Published in final edited form as:

Anesth Analg. 2015 November ; 121(5): 1316–1320. doi:10.1213/ANE.0000000000000912.

Anesthetic Management of Patients with Congenital Insensitivity to Pain with Anhidrosis: A Retrospective Analysis of 358 Procedures Performed Under General Anesthesia

Alexander Zlotnik, MD, PhD[*], **Dmitry Natanel, MD**[*], **Ruslan Kutz, MD**[*], **Matthew Boyko, PhD**[*], **Evgeny Brotfain, MD**[*], **Benjamin F. Gruenbaum, MD**[†], **Shaun E. Gruenbaum, MD**[†], and **Lipa Bodner, MD**[‡]

[*]Department of Anesthesiology and Critical Care, Soroka Medical Center, Ben-Gurion University of the Negev, Faculty of Health Science, Beer-Sheva, Israel

[†]Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut

Address correspondence to Alexander Zlotnik, MD, PhD, Department of Anesthesiology and Critical Care, Soroka Medical Center, P.O. Box 151, Beer-Sheva 8410101, Israel. zlotnika@bgu.ac.il.

The authors declare no conflicts of interest.

LMA is a registered trade mark of The Laryngeal Mask Company Limited, an affiliate of Teleflex Incorporated.

Reprints will not be available from the authors.

DISCLOSURES

Name: Alexander Zlotnik, MD, PhD.
Contribution: This author was in some way involved in the study design, conduction of the study, data analysis, and manuscript preparation.
Attestation: Alexander Zlotnik approved the final manuscript.
Name: Demitry Natanel, MD.
Contribution: This author was in some way involved in the study design, conduction of the study, data analysis, and manuscript preparation.
Attestation: Demitry Natanel approved the final manuscript.
Name: Ruslan Kutz, MD.
Contribution: This author was in some way involved in the study design, conduction of the study, data analysis, and manuscript preparation.
Attestation: Ruslan Kutz approved the final manuscript.
Name: Matthew Boyko, PhD.
Contribution: This author was in some way involved in the study design, conduction of the study, data analysis, and manuscript preparation.
Attestation: Matthew Boyko approved the final manuscript.
Name: Evgeny Brotfain, MD.
Contribution: This author was in some way involved in the study design, conduction of the study, data analysis, and manuscript preparation.
Attestation: Evgeny Brotfain approved the final manuscript.
Name: Benjamin F. Gruenbaum, MD.
Contribution: This author was in some way involved in the study design, conduction of the study, data analysis, and manuscript preparation.
Attestation: Benjamin F. Gruenbaum approved the final manuscript.
Name: Shaun E. Gruenbaum, MD.
Contribution: This author was in some way involved in the study design, conduction of the study, data analysis, and manuscript preparation.
Attestation: Shaun E. Gruenbaum approved the final manuscript.
Name: Lipa Bodner, MD.
Contribution: This author was in some way involved in the study design, conduction of the study, data analysis, and manuscript preparation.
Attestation: Lipa Bodner approved the final manuscript.
This manuscript was handled by: James A. DiNardo, MD.

‡Department of Oral and Maxillofacial Surgery Soroka Medical Center, Ben-Gurion University of the Negev, Beersheba, Israel

Abstract

BACKGROUND—Congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive disorder characterized by recurrent episodic fevers, anhidrosis, absent reaction to noxious stimuli, self-mutilating behavior, and mental retardation. The anesthetic management of patients with CIPA is challenging. Autonomic nervous system abnormalities are common, and patients are at increased risk for perioperative complications.

METHODS—In this study, we describe our experience with 35 patients with CIPA who underwent 358 procedures requiring general anesthesia between 1990 and 2013.

RESULTS—During surgery, 3 patients developed hyperthermia intraoperatively (>37.5°C) without prior fever. There were no cases of intraoperative hyperpyrexia (>40°C). Aspiration was suspected in 2 patients, and in another patient aspiration was prevented by the use of endotracheal tube, early detection of regurgitation, and aggressive suctioning. One patient had cardiac arrest requiring cardiopulmonary resuscitation. Intraoperative bradycardia was observed in 10 cases, and postoperative bradycardia was observed in 11 cases.

CONCLUSIONS—Regurgitation, hyperthermia, and aspiration were uncommon, but the incidence of bradycardia was higher than has been reported in previous studies. CIPA remains a challenge for anesthesiologists. Because of the rare nature of this disorder, the risk of various complications is difficult to predict.

Congenital insensitivity to pain with anhidrosis (CIPA), or hereditary sensory and autonomic neuropathy type IV, is an autosomal recessive disorder that manifests with recurrent episodic fevers, anhidrosis, defects in nociceptive reception, self-mutilating behavior, and intellectual disability.[1] The human *TRKA* gene (NTRK1), found on chromosome 1q21-q22, has been reported to be responsible for CIPA, encoding the neurotrophic tyrosine kinase receptor for nerve growth factor.[2,3] The mutation in NTRK1 hinders the ability of nerve growth factor to bind to the receptor properly, leading to the characteristic lack of nociceptive reception. The anomalous pain and temperature sensation and anhidrosis in CIPA result from a loss of afferent unmyelinated and small myelinated nerves and a loss of unmyelinated axons in peripheral nerves surrounding eccrine sweat glands, respectively.[4] The pathophysiological mechanisms of these morphological changes are unknown but are thought to reflect a developmental defect.

There is no cure for CIPA, and therapy is largely preventive or supportive. If hyperpyrexia is not well controlled, CIPA can be fatal in the first few years of life. In younger children, self-mutilation such as tongue or finger biting is very common and requires dental extractions. In older children, osteomyelitis and bone/joint deformities require frequent surgical procedures, including amputations.[5,6] Special training programs to prevent self-mutilation and accidental injuries are necessary but may be hampered by the patients' cognitive deficiencies.[7]

The anesthetic management of patients with CIPA is challenging. Autonomic nervous system abnormalities are common, making CIPA patients subject to numerous anesthetic

complications, including an increased risk of regurgitation and aspiration, hyperthermia, hypotension, and bradycardia.[2,7,8] However, CIPA is rare, and there is insufficient data in the literature regarding the rate of complications. In the largest analysis of anesthetics in CIPA patients to date, the experience of 40 cases from our institution was described.[9]

In Israel, there are 2 Bedouin families with CIPA. One family from southern Israel has a 1926-ins-T mutation in *TRKA* gene. A second family from northern Israel has a Pro-689-Leu mutation in the *TRKA* gene.[2]

Soroka University Medical Center (SUMC), a 1100-bed hospital, is the primary referral center for the entire southern region of Israel. At our institution, CIPA patients have undergone a wide range of surgical procedures. In this study, we present a retrospective analysis of our experience with 35 patients with CIPA who underwent 358 procedures requiring general anesthesia between 1990 and 2013.

METHODS

This study was conducted according to the recommendations set by the Helsinki committee and was approved by the ethics committee of Ben-Gurion University of the Negev, Beer-Sheva, Israel.

Forty-six patients with CIPA are currently being followed by the pediatric ambulatory center at SUMC. After obtaining IRB approval, we retrospectively reviewed the patients' medical histories for surgical procedures requiring general anesthesia. Three hundred fifty-eight cases of general anesthesia in 35 CIPA patients from 1990 through 2013 were found. Only one procedure was performed during each anesthetic. We analyzed the preoperative anesthetic assessment, anesthesia record, and postanesthesia care unit (PACU) records for demographic data, including age, gender, weight, duration of anesthesia and surgery, and type of surgery. We further recorded perioperative alterations in body temperature, blood pressure, and heart rate. Lastly, we evaluated induction and maintenance drugs, postoperative analgesics, and the incidence of nausea, vomiting, and other adverse events (hypotension, hypertension, bradycardia, tachycardia, hyperthermia, aspiration, bronchospasm, cardiac arrest, and hyperpyrexia).

Hyperthermia was defined as a body temperature exceeding 37.5°C (99.5°F) and hyperpyrexia as body temperature exceeding 40.0°C (104°F). Hypotension and hypertension were defined as a decline or elevation in blood pressure by at least 20% from baseline, respectively. Baseline blood pressure was obtained either from the preanesthetic assessment record or from the first set of vital signs during the surgical case. Bradycardia was defined as a heart rate <80 beats per minute in patients from age 1 month to 1 year or <60 beats per minute in patients older than 1 year of age. Tachycardia was defined as 20% elevation above baseline values.

RESULTS

Thirty-five CIPA patients (21 men and 14 women) age 2 months to 22 years underwent 358 procedures under general anesthesia at SUMC from 1990 to 2013 (Table 1). All patients had

complete congenital analgesia accompanied by mental retardation. Perioperative monitoring included 6-lead electrocardiogram, noninvasive blood pressure, endtidal carbon dioxide, and pulse oximeter. Body temperature (rectal or nasopharyngeal) was measured continuously in 24% of cases (*n* = 85). Active warming, including forced air warming mattress, pediatric bed warmer, or heating blanket, was used in 12% of cases (*n* = 44).

Of the procedures performed, 248 were orthopedic, 64 were dental, and 23 were ophthalmic (Table 2). The most frequent procedure was incisional drainage and debridement, which comprises almost half of all procedures (163 of 358 cases). The duration of surgical procedures ranged from 6 minutes (debridement) to 5 hours (open reduction of a femoral fracture). Six patients had not fasted for at least 6 hours before general anesthesia (each of these emergent cases), 29 patients had a temperature higher than 37.5°C (99.5°F) at the start of the procedure, and 1 was hyperpyretic with a temperature of 40.0°C (104.0°F). No sedative premedication was given to patients before surgery.

General anesthesia was predominantly induced with IV anesthetics, in which propofol was used in 71% of cases (*n* = 254; Table 3). Rapid sequence induction with the application of cricoid pressure was done in 3% of cases (*n* = 12). Muscle relaxants, both depolarizing and nondepolarizing, were used in 27% of cases (*n* = 96) on induction. Fentanyl was used during induction in 8% of cases (*n* = 28).

The airway was secured with an endotracheal tube in 40% of cases (*n* = 142), laryngeal mask in 15% of cases (*n* = 53), and facemask in 20% of the patients (*n* = 70). In the remaining 93 procedures, there was no information about airway management. General anesthesia was maintained by repeated boluses of propofol in 29% of cases (*n* = 105) or volatile anesthetics, including isoflurane in 11% of cases (*n* = 40), halothane in 7% (*n* = 26), and sevoflurane in 3% (*n* = 12). Nitrous oxide was used in 46% of cases (*n* = 166). During maintenance of anesthesia, muscle relaxants and opioids (fentanyl) were used in 6% (*n* = 21) and 2% (*n* = 7) of all cases, respectively.

Three patients developed hyperthermia intraoperatively without prior fever (Table 4). The warming blanket had actively warmed 2 of these patients. No patients developed intraoperative hyperpyrexia; however, in addition to the 3 cases of hyperthermia, 1 patient was hyperpyretic before surgery. This case of preoperative hyperpyrexia was thought to be because of sepsis, and the patient was administered rectal paracetamol before surgery with a subsequent normothermic intraoperative temperature. Aspiration was suspected in 2 patients: one during maintenance with an LMA™, and the other in the postanesthesia care unit (PACU) after surgery. Both patients had fasted for >8 hours before surgery. One patient had massive regurgitation during anesthesia but did not aspirate because of the presence of an endotracheal tube, early detection, and aggressive suctioning. One child developed bronchospasm on induction. One patient, who was induced with propofol and maintained with halothane 2% delivered with a mixture of 2:1 N_2O/O_2 under spontaneous respiration, went into cardiac arrest after a period of bradycardia 30 minutes into the operation. This was a 19-month-old male who underwent release of a first toe contracture and has been described in the literature by Rozentsveig et al.[9] With resulting loss of all electrical activity, cardiopulmonary resuscitation was performed for 40 minutes with restoration of the

heartbeat and blood pressure. The patient remained in a vegetative state for 6 days in the intensive care unit and then died. The parents refused autopsy, so the exact cause of death remains unknown.

Intraoperative bradycardia was observed in 2.8% of cases (10 cases in 5 different patients). Three patients were bradycardic during 1 procedure, 1 patient was bradycardic during 3 procedures, and 1 patient was bradycardic during 4 procedures. Each of these patients was older than 1 year. Propofol was the induction agent in all the 10 cases, and in 7 cases, it was also used for maintenance. One patient was administered propofol and fentanyl, and another patient was administered succinylcholine and halothane. Of all 10 cases of bradycardia, halothane was used only in a single case. Intraoperative bradycardia was treated with atropine in 6 cases and with ephedrine in 2 cases (in both of these, bradycardia was associated with hypotension).

Eleven patients had postoperative bradycardia, which included 2 of the patients who experienced intraoperative bradycardia. Of the patients who had postoperative bradycardia, propofol was used for induction in 9 cases and with thiopental in 2 cases. Propofol was used for maintenance in 7 of the 11 cases. Halothane was used in 3 cases, and isoflurane was used in 1 case. Postoperative bradycardia was treated with atropine in 3 cases.

Tachycardia appeared in 11 patients within the first 10 minutes after induction, 3 cases of which continued later in the case. One case of tachycardia was associated with hypotension, with no mention of hemorrhage in the intraoperative documentation.

Of the 14 patients who experienced intraoperative hypotension, 3 patients experienced concomitant bradycardia. Twelve patients were induced with propofol, and the other 2 patients were maintained with halothane.

DISCUSSION

In this study, we analyzed our experience with 358 cases of general anesthesia in patients with CIPA. This is the largest such series of general anesthetics described in CIPA patients.

CIPA is a rare hereditary cause of sensory autonomic neuropathy. The primary anesthetic concern in patients with CIPA is autonomic nervous system dysfunction, which may predispose the patients to an increased risk of regurgitation of gastric contents and subsequent aspiration.[10] Patients are also prone to hemodynamic instability, bradycardia, and inability to regulate body temperature.

Because of their innate analgesia, patients with CIPA are unique with regard to perioperative pain control. Of the 358 cases of general anesthesia, only 28 patients were administered fentanyl on induction and 7 patients during maintenance. Because the study is retrospective, we can only infer that fentanyl was used during induction to eliminate the stress response to airway manipulation and the hemodynamic changes associated with this. CIPA patients, despite the lack of peripheral pain sensation, do respond to airway manipulation. Only 2 patients were administered pain medicine in the PACU: a 20-year-old patient on 2 occasions

was administered IV morphine 2 mg and 3 mg, and a 1-year-old patient was administered a rectal suppository of paracetamol 150 mg. No regional anesthetic techniques were used.

Hyperpyrexia can be fatal in approximately 20% of CIPA patients in the first 3 years of life.[7] Consequently, strict perioperative temperature control has been advocated to maintain a core body temperature <37°C (98.6°F).[7,8,11] Although hyperthermia was historically considered a primary concern in the anesthetic management of CIPA patients, study seems to suggest that this is an extremely rare complication. Only 1 child without prior fever had an elevation in body temperature from 37.4°C (99.3°F) to 38.2°C (100.7°F) without being actively warmed. However, because temperature was not monitored in 76% of patients, we could not determine the true incidence of intraoperative hyperthermia.

Similar to patients with uncontrolled diabetes mellitus, the autonomic nervous system abnormalities in patients with CIPA may predispose to gastroparesis and delayed gastric emptying,[12] as well as an increased risk of regurgitation and aspiration.[13] In this study, we observed only 2 cases of regurgitation with aspiration and 1 case of regurgitation without aspiration, representing about 0.8% of the cases. It has previously been suggested that all CIPA patients should be considered having a “full stomach,” regardless of their nil per os status, because of their risk of aspiration. Therefore, rapid sequence induction with an endotracheal tube may be the most appropriate management in these patients.[13]

In our experience, 2.8% of patients (10 of 358 cases) experienced bradycardia during general anesthesia. This is higher than the previously published incidence of bradycardia during general anesthesia: 0.32% to 1.27% in infants and 0.07% to 0.98% in patients older than 1 year.[14,15] The exact mechanism of the bradycardia and hypotension in this population remains unknown. The effects of propofol cannot be ruled out, however; propofol was used for induction in >70% of all 358 cases. It is also possible that autonomic dysfunction may play a role in cardiovascular stability. The exact mechanism, however, remains to be investigated. Tachycardia appeared in 3% of patients, but in 73% of these cases it occurred immediately after induction and may have been a result of sympathetic discharge after airway manipulation.

The main drawback of our investigation is the retrospective nature of the study. For instance, there was no documentation for the airway management in 93 cases. Although it is likely that these cases were conducted via spontaneous ventilation with no artificial airway, we cannot confirm this. Similarly, temperature was not followed in 76% of the patients intraoperatively, likely because many of the surgeries were brief. It would have further been helpful to have information in the medical records regarding pain assessment or scores; however, routine assessment of pain scores in this population was not performed, likely because they rarely experience pre- or postoperative pain. However, pain assessment and assignment of objective pain scores should be performed and documented in patients with this condition.

In conclusion, the intraoperative management of patients with CIPA presents numerous challenges to anesthesiologists. Perioperative care should focus on prevention of regurgitation and aspiration and maintenance of body temperature. Autonomic dysfunction

may also result in hemodynamic instability, and although hyperpyrexia and aspiration were uncommon in our experience, bradycardia was more common than previously reported.

Acknowledgments

Funding: None.

REFERENCES

1. Swanson AG. Congenital insensitivity to pain with anhydrosis A unique syndrome in two male siblings. Arch Neurol. 1963; 8:299–306. [PubMed: 13979626]
2. Shatzky S, Moses S, Levy J, Pinsk V, Hershkovitz E, Herzog L, Shorer Z, Luder A, Parvari R. Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: genetic heterogeneity, novel mutations in the TRKA/NGF receptor gene, clinical findings, and results of nerve conduction studies. Am J Med Genet. 2000; 92:353–360. [PubMed: 10861667]
3. Indo Y, Mardy S, Miura Y, Moosa A, Ismail EA, Toscano E, Andria G, Pavone V, Brown DL, Brooks A, Endo F, Matsuda I. Congenital insensitivity to pain with anhidrosis (CIPA): novel mutations of the TRKA (NTRK1) gene, a putative uniparental disomy, and a linkage of the mutant TRKA and PKLR genes in a family with CIPA and pyruvate kinase deficiency. Hum Mutat. 2001; 18:308–318. [PubMed: 11668614]
4. Langer J, Goebel HH, Veit S. Eccrine sweat glands are not innervated in hereditary sensory neuropathy type IV An electron-microscopic study. Acta Neuropathol. 1981; 54:199–202. [PubMed: 6167137]
5. Bodner L, Woldenberg Y, Pinsk V, Levy J. Orofacial manifestations of congenital insensitivity to pain with anhidrosis: a report of 24 cases. ASDC J Dent Child. 2002; 69:293–296. 235. [PubMed: 12613315]
6. Machtei A, Levy J, Friger M, Bodner L. Osteomyelitis of the mandible in a group of 33 pediatric patients with congenital insensitivity to pain with anhidrosis. Int J Pediatr Otorhinolaryngol. 2011; 75:523–526. [PubMed: 21281970]
7. Rosemberg S, Marie SK, Kliemann S. Congenital insensitivity to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV). Pediatr Neurol. 1994; 11:50–56. [PubMed: 7527213]
8. Oliveira CR, dos Santos FA, Nogueira CS, Mainardes EJ. Spinal anesthesia in a patient with congenital insensitivity to pain with anhidrosis. Anesth Analg. 2007; 104:1561–1562. [PubMed: 17513658]
9. Rozentsveig V, Katz A, Weksler N, Schwartz A, Schilly M, Klein M, Gurman GM. The anaesthetic management of patients with congenital insensitivity to pain with anhidrosis. Paediatr Anaesth. 2004; 14:344–348. [PubMed: 15078381]
10. Tomioka T, Awaya Y, Nihei K, Sekiyama H, Sawamura S, Hanaoka K. Anesthesia for patients with congenital insensitivity to pain and anhidrosis: a questionnaire study in Japan. Anesth Analg. 2002; 94:271–274. [PubMed: 11812683]
11. Okuda K, Arai T, Miwa T, Hiroki K. Anaesthetic management of children with congenital insensitivity to pain with anhidrosis. Paediatr Anaesth. 2000; 10:545–548. [PubMed: 11012960]
12. Brüssel T. [Anesthesia and diabetes mellitus]. Anaesthesist. 1994; 43:333–346. [PubMed: 8042763]
13. Zlotnik A, Gruenbaum SE, Rozet I, Zhumadilov A, Shapira Y. Risk of aspiration during anesthesia in patients with congenital insensitivity to pain with anhidrosis: case reports and review of the literature. J Anesth. 2010; 24:778–782. [PubMed: 20632040]
14. Murat I, Constant I, Maud'huy H. Perioperative anaesthetic morbidity in children: a database of 24,165 anaesthetics over a 30-month period. Paediatr Anaesth. 2004; 14:158–166. [PubMed: 14962332]
15. Keenan RL, Shapiro JH, Kane FR, Simpson PM. Bradycardia during anesthesia in infants An epidemiologic study. Anesthesiology. 1994; 80:976–982. [PubMed: 8017662]

Table 1

Demographic Data

Variable	Value
Gender (males/females)	21/14
Age	
Mean, years ± SD	7 ± 4.9
Range	2 months to 22 years

Table 2

General Anesthesia Cases

Name of the procedure	Number of procedures
Orthopedic surgeries, total	248
Debridements	82
I&Ds	81
Toe amputations	21
Arthrotomies	12
Skin grafts	12
Spicas	8
ORIF femur	7
Other orthopedics	BKA 4, AKA 2, TEN 2, second look 2, muscle fap 2, biopsy 2, ankle fusion 1, ORIF elbow 2, CRIF elbow 1, ORIF forearm 1, knee arthrodesis 1, IMN removal 1, osteotomy 1, pin removal 1, contracture release 1
Dental surgeries, total	64
Teeth extractions	60
Other dental	ORIF mandible 2, mandible plate removal 1, suture removal 1
Other procedures, total	42
Ophthalmic surgery	23
Anesthesia for diagnostic imaging	11
Miscellaneous procedures	Hickman insertion and removal 2, PEG 2, duodenoileostomy 1, Nissen fundoplication 1, subdural hematoma evacuation 1
Average duration, min ± SD	61 ± 43
Range	6 min to 5 h

I&D = incision and drainage; ORIF = open reduction and internal fixation; BKA = below the knee amputation; AKA = above the knee amputation; TEN = toxic epidermal necrolysis; CRIF = closed reduction and internal fixation; IMN = ischemic monomelic neuropathy; PEG = percutaneous endoscopic gastrostomy.

Table 3

Anesthetic Management

Variable	% of cases (*n*)
Monitoring in addition to the standard	
Temperature monitored	24 (85)
Active warming	12 (44)
Induction drugs	
Propofol	71 (254)
Ketamine	27 (98)
Thiopental	4 (16)
Sevoflurane	2 (8)
Halothane	0 (1)
Airway management	
Endotracheal tube	40 (142)
Laryngeal mask	15 (53)
Mask only	20 (70)
Unknown	26 (93)
Rapid sequence induction	3 (12)
Opioids, induction/maintenance	
Fentanyl	8 (28)/2 (7)
Muscle relaxants, induction/maintenance	
Atracurium	18 (64)/3 (12)
Rocuronium	4 (13)/1 (3)
Succinylcholine	3 (9)/1 (2)
Vecuronium	2 (6)/1 (2)
Pancuronium	1 (2)/1 (2)
Mivacurium	1 (2)/0 (0)
Total relaxants	27 (96)/6 (21)
Maintenance technique	
Propofol boluses	29 (105)
Isoflurane	11 (40)
Halothane	7 (26)
Sevoflurane	3 (12)
Nitrous oxide as an adjunct	46 (166)

There was no documentation for the airway management in 93 cases. In some cases, several induction agents were used.

Table 4

Complications During Anesthesia

Variable	% of cases (*n*)
Hypotension	4.0 (14)
Hypertension	0.6 (2)
Bradycardia	2.9 (10)
Tachycardia	3.1 (11)
Hyperthermia	0.9 (3)
Aspiration	0.6 (2)
Bronchospasm	0.3 (1)
Cardiac arrest	0.3 (1)
Hyperpyrexia	0