures done only before HSCT. Before HSCT, there were 12 complications in 62 anesthetics (19.4%). After HSCT, there were 2 complications in 65 anesthetics (3%). The numbers of complications per patient before and after HSCT are shown in Table 2. The complications are described in Table 3.

The data were considered paired observations, and an exact Wilcoxon signed rank test was used to compare them. Ten patients were used in the analysis; patient #3 was excluded (no procedures performed after HSCT). There was no evidence of a difference in the pre- and post-HSCT complication rates as defined above (p=0.125; exact Wilcoxon signed rank test).

Discussion

In our study, the overall rate of anesthesia-related complications was 11%. To place the results in the context of general pediatric surgical patients, one large study reported a 3% rate of intraoperative anesthesia-related complications in patients younger than 17 years (11). The only other study of anesthesia for patients with MIOP reported an even higher rate of anesthesia complications, with airway difficulties in 17.7% of patients (10). In our cohort however, there were no anesthetic-related deaths, compared with a 3.2% death rate in the previously reported study (10). A possible explanation for their higher mortality is that the patients in that study were older (65% were 5 years or older versus only 9% in our study), which may tend to worsen anesthetic outcome in this degenerating condition (10).

Not only were the anesthesia-related complications in this group of patients fairly common, but they were all airway or respiratory in nature. In the aforementioned study of pediatric surgical patients, only 2% of children younger than 8 years had adverse respiratory events (11), compared with 11% in this study. This propensity in the osteopetrotic patient for airway obstruction and oxygen desaturation is probably multifactorial. Patients commonly have mandibular abnormalities, with hypoplasia reported in younger patients (12) and narrowing of the area between the base of the tongue and the posterior pharyngeal wall (6). A high and narrow hard palate is believed to contribute to airway obstruction (5), and nasal obstruction and congestion is almost universal in infants with MIOP (12). Thrombocytopenia is common and may increase the possibility of bleeding during airway manipulation (1). Episodes of oxygen desaturation are undoubtedly made more frequent due to multiple coexistent respiratory abnormalities. Patients with MIOP usually have a small and poorly compliant chest wall (5), and extra medullary hematopoiesis causes hepatosplenomegaly (13), which reduces functional residual capacity even further (10). Primary pulmonary hypertension has been reported, and patients have an increased incidence of persistent pulmonary infections (14). The common observance of obstructive sleep apnea and chronic hypoxemia in patients with MIOP (6,15) suggests that anesthesia is not necessarily required for these issues to become a problem.

We found that the rate of complications was higher before HSCT (19.4%) than afterward (3%); however this difference was not statistically significant. There are several factors to consider when interpreting these proportions. This study included a small number of patients and follow-up times varied widely among patients. Follow-up may have been of an insufficient duration to alter the pathophysiological features of MIOP that affect anesthetic outcome. During the study, patients obviously got older, and the incidence of anesthetic complications may be influenced by the aging of the patient (11). Another possible factor is the institutional “learning” that occurs for a well known patient. Complications may tend to become less likely as practitioners become familiar with patients and anticipate their anesthetic problems. Only a randomized controlled trial can truly address all these problems, but such a study would be challenging to conduct due to the small numbers of these patients.

In this study 11.5% of oral endotracheal intubations were described as difficult or moderately difficult. This rate is similar to that found in the only other study of anesthesia for patients with MIOP which reported intubation difficulty in 14.5% of patients (10). In the general pediatric population, a large study conducted at a tertiary referral center reported 0.2% of patients had unanticipated difficult intubation, although that included patients up to 16 years of age (11). Difficult oral intubation in patients with MIOP may be due to the mandibular and facial abnormalities that are frequently present (16).

There were several limitations to this study. The study design was retrospective, so we relied on accurate record keeping. It is therefore possible that we have underreported the frequency

of complications in this cohort of patients. The description of the ease of intubation was taken from the anesthesia record and did not meet any accepted definition other than the opinion of an experienced pediatric anesthesia provider. The number of patients was small, and they were a select group who had all been referred to a tertiary center. They may not be representative of patients with MIOP in general. The anesthetics were frequently provided for minor and noninvasive procedures, and often did not require instrumentation of the airway. Our results therefore may not be generalizable to typical operating room situations.

We have examined our experience anesthetizing infants and children with MIOP before and after HSCT and found that anesthetic complications were common, and were usually due to airway obstruction and arterial oxygen desaturation.. The incidence of difficult or moderately difficult oral endotracheal intubation was high, and probably due to the same structural airway abnormalities that lead to airway obstruction. Although HSCT may reverse the anatomic abnormalities of MIOP, our numbers were too small to confirm a reduction in the risk of anesthetic-related complications.

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Table 1

Comorbid conditions present before HSCT

Patient number	Sex	Nasal congestion	High arched palate/changes in mandibular size/osteomyelitis	Macrocephaly/frontal bossing/ hydrocephalus	Hepatosplenomegaly	Thrombocytopenia/ anemia	Fractures	Vision impairment	Obstructive sleep apnea
1	F	+	+/+/−	+/+/−	+	+/+	+	+	+
2	M	+	+/−/−	+/+/−	−	−/−	−	+	+
3	M	+	−/−/−	+/+/+	+	−/+	+	+	−
4	M	+	−/−/−	−/+/−	+	−/+	−	+	−
5	M	+	+/−/−	+/+/+	−	+/+	−	+	+
6	M	+	+/−/−	−/+/−	−	−/−	−	+	+
7	F	+	−/+/−	+/+/−	−	+/+	−	+	+
8	M	+	+/−/−	+/−/−	+	−/−	−	+	+
9	M	+	+/−/−	+/+/+	+	−/−	+	−	+
10	M	−	◇	+/−/+	+	+/+	−	+	−
11	F	◇	−/−/+	−/−/+	+	+/+	−	+	+

*Plus sign indicates presence of condition; Minus sign indicates absence of condition; ◇ indicates not mentioned on history or physical examination

Table 2

The numbers of complications per patient before and after HSCT

		Before HSCT				After HSCT			
Pt #	**Age at first HSCT (months)**	**# of procedures**	**# of complications**	**Complication Rate^**	**Months from diagnosis to first HSCT**	**# of procedures**	**# of complications**	**Complication Rate^**	**Months from first HSCT to death or last contact**
1	8	6	1	17%	8.0	4	0	0%	4.5
2	8.4	6	2	33%	6.7	2	1	50%	3.1
3	18.5	4	2	50%	18.5	0	0	.	2.0
4	5.2	4	0	0%	1.9	1	0	0%	0.9
5	10.8	3	0	0%	6.7	2	0	0%	3.8
6	7.4	6	3	50%	7.4	4	0	0%	4.1
7	14	3	1	33%	6.0	7	0	0%	42.1
8	8	6	1	17%	8.0	10	0	0%	6.6
9	6.5	6	0	0%	6.5	27	1	4%	36.2
10	13.3	7	0	0%	13.3	3	0	0%	4.1
11	63.4	11	2	18%	63.4	5	0	0%	9.3
TOTAL		**62**	**12**	**19%**		**65**	**2**	**3%**	

HSCT = hematopoietic stem cell transplantation

^Number of anesthesia-related complications divided by the number of procedures performed

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Table 3

Description of recorded complications

Complication #	Patient #	Age	Procedure	Airway device	Complication	Pre or post
1	1	7 months	MRI	Tracheostomy	Propofol TIVA and spontaneous ventilation. Desaturation during the MRI. Patient removed from scanner and manually ventilated via tracheostomy. Event possibly due to tracheostomy being inadvertently kinked.	Pre HSCT
2	2	6 months	Femoral line insertion	FM	Propofol TIVA and spontaneous ventilation in the ICU. Several brief episodes of oxygen desaturation responding to airway repositioning.	Pre HSCT
3	2	7 months	CT	Tracheostomy	Propofol TIVA and spontaneous ventilation. Several brief episodes of oxygen desaturation responding to repositioning and suction of the tracheostomy.	Pre HSCT
4	2	9 months	BMA and biopsy	Tracheostomy	Propofol TIVA and spontaneous ventilation. Several episodes of desaturation responding to manual ventilation, suctioning and repositioning.	Post HSCT
5	3	14 months	VER	FM/LMA	Propofol TIVA and spontaneous ventilation planned. Airway obstruction and desaturation not responding to LMA insertion, procedure cancelled.	Pre HSCT
6	3	18 months	VER	ETT	Moderately difficult to intubate with some desaturation. Airway bleeding and upper body petechiae noted after procedure.	Pre HSCT
7	6	5 months	DLHL insertion	ETT	Difficult to intubate. During central line tunnelling patient became difficult to ventilate. Desaturation with bradycardia. High airway pressures required with manual ventilation.	Pre HSCT
8	6	6 months	ABR and echo/EKG	FM	Propofol TIVA and spontaneous ventilation. Airway obstruction, desaturation responding to oral airway insertion and repositioning.	Pre HSCT
9	6	6 months	Adenotonsillectomy	ETT	IV induction followed by intubation. Bronchospasm and desaturation to 70% noted. Patient recovered slowly. Procedure cancelled.	Pre HSCT
10	7	8 months	BMA and biopsy	FM	Propofol TIVA and spontaneous ventilation. Patient had decreased respiratory effort and desaturated. Did not respond rapidly to bag mask ventilation. Intubated emergently. Slow to emerge from anesthesia.	Pre HSCT
11	8	7 months	CT and echo/EKG	FM	Propofol TIVA and spontaneous ventilation. Mild desaturation during transport that responded to airway positioning and bag mask ventilation. Echo cancelled.	Pre HSCT
12	9	6 months	Emergency intubation in OR	ETT	Intubation attempted during deep sevoflurane anesthesia. Failed intubation with presumed laryngospasm. Paralysed and intubated successfully.	Post HSCT
13	11	5 years	Emergency head CT	FM	Propofol TIVA and spontaneous ventilation. Short episodes of apnea which recovered without intervention.	Pre HSCT
14	11	5 years	Bone scan	Tracheostomy	Propofol TIVA and spontaneous ventilation. Transient apnea during induction which responded rapidly to manual ventilation via tracheostomy.	Pre HSCT

MRI = magnetic resonance imaging, CT = computed tomography, BMA = bone marrow aspiration, VER = visual evoked responses, DLHL = double lumen Hickman Line, ABR = auditory evoked brainstem responses, Echo = echocardiogram, EKG = electrocardiogram, FM = face mask, LMA = laryngeal mask airway, ETT = endotracheal tube, HSCT = hematopoietic stem cell transplantation