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The Anesthetic Management of Children with Neonatal-Onset Multi-System Inflammatory Disease

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Abstract

BACKGROUND—Neonatal-onset multi-system inflammatory disease (NOMID), a rare autosomal dominantly inherited disease, belongs to a growing spectrum of autoinflammatory diseases, is characterized by urticarial rash, arthropathy, and chronic aseptic meningitis, and is associated with mutations in the cold-induced autoinflammatory gene, *CIAS1*, the gene that encodes the protein, cryopyrin. As little is known about the anesthetic considerations of the disease, we sought to identify the main features and respective anesthetic and perioperative implications of NOMID.

METHODS—We examined perianesthetic records of children with NOMID who were anesthetized for invasive diagnostic and therapeutic interventions between 2003 and 2006. In addition, we conducted an extensive literature review of the genetic, clinical, and biochemical abnormalities of the disease.

RESULTS—Seventeen children with NOMID (median age 8 yr, range 9 mo to 11 yr) were anesthetized for diagnostic and therapeutic procedures. All patients had neurological involvement, including increased intracranial pressure, chronic aseptic meningitis, and developmental delay; 7 had bony overgrowth, 15 ocular, and 14 otological manifestations of NOMID. Despite the complexity of the disease, the perioperative course was uncomplicated, and no serious adverse events were observed.

CONCLUSIONS—This study is the first to investigate the anesthetic implications of NOMID, an autoinflammatory disease associated with arthropathy, recurrent fevers, urticarial rash, and chronic aseptic meningitis. While for the pediatric anesthesiologist, the presence of fever and aseptic meningitis might make the conduct of anesthetics for elective procedures less desirable, our findings suggest that without evidence of active infection, even in the presence of fever and chronic aseptic meningitis, general and regional anesthesia may be conducted in patients with NOMID without untoward complications.

Neonatal-onset multi-system inflammatory disease (NOMID), also known as chronic infantile neurologic, cutaneous, articular syndrome (CINCA), is an autosomal dominant autoinflammatory disease characterized by a cardinal triad of urticarial rash, arthropathy, and neurological involvement (1–3). NOMID belongs to a group of periodic fever

syndromes also called “autoinflammatory diseases” based on the occurrence of seemingly unprovoked inflammatory episodes which, contrary to autoimmune diseases, are not associated with high-titer autoantibodies or antigen-specific T cells (4). Of the autoinflammatory diseases, eight are recognized to be caused by mutations in genes that regulate inflammation, cytokine processing, and apoptosis. These include the following: pyogenic sterile arthritis, pyoderma gangrenosum, and acne; familial Mediterranean fever (FMF); hyperimmunoglobulinemia D with periodic fever syndrome; tumor necrosis factor receptor-associated periodic syndrome; Blau syndrome; and the group of diseases associated with mutations in the *CIAS1* gene, including familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and NOMID/CINCA syndrome (4,5).

NOMID is caused by missense mutations in exon 3 of the cold-induced autoinflammatory gene, *CIAS1* (also called *NALP3* or *PYPAFI*), which is located on chromosome 1q44 and encodes the protein cryopyrin (6,7). Cryopyrin is highly expressed in polymorphonuclear cells and chondrocytes (6) and belongs to a group of proteins that can assemble to form a multi-molecular complex known as the “inflammasome” (8,9). Assembly of the inflammasome, which in healthy individuals is caused by infectious agents, leads to activation of caspase-1, also known as interleukin (IL)-1 converting enzyme (8–10). In turn, activated caspase-1 cleaves proIL-1 β into its active form IL-1 β (8–10). Patients with mutations within the *CIAS1* gene constitutively assemble the inflammasome and constitutively produce large amounts of IL-1 β which in turn leads to upregulation of other potent proinflammatory cytokines, including IL-6 and tumor necrosis factor (7). Mutations within the *CIAS1* gene were initially described in two dominantly inherited familial syndromes, FCAS and MWS (5,7,11). A third disease, NOMID, shares clinical features with MWS, has a more severe phenotype, and occurs spontaneously in families without genetic diseases. Interestingly, 40%–50% of patients with clinical NOMID do not have mutations in exon 3 of *CIAS1* (7,12). The common mutations in the *CIAS1* gene among the three diseases (FCAS, MWS, and NOMID) and the clinical overlap of skin manifestations and systemic inflammation led to the notion that these three syndromes reflect a spectrum of disease severity rather than different disease entities, with NOMID being at the most severe end of the spectrum (5,7).

NOMID presents in infancy with an urticaria-like rash, fever, and neurological symptoms, comprising headaches, chronic aseptic meningitis, developmental delay, papilledema, and sensory organ involvement, including visual impairment and progressive perceptual hearing loss (1,3,5,6,13,14). Musculoskeletal abnormalities include nonspecific arthralgias and characteristic patellar bony enlargement (3). The severity of symptoms appears to persist throughout the lifespan of a patient; persistent remissions have not yet been reported (6), and mortality rate before adulthood is estimated to be around 20% (2). Patients are typically treated with steroids, nonsteroidal antiinflammatory drugs, and methotrexate (6,15). Recently, the recombinant IL-1 receptor antagonist, anakinra, has been used to treat patients with NOMID (1,16,17). Anakinra binds with high affinity to IL-1 receptors (18) and blocks IL-1 signaling (19,20). In patients with NOMID, anakinra improves rash, arthralgias, and headaches; decreases markers of inflammation (C-reactive protein, erythrocyte sedimentation rate); and improves the cochlear and leptomeningeal lesions on magnetic resonance imaging (1).

Although the broad spectrum of disease manifestations and potential increase in lifespan with advances in therapy increase the need for invasive diagnostic and therapeutic interventions, little has been reported on the anesthetic management of patients with NOMID or other autoinflammatory diseases. In this study, we examined 71 anesthetics in 17 children with confirmed diagnosis of NOMID.

METHODS

The IRB of the National Institutes of Arthritis and Musculoskeletal and Skin Diseases approved the study, which was conducted as part of an investigational protocol of the pathophysiology and therapy of autoinflammatory diseases. Results of the effects of anakinra in some of the patients included in this study were previously reported (1). Consent for anesthetics and procedures was obtained from parents or guardians. The selection of anesthetic techniques used for each patient was made at the discretion of the anesthesiologist in a tertiary clinical research center.

We examined the records between 2003 and 2006 of patients with NOMID who required anesthesia for diagnostic and therapeutic surgical procedures. We collected data on patient demographics, primary diagnosis, medications, physical findings, genetic analysis of mutations in *CIAS1*, diagnostic and therapeutic procedures, anesthetic techniques, drugs used, length of anesthetics, and perianesthetic events. When assessing complications, we focused on the anesthetic and procedural complications and noted those clinical findings (temperature changes, airway complications, decreases in oxygen saturation, postdural puncture headaches) during the perioperative period up to 48 h after the procedure.

We also reviewed the literature on the clinical characteristics and therapy of NOMID and autoinflammatory diseases as well as on anesthetic management of these syndromes. We searched EMBASE (1974 to October 2006) and MEDLINE (1968 to October 2006), scanned references from all included reports using MeSH headings (carrier proteins, anesthesia and analgesia), subheadings (diagnosis, classification, etiology), and keywords (neonatal-onset multi-system inflammatory disease, NOMID, autoinflammatory, anesthesia, CINCA).

Descriptive results are presented as means, medians, and mean $\pm$ SD as indicated. The significance of differences was evaluated with the Student's *t*-test and *P* values lesser than 0.05 were considered significant.

RESULTS

Patients

We identified 17 children who met the diagnostic criteria for NOMID and who received 71 anesthetics for diagnostic and/or therapeutic procedures between April 2003 and November 2006. Table 1 lists demographic characteristics and Table 2 major clinical findings of the 17 patients with NOMID. Thirteen (71%) patients were taking chronic glucocorticosteroids, nine (64%) were taking non-steroidal anti-inflammatory drugs, six (43%) were receiving carbonic anhydrase inhibitors, and four (29%) were taking disease-modifying anti-rheumatic drugs. After baseline studies, all patients were treated with daily subcutaneous injection of anakinra.

All patients had an urticaria-like rash, which was present around birth and 16 patients (94%) had a history of chronic fever. Sixteen patients (94%) had increased intracranial pressure (defined as presence of headaches and cerebral spinal fluid opening pressure more than 180 mm of water) before therapy with anakinra, 13 (76%) had papilledema, 10 chronic aseptic meningitis (59%), and 14 (82%) had cognitive impairment (Tables 1 and 2). All patients had manifestation of arthropathy, including arthralgias, patellar hypertrophy/overgrowth, epiphyseal overgrowth, synovial fluid effusion (seven patients [41%]), clubbing of fingers and toes without signs of pulmonary disease (five patients [29%]). One patient (Patient 7, Figure 1) had severe joint abnormalities with disabling fixed joint contractures and required repeated orthopedic interventions. Fifteen patients (88%) had ophthalmologic involvement,

manifested by optic nerve disk elevation, conjunctivitis, uveitis, visual field defects, and amblyopia with strabismus. Fourteen patients (82%) had sensorineural hearing loss. Ten patients (63%) had true vocal cord edema on indirect laryngoscopy previously conducted by an otolaryngologist. In 5 of these 10 patients, an endotracheal tube of age-appropriate size was inserted without difficulties during anesthetics. All patients had laboratory findings suggestive of inflammation, which included an increased erythrocyte sedimentation rate and C-reactive protein as well as increase of the serum amyloid A protein. As a consequence of inflammation, all patients had leukocytosis, anemia, and thrombocytosis. One patient (Patient 10) had a history of deep vein thrombosis and factor V Leiden polymorphism associated with an increase in clotting abnormalities, and two patients (Patients 7 and 15) had a lupus anticoagulant and/or high titer anticardiolipin antibodies.

Procedures and Anesthetic Management

Several procedures were conducted for diagnostic purposes, others for evaluation of therapeutic efficacy of IL-1 receptor antagonist therapy, and still others for therapeutic purposes. Table 3 lists the procedures performed and Table 4 the anesthetic management of the patients. As some patients presented with fever (six patients had a temperature 37.5°C , Table 5) just before the anesthetic, the criteria used to proceed with the planned procedure was as follows: the pattern of symptoms was similar to the patients' usual NOMID flare and no additional symptoms to suggest presence of an active infection were present. Using these criteria, no planned procedure was canceled or postponed because of increases in temperature. The duration of anesthesia was 155 ± 67 (mean $\pm$ SD) minutes and often entailed transportation of the patients between different procedure areas. In 33 cases, anesthesia was induced with propofol, in 34 with inhaled anesthetics (sevoflurane and nitrous oxide). With regard to Patient 4, because of a history of allergy to eggs and request from the parent not to use propofol, in three procedures, anesthesia was induced with etomidate and, in another, with sodium thiopental. After induction of anesthesia, in 15 anesthetics administered to 10 of the patients, endotracheal intubation was performed without difficulties. All intraoperative courses were uncomplicated, except that one patient displayed mild hypothermia. There was no evidence of hemodynamic lability, signs of hypermetabolism, or interruption of procedures. One patient (Patient 8) had a seizure during emergence from anesthesia with sevoflurane. This child had a history of seizures and was treated with midazolam.

All lumbar punctures were performed after acquisition of brain imaging. In 15 patients at the first anesthetic (baseline study), and before IL-1 receptor antagonist therapy, mean opening pressures were 25.8 ± 12.5 cm H₂O and mean closing pressures after removal of cerebrospinal fluid were 17.4 ± 7.2 cm H₂O (mean $\pm$ SD). We compared opening and closing pressures obtained with controlled versus spontaneous ventilations in 40 anesthetics (both before and after initiation of IL-1 receptor antagonist therapy). In 8 of these procedures, patients had an endotracheal tube and ventilation was controlled, whereas in 32 procedures, patients were breathing spontaneously and had a laryngeal mask airway (10 anesthetics), nasal cannula (18), or facemask (4). There were no significant differences between opening (21.3 ± 7.6 cm H₂O) and closing (16.5 ± 7.6 cm H₂O) pressures in patients on controlled ventilation compared with those patients breathing spontaneously (23.9 ± 10.6 and 17.9 ± 7.9 cm H₂O opening and closing pressures respectively), both $P > 0.4$. Similarly, there were no significant differences between opening and closing pressures upon comparing patients anesthetized with propofol versus those who inhaled anesthetics ($P = \text{NS}$, data not shown).

For most patients, postoperative courses were unremarkable except for Patients 9 and 14 who had episodes of decrease in oxygen saturation postoperatively that resolved with supplemental oxygen. Both children recovered without other sequelae and were discharged

24 h after the procedure. None of the five patients with pre-existing true vocal cord edema on indirect laryngoscopy showed airway complications after extubation of the trachea. After the 71 anesthetics, there were two episodes of postdural puncture headaches that resolved with IV hydration and bed-rest (Patients 1 and 4), and three episodes of short-lived fever (Patients 8 [38.4°], 14 [39.5°C], 16 [39°C]) after discharge from the recovery area that resolved spontaneously. Table 5 shows temperatures of the 17 children during the perianesthetic period.

Review of the literature

We found no reports of the anesthetic implications or management in patients with NOMID.

DISCUSSION

Given the inflammatory involvement of multiple organs in children with NOMID, a multitude of diagnostic and therapeutic procedures are required for diagnosis and monitoring of response to therapy and, because many of these procedures are done in small children and developmentally challenged adolescents, anesthesia is frequently required. Although there is a growing number of recognized autoinflammatory diseases, many of which are caused by mutated genes that encode proteins involved in the regulation of inflammatory and apoptotic pathways, there have been few reports on the anesthetic implications of these diseases. We found one report of a patient with FMF and amyloidosis who had an uncomplicated regional anesthetic for a cesarean delivery (21); however, reports of anesthetic implications in larger series of patients are lacking. To our knowledge, this is the first series of anesthetics in children with NOMID, one of the most severe diseases of any currently recognized autoinflammatory syndromes. We believe that some of the principles exemplified by this disease can likely be applied to other autoinflammatory diseases as well.

Among the features that can have anesthetic implications in children with NOMID is increased intracranial pressure. Almost all children with NOMID present with increased intracranial pressure (1), a finding that appears to be present in most patients who also have chronic aseptic meningitis. Clinically, patients present with headaches with or without nausea and vomiting and papilledema. In our patients, lumbar punctures and opening pressure measurements were performed for diagnostic purposes and were repeated serially after therapy with anakinra to evaluate its therapeutic effect on intracranial pressure and meningeal inflammation. Although some studies have shown that opening pressures measured during general anesthesia may differ from those measured while children regain consciousness (22), we were able to longitudinally follow the effect of the therapy as children had repeated measurements under similar anesthetic conditions (1). In addition, as this study was not prospectively designed to evaluate the effects of anesthetics or mode of ventilation on opening pressures, the anesthetic technique used for procedures was chosen based on clinical indications and preference of the anesthesiologist. However, the authors were able to compare opening pressures among patients undergoing lumbar punctures with different anesthetic techniques. While some have shown that in patients with supratentorial tumors, intracranial pressure measured after craniotomies is lesser during propofol anesthesia compared with inhaled anesthetics (23), we used both modalities for maintenance of anesthesia and observed no significant differences on opening and closing pressures. Most importantly, while some patients had postdural puncture headaches, no patient showed signs of deterioration or worsening of baseline neurological signs and symptoms after any of the anesthetics.

Another issue an anesthesiologist is likely to face when caring for children with NOMID is the presence of fever just before administration of some anesthetics. Patients with NOMID, when untreated, present with recurrent seemingly unprovoked febrile episodes that are not

caused by infection and are chronic manifestations of the disease. One report advocates avoiding any type of anesthesia during acute episodes of fever in patients with autoinflammatory syndromes (24). In our series of patients, given that recurrent episodes of fever are seen in most autoinflammatory syndromes, and that fevers are typically not associated with infections, we chose not to postpone any procedure because of fever unless a child had evidence of active infection. During the postoperative period, after the children were discharged from the recovery area, three of our patients developed fever that was transient, not associated with infections, and that resolved without sequelae. As observations in patients with NOMID can likely be extrapolated to other autoinflammatory syndromes, one could argue that the presence of fever alone, in the absence of additional signs and symptoms to suggest active infection, does not necessarily warrant cancellation of procedures requiring anesthesia in patients with other autoinflammatory diseases.

Some advocate that regional anesthesia is best avoided in patients with autoinflammatory syndromes (24). This concern may particularly apply to children with NOMID who have chronic aseptic meningitis and increased intracranial pressures. Although we found no report of neuraxial block in patients with NOMID, it is conceivable that chronic meningitis might alter pharmacokinetics and pharmacodynamics of anesthetic drugs deposited around the neuraxis. Interestingly, one published study reports the injection of intrathecal methotrexate in a child with aseptic meningitis who responded with amelioration of the meningitis (15). Although we have seen postspinal headaches in two children in our series, we have performed multiple lumbar punctures that were generally well tolerated. However, there remains a theoretical concern that NOMID patients may be more likely to develop postdural puncture headache, or that intrathecal injection of anesthetics may worsen the pre-existent increased intracranial pressure or inflammation of the meninges. In addition, it is also unknown whether patients with NOMID are more prone to epidural infections. Although these risks are hypothetical, there are no data to suggest that children with NOMID should not receive regional anesthesia when indicated. In our series, we conducted two anesthetics for orthopedic procedures with combined general anesthesia and epidural block. We considered the possible risks but thought they would be outweighed by benefits of neuraxial block in controlling postoperative pain, and the patient tolerated both anesthetics and procedures well. Therefore, one could argue that NOMID presents no absolute contraindications for use of neuraxial block in children. Further, we propose that the technique of neuraxial block, and proceeding with the block in these patients, does not contradict the current guidelines for use of regional anesthesia in the febrile and immunocompromized patients (25,26).

The involvement of other organs in NOMID should also be considered when planning the anesthetic for these patients. For example, the presence of laryngeal involvement, evident on indirect laryngoscopy in some patients, warrants concerns about airway manipulation in these children. However, while some of our patients had pre-existent true vocal cord edema on indirect laryngoscopy performed by an otolaryngologist, we used age-appropriate endotracheal tube sizes and observed no clinical evidence of airway complications. With regard to the joint abnormalities in NOMID (Figure. 1), they can lead to asymmetry and deformities of limbs and/or impairment of function. Therefore, careful positioning of these patients is essential for the conduct of a safe anesthetic. Many of our patients had uveitis, redness of conjunctiva, all of which warrant careful attention to eye protection during general anesthesia. Developmental delay and sensorineural hearing loss may pose a challenge for the anesthesiologist when planning for separation from the parents. Since most of these children are treated with glucocorticosteroids, the use of stress doses of steroids must be considered. As some children are taking carbonic anhydrase inhibitors, nonsteroidal anti-inflammatory, and cytotoxic drugs, depending on the nature of the procedure, monitoring of acid base and metabolic profile should also be considered. Furthermore,

although we did not measure levels of proinflammatory cytokines preoperatively and postoperatively to evaluate the effect of the stress of invasive procedures on cytokine activation, we observed no clinical evidence of worsening of the autoinflammatory state after the anesthetics.

In summary, we examined the administration of anesthesia in 17 children with NOMID who underwent a total of 71 procedures. Factors that warrant careful attention when planning an anesthetic for these children include pre-existent increased intracranial pressure, chronic aseptic meningitis, bone and coagulation abnormalities, and chronic febrile episodes. While for the pediatric anesthesiologist, the presence of fever and aseptic meningitis might make the conduct of anesthetics for elective procedures less desirable, our experience with patients with NOMID suggests that without evidence of active infection, even in the presence of fever and chronic aseptic meningitis, general and regional anesthesia may be conducted without untoward complications. Therefore, once all possible co-morbidities in patients with NOMID are defined, anticipated, and addressed, the intraoperative anesthetic courses are likely to be uncomplicated and, for the most part, uneventful.

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Figure 1. Eleven-year old boy (Patient 7) with neonatal-onset multisystem inflammatory disease (NOMID) and severe joint deformities, which warranted repeated orthopedic procedures. The child also had severe neurological involvement.

Table 1

Demographics and Clinical Presentation of Patients with NOMID^a

Patient	Age (yr)	Sex	Weight, kg (percentile)	Height, cm (percentile)	CIAS1 mutation	Fever	Rash
1	8	M	29.6 (81)	115.2 (<3)		N	Y
2	8	M	15.6 (<3)	92.3 (<3)		Y	Y
3	8	F	19.7 (4)	126.3 (43)	G569R	Y	Y
4	4	M	14.4 (16)	100.8 (39)	G326E	Y	Y
5	4	F	18.2 (83)	94.3 (6)		Y	Y
6	9	F	49.7 (>97)	150.3 (>97)	D303N	Y	Y
7	11	M	13.0 (<3)	81.5 (<3)		Y	Y
8	8	F	19.3 (<3)	89 (<3)	A374N	Y	Y
9	11	F	40.9 (68)	139 (26)	V262A	Y	Y
10	8	M	25.9 (54)	114 (<3)	L632F	Y	Y
11	7	M	26.9 (37)	125.6 (10)	F523C	Y	Y
12	1	F	10.8 (62)	83.7 (>97)	L264F	Y	Y
13	8	F	15.2 (<3)	93.8 (<3)		Y	Y
14	1	M	15.4 (>97)	80 (15)	D303N	Y	Y
15	3	F	11 (3)	49.4 (<3)	None	Y	Y
16	1	F	10.4 (75)	74 (50)	G755A	Y	Y
17	0.75	F	6 (<3)	45.5 (<3)	I334F	Y	Y

^aY indicates presence and N absence of the listed abnormality. Age is that at the time of first anesthetic.

Table 2

Major Clinical Findings and Organ Involvement in 17 Children with NOMID^a

Patient	Neurological involvement										Hematological findings
	Increased ICP	Chronic papilledema	Chronic meningitis	Developmental delay	Bony overgrowth	Eye involvement	Ear involvement	Laryngeal involvement			
1	Y	Y	Y	Y	Y		Y	N		Y	
2	Y	Y	Y	N	Y	N	N	Y		Y	
3	Y	Y	Y	Y	Y	Y	Y	N		Y	
4	Y	N	N	Y	N	Y	N	Y		Y	
5	Y	N	N	Y	Y	N	N	N		Y	
6	Y	Y	N	Y	N	Y	Y	Y		Y	
7	Y	Y	Y	Y	Y	Y	Y	Y		Y	
8	Y	Y	N	Y	Y	Y	Y	N		Y	
9	Y	Y	Y	Y	N	Y	Y	Y		Y	
10	Y	Y	Y	Y	N	Y	Y	Y		Y	
11	Y	N	N	N	N	Y	Y	Y		Y	
12	Y	Y	Y	N	N	Y	Y	Y		Y	
13	Y	Y	N	Y	N	Y	Y	N		Y	
14	Y	Y	Y	Y	N	Y	Y	Y		Y	
15	N	N	N	Y	Y	Y	Y	Y		Y	
16	Y	Y	Y	Y	N	Y	Y	N		Y	
17	Y	Y	Y	Y	N	Y	Y	N		Y	

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^a *Anesth Analg*. Author manuscript; available in PMC 2012 June 1.

^a Bony overgrowth includes epiphyseal and/or patellar overgrowth. All children have intermittent arthralgias and five had clubbing. Eye involvement includes uveitis, progressive visual defect, amblyopia with strabismus, photophobia, optic nerve disc elevation, redness of the eyes, or conjunctivitis. Ear involvement includes the diagnoses of hearing loss. Laryngeal involvement includes the diagnosis of true vocal cord swelling made by indirect laryngoscopy. Hematological findings include anemia, leukocytosis, thrombocytosis, or coagulation abnormalities. ICP reflects intracranial pressure.

Y, presence of the listed finding; N, absence of the listed finding.

Table 3Procedures Requiring Anesthetics in 17 Children with NOMID^a

Procedure	Number
Imaging studies	
MRI	54
CT	2
Lumbar puncture, CSF drainage	49
Examination under anesthesia	
Eye exam including retinoscopy	30
Ear exam	20
Auditory steady state response	20
Indirect laryngoscopy	1
Biopsies	
Skin	15
Articular cartilage	1
Bone marrow	2
Orthopedic procedures	4

^aImaging studies included magnetic resonance (MRI) and computerized tomography (CT) imaging of the brain, spine, chest, abdomen, and extremities. Orthopedic procedures included knee arthrotomy, lysis of adhesions, mobilization of the knee, and arthroscopy.

Table 4

Perianesthetic Course in 71 Anesthetics for Invasive Diagnostic and Therapeutic Procedures in 17 Children with NOMID

	Number
Anesthetic technique	
General	69
General and regional	2
Monitoring	
Standard	71
Induction agent	
Inhalation agent (sevoflurane and nitrous oxide)	34
Propofol	33
Etomidate	3
Sodium thiopental	1
Maintenance anesthetic	
Propofol	29
Inhalation agent	15
Propofol and inhalation agent	27
Other intraoperative drugs	
Muscle relaxant	11
Midazolam	34
Intraoperative events	
Seizure	1
Postoperative events	
Postoperative nausea and vomiting	1
Post dural puncture headache	2
Fever after procedure	3
Hypoxia secondary to atelectasis	2

Table 5Pre-, Intra-, and Post-Procedure Temperature Measurements in 71 Anesthetics for 17 Children with NOMID^a

Temperature	Pre-operative (°C)	Intra-operative (°C)	Post-operative (°C)
Median	36.6	36.4	36.6
Mean	36.7	36.5	36.5
Min	35.7	35.6	35.8
Max	39.1	39	38.3
Patients with T ≥ 37.5°C	6	3	4

^aTemperature measurements were obtained from tympanic membrane or temporal artery preoperatively, skin or esophageal intraoperatively, and tympanic membrane postoperative. The intraoperative temperature reported is the highest recorded during the anesthetic and the postoperative is the highest recorded within 24 h after the anesthetic.