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Anesthesia and Patients with Congenital Hyposensitivity to Pain

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Background: **Congenital hyposensitivity to pain or hereditary sensory and autonomic neuropathy represents a variety of disorders characterized by decreased perception of nociception, loss of other modalities of sensation, and variable expression of autonomic dysfunction. Sensory loss, especially that of pain, is associated with self-mutilations that may require frequent operations. Little is known about the safety of anesthesia for these patients.**

Methods: **The authors performed a computerized search of the Mayo Clinic medical records database between January 1996 and November 2005 for patients with congenital hyposensitivity to pain and related disorders who underwent general anesthesia. Medical records were reviewed for demographics, anesthetic techniques and agents, use of opioids, and perioperative complications. In addition, the authors conducted a comprehensive review of the literature to summarize the current knowledge regarding anesthesia for patients with congenital hyposensitivity to pain, and compared it with the patients with hyposensitivity to pain identified at the Mayo Clinic.**

Results: **The authors identified seven patients with hereditary sensory and autonomic neuropathy II, IV, or V and undefined variants of congenital pain hyposensitivity who generated 17 anesthesia records: 12 for orthopedic operations, 3 for sural nerve biopsies, and 2 for ophthalmologic procedures. In all patients, standard doses of volatile agents were used during anesthesia. Small amounts of opioids were used during the course of eight operations. Most patients experienced mild hypothermia (lowest temperature 34.7°C), and none experienced hyperthermia. All patients were hemodynamically stable during otherwise uneventful anesthesia. During recovery from anesthesia, opioids were given to only one patient, a single dose of 1 mg morphine. Even after major orthopedic operations, the patient did not require additional analgesia.**

Conclusions: **The patients with profound congenital hyposensitivity to pain underwent anesthesia without any adverse events. The authors found that despite reduced pain perception, the requirements for volatile anesthetics were within the expected range for population with normal pain perception, but they did not require opioids postoperatively. Intraoperative mild hypothermia was easily managed by adjustment of environmental temperature.**

CONGENITAL hyposensitivity to pain is a group of rare genetic disorders characterized by varying degrees of sensory loss including nociceptive hyposensitivity and various degrees of autonomic dysfunction. Because of an unawareness of pain, these patients suffer self-induced injuries and mutilations (fig. 1)[1] and may require repeated operations.[2] Congenital hyposensitivity to pain disorders were categorized by Dyck *et al.*[3–6] into five different types of hereditary sensory and autonomic neuropathies (HSANs I–V). A different expression of sensory loss is possible within each HSAN category, and some HSAN patients may have variable pain sensation.[6] The various types of HSAN are distinguished by the mode of inheritance, clinical features, variable degrees of autonomic nervous system abnormalities, loss or degeneration of sensory fibers, and increasingly specific molecular genetic abnormalities (table 1).[6] So far, six molecular genetic abnormalities have been linked to five clinical types of HSAN; however, it is likely that more genetic varieties will be delineated in the future.[6] For example, HSAN IV is based on mutation of TrkA (tyrosine receptor kinase A) gene, a gene that is encoding a high-affinity receptor for nerve growth factor, which participates in neural signal transduction.[6] Other gene defects associated with HSAN are listed in table 1 and discussed in more details elsewhere.[6]

The inherited sensory and autonomic neuropathies can be broadly subdivided into three major groups. Group 1, HSAN I, is the only autosomal dominant disorder characterized by later onset in life (table 1) and with sensory deficit which is more pronounced in the legs than in the hands (distal lower limb sensory and autonomic neuropathy with acral mutilations). In HSAN I, sensory deficits overshadow autonomic dysfunction. To date, at least two molecular genetic abnormalities have been described in HSAN I (table 1).[6] General characteristics of group 2 (HSAN II–V) are that the abnormalities are evident at birth, and they tend to affect small sensory fibers more than large fibers. Sensory involvement tends to be greatest in the limbs but extends into axial and cranial structures. The life expectancy is reduced because of severe tissue injuries, infections, and unrecognized (and untreated) hyperpyrexia. So far, group 2 has been linked to four molecular genetic abnormalities. Most patients with HSAN II tend to have pain hyposensitivity of the upper and lower limbs, and many have defective tactile sensation, while a minority may have areas of normal trunk sensation. Pathologically, HSAN II demonstrates a virtual absence of myelinated fibers and a decreased number of unmyelinated fibers in sural nerve biopsies (table 1). Relevant autonomic dysfunction may include episodic hyperthermia and swallowing deficiencies.[7] HSAN III, also known as the Riley-Day syndrome or familial dysautonomia, has higher preva-

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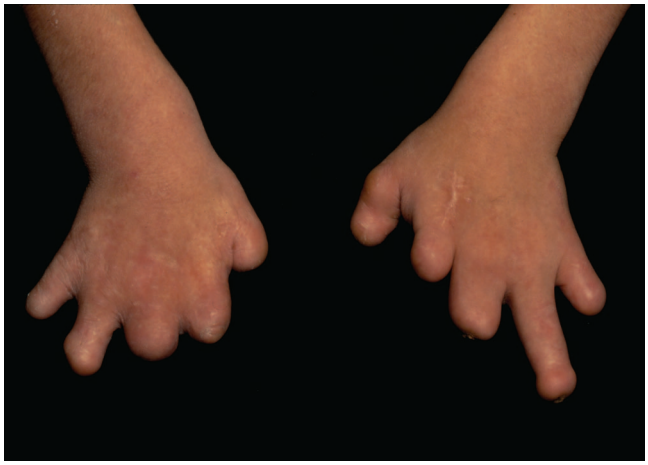

Fig. 1. The hands of a 12-yr-old boy with hereditary sensory and autonomic neuropathy II showing acromutilation. These self-mutilations may be found in all types of recessively inherited hereditary sensory and autonomic neuropathies and are attributed to loss of pain sensation, neglect of injury, excessive surgery, and indifferent personality.

lence in Ashkenazi Jews. These patients typically present in infancy with a profound dysautonomia (poor feeding with repeated vomiting, failure to thrive, temperature and vasomotor dysregulation associated with hypertension or hypotension), recurrent pulmonary infections, diminished peripheral pain, temperature sensation and absence of vibratory perception, and perioperative anesthetic complications (table 1).[6,7] HSAN IV, also known as congenital insensitivity to pain with anhidrosis, is characterized by hyposensitivity to superficial and deep visceral pain, mild to moderate mental retardation, and recurrent episodes of hyperpyrexia due to absence of sweating (no innervation of sweat glands).[7–9] HSAN V (congenital insensitivity to pain without anhidrosis) resembles HSAN IV, but there is a selective absence of small sensory myelinated fibers (Aδ fibers), which are important for sensing the sharp, well-localized, and prickling sensations of pain. These patients typically respond to tactile, vibratory, and thermal stimuli.[7,10] Cognition in these patients is normal. In group 3 of inherited sensory and autonomic neuropathies (called "indifference to pain"), an abnormality of the nerves has not been demonstrated despite abnormality of pain perception. It has been suggested that indifference to pain may be related to abnormalities in central nervous system pain processing or connectivity.[6] A detailed description of correlation between neuropathohistologic findings and signs and symptoms in patients with HSAN and related disorders is detailed in table 1 and in the 2005 edition of textbook *Peripheral Neuropathy* by Klein and Dyck.[6]

There is no consensus regarding the anesthetic risks or intraoperative analgesic needs of HSAN patients. We took an advantage of the large Mayo Clinic medical records database and reviewed the experience with anesthesia in children with HSAN varieties II–V and unclassified HSANs. Not all HSAN types have the same degree of hyposensitivity to pain.[6] In the current review, we included only HSANs whose primary manifestation is a profound reduction of pain perception, *i.e.*, HSANs II, IV, and V (HSAN I is a milder variant, and HSAN III's primary manifestation is dysautonomia with intact visceral and peritoneal pain sensation). HSANs IV and especially V are very rare disorders; therefore, large-scale studies are not feasible. The knowledge regarding anesthetic requirements for opioids and other agents and anesthetic complications is emerging from either small case series[11,12] or individual case reports.[13–16] This report is designed to contribute to this knowledge.

Materials and Methods

After obtaining Mayo Clinic, Rochester, Minnesota, Institutional Review Board approval, we conducted a computerized search of the Mayo Clinic Rochester medical records database from January 1996 to November 2005 for patients with congenital hyposensitivity to pain and related disorders who underwent general anesthesia. We only considered patients with HSANs II, IV, and V, or related variants associated with profound pain hyposensitivity (or "pain indifference"). HSAN type I patients were excluded because their sensory deficits is restricted to feet, with little or no involvement of proximal limbs, trunk, head, and neck. HSAN III patients were excluded because they have intact visceral and peritoneal pain sensations. Anesthesia records were reviewed for demographics (age, sex, year of operation), techniques (type of inhalational anesthesia, induction drugs, maintenance concentrations of anesthetic agents, muscle relaxants, and intraoperative and postoperative use of opioids), hemodynamic alterations (blood pressure and/or heart rate episodes above or below 30% measured before anesthesia induction), and intraoperative use of pressor/chronotropic drugs (phenylephrine, ephedrine, atropine). Finally, we reviewed anesthesia record for intraoperative alterations of body temperature, *i.e.*, hypothermia or hyperthermia.

To review the current knowledge regarding anesthesia for patients with congenital hyposensitivity to pain, we performed a comprehensive literature search of (1) MEDLINE (1966 to present) under following key words: hereditary sensory and autonomic neuropathy, congenital pain insensitivity, and anesthesia, all limited to humans; (2) EMBASE (1988 to present): congenital analgesia, hereditary sensory and autonomic neuropathy, sensory neuropathy, anesthesiology, and anesthesia, all limited to humans; (3) Current Contents (1966 to present) and (4) Scopus (1996 to present) were searched for HSAN or pain insensitivity or congenital insensitivity to pain, and an(a)esthesia.

Table 1. Characteristics of Hereditary Sensory and Autonomic Neuropathies I–V

HSAN	Type I	Type II	Type III, Familial Dysautonomia, Riley-Day Syndrome#	Type IV	Type V
Onset	2nd–4th decade	Infancy	Birth	Infancy	Infancy
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosomal locus and gene defect[6]	9q22 (SPTLC1),* 3q13 (RAB7)	12p13 ("HSN2")†	9q31 (IKBKAP)‡	1q21 (TRKA)§	1p13 (NGFB)‖
Primary sensory neurons (fibers)					
Aα (large myelinated)	+	++	++	Normal	Normal
Aδ (small myelinated)	++	++	++	±	++
C-unmyelinated	++	+	++	++	±
Autonomic neurons	Lumbosacral +	Generalized	Generalized	Generalized	Normal
Sensory deficit	Distal loss of pain sensitivity (more on feet); loss of thermal perception	Sensory, tactile, vibratory, and thermal perception severely impaired	Pronounced impairment of pain and thermal perception; vibratory perception is less affected; corneal insensitivity	Hyposensitivity to superficial and deep visceral pain; thermal hyposensitivity; touch and pressure sensitivity unimpaired	Pain and temperature sensitivity severely affected; proprioception and sensitivity to touch pressure and vibration are unaffected
Autonomic dysfunction	Hypohidrosis, anhidrosis of feet; urinary dysfunction	Hypo- or anhidrosis, fever, apneic episodes, bladder and gastrointestinal dysfunction, tonic pupils	Profound dysautonomia: orthostatic hypotension, episodic hypertension; vomiting, failure to thrive, hyper- or hypohidrosis and unexplained fevers	Severe anhidrosis with recurrent episodes of severe hyperpyrexia	Mild hyperhidrosis
Other neurologic clinical features	Mutilations, ulcers, stress fractures (lower extremities), osteomyelitis, neglect of wounds	Mutilations, severe ulcerations of extremities, painless injuries	Self-mutilations	Mutilations, painless fractures, biting of tongue and fingers; mental retardation	Self-mutilations, painless fractures, ulcers, burns; normal neurologic examination results

* Gene for serine palmitoyl-transferase long chain subunit 1 (SPTLC1) affects sphingolipid biosynthesis; gene for late endosomal GTPase protein (RAB7) affects axonal transport. † Tentatively named "HSN2." ‡ Gene for inhibitor of κ light polypeptide gene enhancer in B cells (IKBKAP). § Gene for tyrosine receptor kinase A (TRKA) affects neurotrophin receptor. ‖ Gene for nerve growth factor β (NGFB) affects nerve growth factor. # More frequent in Ashkenazi Jews.
HSAN = hereditary sensory and autonomic neuropathy; + = affected; ++ = severely affected; ± = may be affected.
Modified from Klein and Dyck[6]; used with permission from Elsevier.

Results

All patients gave written permission for research review of their medical records. We identified seven patients with congenital hyposensitivity to pain who underwent general anesthesia at the Mayo Clinic. Four patients had HSAN types II, IV, and V (table 2), one had either HSAN IV or V, and two had profound congenital hyposensitivity to pain, but the classification was not assigned by the examining neurologist. Despite the fact that the original classification of HSAN disorders in five groups[3] is still widely quoted, neurologists occasionally encounter variants of congenital hyposensitivity to pain that cannot be classified. For example, in patient 7 (table 2), electron-micrographic histologic examination of nerve biopsy was consistent with HSAN IV, but the patient had no anhidrosis (anhidrosis is an essential symptom of HSAN IV). Similarly, patient 3 had profound congenital hyposensitivity to pain but did not meet criteria to be classified in any of the five HSAN categories.

There were 17 anesthesia records regarding these seven patients: 12 for orthopedic operations (71%), 3 for diagnostic sural nerve biopsies, and 2 for ophthalmologic procedures (table 2). All patients were under the age of 16 yr (mean age, 8.6 ± 4.2 yr). In all patients, the anesthesia was conducted with concentrations of volatile agents expected to be administered to patients without hyposensitivity to pain. In eight cases, opioids were used intraoperatively, and only one received an opioid in the recovery room (a single intravenous 1-mg dose of morphine). Most patients experienced mild hypothermia (34.7°, lowest temperature recorded) intraoperatively. Temperature homeostasis was easily managed with either the use of warming blankets or adjustment of environmental temperature. Significant hemodynamic

Table 2. Demographics and Other Characteristics of the Patients with Congenital Hyposensitivity to Pain

Characteristic	Patient 1	Patient 2*	Patient 3†	Patient 4	Patient 5	Patient 6	Patient 7‡
Pain disorder	HSAN II	HSAN IV (possible)	Unclassified HSAN	HSAN V	HSAN V	HSAN IV	Unclassified HSAN
Year of birth, sex	1987, Female	2000, Female	2000, Male	1979, Male	1979, Male, died in 1993—anaphylaxis	1994, Male	1993, Female
Cognitive status	Attention deficit/hyperactivity	Normal	Normal	Normal	Mild cognitive delay	Developmental delay	Developmental delay
Comorbidities	Mutilations	Anhidrosis; asthma	Hypohidrosis; mutilations of bones/eyes	Mutilations; neuropathic joint injuries	Mutilations; neuropathic joint injuries; hypothyroid	Anhidrosis; absent lacrimation; fracture; mutilations	Mutilations; failure to thrive; chronic diarrhea
Year of first operation	1991	2002	2004	1995	1993	2000	1997
Subsequent operation	1994,1995, 1996 × 4	None	2004	1995	1993	2002	None
Type of operation(s)	Orthopedics; wound debridement; multiple skin grafts	Sural nerve biopsy	1. Keratectomy; 2. Eye	1. Humerus; 2. Radial head	1. Leg; 2. Meniscectomy	1. Humerus; 2. Sural nerve biopsy	Sural nerve biopsy
Anesthesia induction							
Agent(s)	HAL, thiopental propofol, midazolam	SEV	SEV	1. ISO 2. ISO	1. Thiopental 2. Thiopental	1. Thiopental 2. ISO	SEV
Opioid(s)	F 25–50 μg on 3 surgeries	No	No	1. No; 2. F 250 μg	1. Oxy-M 0.5 mg; 2. F 25 μg	1. No; 2. No	No
Muscle relaxant	Vecuronium, Mivacurium	Atracurium	No	Mivacurium	Atracurium	1. No; 2. No	Mivacurium
Anesthesia maintenance							
Agent(s)	ISO 0.4–1.25%	SEV 2.6%	1. SEV 3.7 %; 2. SEV 4.5%	1. ISO 0.6%; 2. ISO 0.8%	1. ISO 1.0%; 2. ISO 1.5%	1. ISO 1%; 2. ISO 1%	SEV 2%
N_2O	Yes, on all	Yes	1. No; 2. Yes	Yes	Yes	Yes; 2. No	No
Opioid(s) given	3 surg. none; 3 surg. F 25 μg; 1 surg. M 2 mg	F 30 μg	No	1. No; 2. Oxy-M 1 mg	1. Oxy-M 0.3 mg; 2. F 50 μg	1. Oxy-M 0.4 mg; 2. No	No
Muscle relaxants given	No	No	No	No	No	No	No
Surgery duration, min	75–195	105	1. 15; 2. 90	1. 158; 2. 69	1. 118; 2. 120	1. 84; 2. 42	40
Intraoperative							
Hypotension	No	No	No	No	No	No	No
Hypertension	No	No	No	No	No	No	No
Bradycardia	No	No	No	No	No	No	No
Tachycardia	No	No	No	No	105 beats/min	No	No
Highest temperature, °C	37.9 to 36.6	36.0	1. 36.0; 2. 36.6	1. 36.1; 2. 36.1	35.7; NR	1. 36.9; 2. 35.7	NR
Lowest temperature, °C	35.9 to 36.6	35.1	1. 36.3; 2. 36.6	1. 35.4; 2. 35.7	35.1; NR	1. 36.1; 2. 34.8	NR
Recovery room							
Regional anesthesia	No	No	No	No	No	No	No
Opioid(s) given	No	No	No	No	1. No; 2. M 1 mg	No	No
Anesthesia complication(s)	None	None	None	None	None	None	None

* Patient of Syrian ancestry; sural nerve biopsy did not disclose clear neuropathic abnormality of myelinated fibers, just "epineural inflammatory cells." Thermoregulatory sweat distribution test showed anhidrosis, suggesting widespread sympathetic sudomotor impairment characteristic of hereditary sensory and autonomic neuropathy (HSAN). † Unmyelinated fibers were normal in size and number, which excludes HSAN IV. At the same time, Aδ fibers were not reduced which excludes HSAN V. Therefore, this patient had nonclassified insensitivity to pain with mild hypohidrosis. ‡ Electron-micrography findings were consistent with HSAN IV but without anhidrosis.

1. and 2. denote first and second operations; F = fentanyl; HAL = halothane; ISO = isoflurane; M = morphine; N_2O = nitrous oxide; NR = not reported; Oxy-M = oxymorphone; SEV = sevoflurane.

instabilities (as defined by our established criteria in the Materials and Methods), and/or alterations that would trigger interventions with vasopressor and/or chronotropic agents were not observed. We did not identify any intraoperative or postoperative complications. Finally, no child reported pain postoperatively.

Our comprehensive literature search of anesthetic management of patients with "congenital insensitivity to pain" identified 10 case reports (4 in Japanese, 1 in Chinese, 1 in Spanish, and 4 in English journals) and three case series (English). Two case series were based on review of medical records, whereas the third review was based on a questionnaire distributed to anesthesia providers caring for these patients. Including the current study, experiences with 134 anesthetics in 59 patients were published since 1966 and included the following operations: orthopedic (n = 91); dental (n = 17); urologic (n = 2); wound debridement and irrigation (n = 10); ophthalmologic (n = 8); abdominal (n = 2); ear, nose, and throat (n = 1); and nerve biopsies (n = 3).

Discussion

Besides hyposensitivity to pain, HSAN patients have various degrees of other modalities of sensory loss and autonomic dysfunction that may affect the course of anesthesia.[17–19] We describe management and outcomes of anesthesia in five patients with HSANs II, IV, and/or V and in two patients with unclassified congenital variants of pain hyposensitivity. All patients underwent general anesthesia without significant alterations of blood pressure, heart rate, or temperature. The requirements for volatile anesthetics were within the range one would expect to find in a population with normal pain perception. Intraoperative opioids either were not administered or were administered in minute amounts for either minor or major orthopedic operations. Although the reasoning why intraoperatively opioids were given to some of our patients is not clear, it is more important to note that our patients did not require opioids postoperatively, regardless of the type of surgery. We can presume that the opioids may have been given because of anesthesiologists' unfamiliarity with the opioid requirements in HSAN patients. Furthermore, some patients with HSAN may have partially preserved nociception, and others may have preserved mechanoceptor, cooling, and warming sensations[6]; therefore, they may sense some aspects of intense surgical stimulation. Alternatively, when given before anesthetic induction or in the recover room, opioids may have been used as sedatives or anxiolytics.

Congenital hyposensitivity to pain is a rare disease, and there is limited information regarding anesthetic treatment of these patients. Our MEDLINE search of the past 40 yr identified 10 case reports[13–16,20–25] and three case series (table 3).[11,12,26] This search encompasses anesthesia experience of 52, mostly HSAN IV, patients who underwent 117 operations. The vast majority of reports (n = 79, 68%) describe experience with anesthesia for orthopedic operations. Five case reports[13,20,23–25] demonstrated uneventful inhalational anesthesia with no hemodynamic or temperature homeostasis problems (table 3), one reported uneventful use of epidural anesthesia for femur osteosynthesis,[21] and one reported uncomplicated monitored anesthesia care for bilateral lower extremity amputations.[22]

Two case series describe anesthesia for patients with HSAN IV.[11,12] Rozentsveig *et al.*[12] reported 20 patients from a single Bedouin tribe in Israel who generated 40 anesthesia records. Sixteen patients (37.5%) developed complications in the immediate perioperative period: mild hypothermia and cardiovascular events, mostly transient bradycardia and hypotension, in 15 others. In one 19-month-old child, severe bradycardia progressed to fatal cardiac arrest. This child did not receive premedication but received anesthesia with 2% halothane delivered in a mixture of 2:1 N_2O–O_2 with spontaneous breathing. Although this fatal event was listed as complication associated with HSAN IV,[12] these cardiovascular complications were previously described in association with the use of halothane.[27] Morray *et al.*[27] identified that cardiovascular depression from halothane, alone or in combination with other drugs, was responsible for two thirds of all medication-related perioperative pediatric cardiac arrests. In contrast to Rozentsveig *et al.*,[12] who concluded that the perioperative cardiovascular complications were common in patients with the southern Israel variant of HSAN IV, Okuda *et al.*[11] reported 6 patients with HSAN IV who underwent 20 operations during general anesthesia without any adverse events. All patients received standard anesthesia management (table 3) including inhalational agents in doses that are expected to be administered to patients with normal sensitivity to pain. No patient received opioids during operations, and no perioperative complications were noted. Tomioka *et al.*[26] investigated the perioperative management of patients with HSAN IV by distributing a questionnaire to the Japanese HSAN Association. They reviewed 15 patients who had 45 operations during general anesthesia using different inhalational agents within wide range of anesthetic concentrations (table 3). Four patients received opioids intraoperatively, and two received fentanyl-supplemented inhalational anesthesia. Normothermia was maintained in patients with the use of warming or cooling blankets, and no anesthesia-related problems were detected.

Because patients with hyposensitivity to pain feel either none or minimal pain, it is intuitive that perioperative opioid requirements must be altered. Anesthesiologists may assume the same logic toward the use of reduced doses of inhalational anesthetics, but this may not be warranted. Some patients with HSAN do have

Table 3. Summary of Published Reports of Patients with Congenital Hyposensitivity to Pain Who Underwent Anesthesia

Type of Report	No. of Patients/No. of Operations; Type of Operation	Type of Anesthesia Induction/Premedication Agent Used*	Anesthesia Maintenance: Anesthetic and Muscle Relaxant*	Anesthesia Maintenance: Opioid	PACU Opioids	Intraoperative Temperature, °C	Postoperative Events
CR[15]	1/1; Orthopedic	General: midazolam	SEV 0.5–1.0%, vecuronium	No	No	36.8–35.8	None
CR[14]	1/2; Orthopedic, urologic	General: midazolam, propofol	Propofol, N_2O, SEV 0.5–1.5%	No	No	1. 38.1; 2. 38.1, 35.5 after heating blanket was turned off	PONV for 3 days; no PONV after second surgery
CR[16]	1/1; Orthopedic	General: ENF 0.5–3%, N_2O 60%	N_2O 66%, ENF 0.4–2%	NR	NR	36–35.1	None
CR[13]	1/1; Orthopedic	General: propofol, lidocaine	ISO 0.21–0.92%, rocuronium	No	NR	36.3–35.1	NR
CR[24]	1/1; Orthopedic	General: propofol, ketamine, midazolam, droperidol	Propofol, ketamine, vecuronium	No	No	36.9	PONV
CR[25]	1/1; Dental	General, TIVA: propofol, fentanyl	Propofol, fentanyl 10 μg, atracurium	Fentanyl 10 μg	No	37.2–36.3	None
CR[20]	1/1; Orthopedic	General: thiopental	DES 5–6%, atracurium	No	No	Normothermia	None
CR[21]	1/1; Orthopedic	Epidural anesthesia	Lidocaine 2%	No	"Minimal"	Normothermia	None
CR[22]	1/1; Orthopedic	MAC (3 h)	Midazolam 20 mg, Thiopental 700 mg	No	No	NR	None
CR[23]	2/2; Orthopedic	General: diazepam, thiopental	N_2O, HAL 0.3–0.4%, pancuronium, succinylcholine	No	No	1. 38.0–39.0 for 48 h; 2. 35.0	None
CS[12]	20/40; Amputation (n = 14), wound I&D (n = 10), dental (n = 10), eye (n = 5), ENT (n = 1)	General: propofol, ketamine, midazolam, thiopental, HAL, ISO	Various halogenated agents, N_2O in all cases	No	NR	Normothermia in all	37.5% had cardiovascular instability, bradycardia; 1 cardiac arrest
CS[11]	6/20; Orthopedic (n = 15), dental (n = 5)	General: thiopental, HAL, SEV	HAL 0.2–2%, ENF 0.6–3.0%, SEV 0.2–2%, ISO 1%, succinylcholine, vecuronium	No	NR	35.8–38.2	PONV (n = 3), temperature 38°C within 24 h (n = 4)
CS[26]	15/45; Orthopedic (n = 40), abdominal (n = 2), dental (n = 1), eye (n = 1), urologic (n = 1)	General: barbiturates, ketamine benzodiazepines, propofol, HAL, ENF, SEV	HAL 0.3–1.0%, ENF 0.5–2.0%, ISO 0.5%, SEV 0.2–3.0%, N_2O, propofol, succinylcholine, vecuronium, pancuronium	Fentanyl, pentazocine	NR	No hypothermia or hyperthermia	PONV (n = 2), hyperthermia (n = 3)

* Indicates induction agent, sedative, inhalational agent used during any of the reported operation. Inhalational anesthetic concentrations are ranges used during single or multiple operations.

1. and 2. denote first and second operations; CR = case report; CS = case series; DES = desflurane; ENF = enflurane; ENT = ear, nose, and throat; HAL = halothane; I&D = irrigation and debridement; ISO = isoflurane; MAC = monitored anesthesia care; N_2O = nitrous oxide; NR = not reported; PACU = postoperative anesthesia recovery unit; PONV = postoperative nausea and vomiting; SEV = sevoflurane; TIVA = total intravenous anesthesia.

tactile hyperesthesia, and some may have partially preserved pain sensation[6]; therefore, the use of volatile anesthetics in standard concentrations has been reported in the literature. In addition, anesthetics are necessary to ensure cooperation and immobility during surgery for pediatric patients, especially for those with

mental retardation. Okuda *et al.* [11] described the difference of inhaled anesthetics requirements for orthopedic *versus* dental surgery in patients with HSAN IV; orthopedic patients required higher volatile agent concentrations. This suggests that HSAN patients have anesthetic requirements comparable to the population with normal pain perception. The optimal dose of anesthetics for patients with HSAN has yet to be determined. On two occasions,[13,24] anesthesiologists used processed electroencephalogram to guide the administration of anesthetics in patients with HSAN. Brandes and Stuth[13] found that when processed electroencephalographic monitoring (A-2000 BIS monitor; Aspect Medical Systems, Natick, MA) was used to gauge unconsciousness and amnesia, the isoflurane concentrations ranged between 0.21% and 0.92%. However, the validity of this tool for gauging anesthetic administration has yet to be proven. Therefore, at present, the inhalational anesthetics should be titrated in accordance with the patient's hemodynamic response.

A single case reported by Layman[22] is very instructive and demonstrates that major lower extremity surgery, in a 30-yr-old man with congenital insensitivity to pain, can be performed during heavy sedation (20 mg midazolam, and intermittent administration of thiopental totaling 700 mg over the 3-h surgery) but without the use of opioids and/or general anesthesia. The large amount of sedation rendered this patient amnestic for the operation. Most of the other reports illustrate minimal or no use of opioids perioperatively in HSAN IV patients,[11,12] which is in agreement with the observation in our study. In cases when opioids were used perioperatively, the literature does not offer reasoning for their use.[26] We can postulate that the use of opioids in these patients followed the anesthesiologists' daily practice to administer opioids with every anesthetic. This "automatism" may be based on fact that HSAN is a disorder rarely encountered by anesthesiologists, as well as that scarce information and no recommendations exist regarding opioid requirements for these patients.

Another important element of anesthesia is prevention of autonomic reflexes, and the majority of HSAN patients have associated autonomic imbalance. Because HSAN IV patients have anhidrosis, management of temperature homeostasis in daily life may be difficult. One study revealed that almost 20% of these patients died of hyperpyrexia during the first 3 yr of life.[18] Therefore, perioperative thermoregulation is a concern, and continuous temperature monitoring is of utmost importance in these patients. However, there is only one report of intraoperative hyperthermia in a patient with hyposensitivity to pain,[23] whereas in general, normothermia can be easily maintained with cooling or warming blankets or regulation of operating room temperature.[14,15,26] Kawata *et al.*[23] described an HSAN IV patient whose intraoperative temperature increased to 37.7°C and remained between 38° and 39°C for 2 days. This patient was given 0.5 mg atropine intramuscularly as a part of premedication. Because atropine inhibits the activity of the sweat glands, it may result in hyperthermia, especially in children. However, because children with HSAN IV lack innervation of sweat glands,[9] the use of atropine *per se* should not be associated with hyperthermia.[11,26] None of our patients experienced hyperthermia, and the majority had mild hypothermia, which may be attributed primarily to environmental conditions encountered during anesthesia, rather than to the HSAN disorder itself. Of note, there is no association between malignant hyperthermia and HSAN IV, because the genetic mechanisms of precipitating hyperpyrexia in malignant hyperthermia and HSAN IV are fundamentally different. All triggering agents associated with malignant hyperthermia (succinylcholine, halogenated agents, and others) have been used without any complications in these patients.

In conclusion, knowledge regarding the safety of anesthesia in patients with HSANs II, IV, and V is scarce. Despite the fact that patients with profound congenital insensitivity to pain may undergo major orthopedic surgery without general anesthesia and opioids,[22] the majority of patients reported in the literature received standard anesthesia for surgery. Factors beyond analgesia (immobilization, prevention of autonomic reflexes, anxiolysis, and sedation) are equally important aspects of these patients' anesthetic management. Generally, HSAN II, IV, and V patients do not need opioids postoperatively even after major operations. Because these disorders are so infrequent, it is impossible to conduct large-scale studies. In the interim, we will continue to learn from the anesthesia experience reported in individual cases. So far, the balance of safety is on the side of positive outcomes, and anesthesia seems to be free of any major adverse events in patients with HSAN disorders.

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