Anesthetic Management of Patients with Huntington Disease

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BACKGROUND: Huntington disease (HD) is a rare autosomal dominant disease with symptoms of chorea, dystonia, incoordination, cognitive decline, and behavioral difficulties. Abnormal responses to anesthesia have been reported in case reports and raised concerns regarding the safety of anesthesia in this patient population.
METHODS: We performed a computerized search of the Mayo Clinic medical records database searching for patients with HD who underwent general anesthesia. Medical records were reviewed for anesthetic technique, medications used, and postoperative complications.
RESULTS: We identified 11 patients with genetically confirmed HD who underwent 17 general anesthetics. Psychiatric medication use was common, with 6 patients using antipsychotics, 7 patients using antidepressants, and 3 patients using benzodiazepines. Succinylcholine was used in 7 anesthetics, and nondepolarizing neuromuscular blocking drugs in 11 anesthetics, all without adverse effects. Patients had normal responses to induction and maintenance of anesthesia without adverse effects. Serious postoperative complications did not occur.
CONCLUSION: Contrary to previous case reports, we found that patients with HD have normal responses to general anesthesia. However, the anesthesiologist should be aware of interactions between anesthetics and psychiatric medications frequently used by these patients. Measures should also be taken to minimize the risk of pulmonary aspiration because bulbar dysfunction may be a manifestation of this disease.
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Huntington disease (HD) is a rare autosomal dominant disease that affects 5 to 7 per 100,000 individuals.[1] HD presents with symptoms of chorea, dystonia, incoordination, cognitive decline, or behavioral difficulties between the third and fifth decade of life. Adverse responses to anesthetics have been reported in these patients including prolonged paralysis after administration of depolarizing neuromuscular blocking drugs[2] and prolonged recovery after sodium thiopental (STP)[3] and midazolam use.[4] Because of these rare reports, recommendations to avoid STP, succinylcholine, and midazolam in patients with HD have been suggested.

Given that HD is rare, a large prospective study to define the risks of anesthesia has never been attempted. To further assess anesthesia outcomes in patients with HD, we used the Mayo Clinic medical records database to identify patients with HD who underwent surgery under general anesthesia and reviewed their anesthetic course.

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METHODS

After obtaining approval from the IRB of Mayo Clinic, Rochester, MN, a computerized search of the Mayo Clinic Rochester medical records database from 1990 through 2008 was conducted to identify patients with HD who underwent general anesthesia. We only included patients with symptoms and genetically confirmed HD with >41 CAG (Cytosine-Adenine-Guanine) trinucleotide repeats.[1] Patients with clinical diagnosis only, as well as asymptomatic patients with genetically confirmed HD, were excluded. Anesthetic records were reviewed by one of the authors (JEK). Data were entered into standardized data collection form, and all questionable entries were discussed with the senior author (TNW). We reviewed demographics (age and gender), anesthetic techniques, hemodynamic variability (arterial blood pressure and/or heart rate episodes that were 30% above or below those measured before anesthesia induction), hemodynamic instability (need for any vasopressor/chronotropic drugs), and intraoperative body temperature. We also recorded postoperative respiratory complications, shivering, psychosis or delirium, and notes regarding residual paralysis from the use of muscle relaxants. A detailed history of the clinical course of HD in each patient was also abstracted including date of diagnosis, number of CAG trinucleotide repeats, disease symptoms, and list of medications.

Table 1. Demographics and Other Characteristics of Our Patients with Huntington's Disease

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Year of birth, sex	1927, F	1948, M	1953, M	1948, F	1945, M
No. of CAG repeats	42	43	46	42	44
Symptoms	Chorea, dementia, depression, and dysarthria	Chorea, dementia, depression, and dysphagia	Chorea, dementia	Chorea, dysarthria	Chorea, depression, and dysarthria
Year of operation	2002	1. 2000 2. 2005 3. 2007	2004	1. 2000 2. 2001 3. 2002 4. 2003	2007
Type of operation	NS	1. Vascular 2. Radiology 3. GS	NS	1. Vascular 2. Vascular 3. Vascular 4. Optho	Optho
Preoperative medications					
Antipsychotic	Haldol	1. None 2. Olanzapine 3. Risperdal	Seroquel	1. None 2. None 3. None 4. Seroquel	Zyprexa
Antiepileptic	None	1. None 2. Depakote 3. Depakene	Depakote	None	None
Antidepressant	Paroxetine	1. Wellbutrin 2. Sertraline 3. Sertraline	Effexor, Trazodone	Sertraline, Trazodone	Trazodone, Celexa
Benzodiazepine	None	1. None 2. Lorazepam 3. None	None	None	None
Anesthesia induction					
Drug	Thiopental	1. Propofol 2. N_2O 3. Propofol	Propofol	1. Ketamine 2. Thiopental 3. Thiopental 4. Propofol	Propofol
Fentanyl	Yes	1. Yes 2. No 3. No	Yes	1. Yes 2. Yes 3. Yes 4. No	No
Midazolam	Yes	1. Yes 2. No 3. Yes	Yes	1. Yes 2. Yes 3. No 4. None	No
Succinylcholine	Yes	1. No 2. No 3. Yes	No	1. No 2. Yes 3. Yes 4. No	No
Anesthesia maintenance					
Agent	SEVO, Isoflurane	1. SEVO, N_2O 2. N_2O 3. Propofol	Propofol	1. ISO, Propofol 2. ISO, N_2O 3. ISO, N_2O 4. DES	N_2O
Muscle relaxant	VEC	None	PAN ROC	1. PAN 2. VEC 3. VEC 4. MIV	None
Surgery duration (min)	237	1. 205 2. 86 3. 86	204	1. 313 2. 518 3. 373 4. 110	27

Table 1. Continued

Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
1959, F 46	1940, M 41	1933, F 42	1948, F 43	1934, F 42	1961, F 44
Chorea, depression, and dementia	Chorea, dysphagia, and dysarthria	Chorea, depression, and dysarthria	Chorea, depression	Chorea, dysphagia	Chorea, dementia, depression, dysphagia, and dysarthria
2006	1. 1999 2. 1999	1994	1995	1. 2004 2. 2009	2005
ENT	1. GS 2. GS	Ortho	Ortho	1. GYN 2. GS	Thoracic
Haldol, Zyprexa	None	None	None	None	None
None	None	None	None	None	None
Celexa	None	None	None	None	Paroxetine
None	Clonazepam	None	None	1. None 2. alprazolam	None
Propofol	1. Unknown 2. ISO	Propofol	Propofol	Propofol	Propofol
Yes	Yes	Yes	Yes	Yes	Yes
No	Yes	No	Yes	Yes	Yes
No	1. Unknown 2. No	Yes	Yes	No	Yes
SEVO, N_2O	1. Unknown 2. ISO	ISO	ISO	1. SEVO 2. ISO	Unknown
VEC	1. CIS 2. CIS	None	None	1. CIS 2. VEC	VEC
106	1. 120 2. 185	280	180	1. 91 2. 155	269

(*Continued*)

Table 1. Continued

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Intraoperative course					
Invasive monitoring	Arterial	None	Arterial	1. Arterial, PA 2. Arterial 3. Arterial 4. None	None
Bolus inotrope	PHE	1. None 2. None 3. Ephedrine	None	1. None 2. Ephedrine 3. Ephedrine 4. PHE	None
Inotrope infusion	None	None	None	1. Dopamine 2. None 3. None 4. None	None
Maximum temperature (°C)	37.8	1. 35.9 2. 37.3 3. 35.4	37.2	1. 37.4 2. 38.1 3. 36.6 4. 36.4	36.0
Postoperative course					
Shivering	None	1. None 2. None 3. Yes	None	None	None
Prolonged apnea	None	None	None	None	None
Aspiration	None	None	None	None	None
Died within 30 d of operation	Yes	No	No	No	No

1, 2, 3, and 4 denote first, second, third, and fourth operation.

GS = general surgery; NS = neurosurgery; optho = ophthalmology; ENT = otolaryngology; ortho = orthopedic; N_2O = nitrous oxide; SEVO = sevoflurane; ISO = isoflurane; DES = desflurane; VEC = vecuronium; PAN = pancuronium; ROC = rocuronium; MIV = mivacurium; CIS = cisatracurium; PHE = phenylephrine.

To review the current knowledge regarding anesthesia complications for patients with HD, we performed a comprehensive literature search of (1) MEDLINE (Medical Literature Analysis and Retrieval System Online) (1966 to present) using the following keywords: general anesthesia, anesthetics and Huntington's disease, limited to humans; and (2) Scopus (1960 to present) using the following text words: Huntington, movement disorders, neurodegenerative disorders, and an(a)esthesia.

RESULTS

In the database, 122 patients were identified with genetically confirmed HD; of these, 11 patients (7 women and 4 men) received 17 general anesthetics (Table 1). Regional anesthesia, sedation, and monitored anesthesia care were not included. The mean age at the time of surgery was 55.8 ± 8 years (range, 43–75 years) (Table 1).

Our patients had a variety of clinical manifestations including chorea in all patients, dysarthria in 6, dysphagia in 4, depression in 7, and dementia in 5. Six of 11 patients (7 of 17 anesthetics) were taking antipsychotic medications at the time of surgery, 2 (3 anesthetics) were taking antiepileptic medications, 7 (12 anesthetics) were taking antidepressant medications, and 3 were taking benzodiazepines preoperatively.

Surgical procedures are summarized in Table 1. Before induction of anesthesia, most patients received 2 mg IV midazolam and 1 to 2 μg/kg IV fentanyl. Inductions typically consisted of IV using propofol, STP, or ketamine. Endotracheal intubation was facilitated with succinylcholine (7 patients). Nondepolarizing neuromuscular blocking drugs were used in 12 patients. Muscle relaxant administration was titrated according to train-of-four muscle contractions in response to peripheral neuromuscular stimulation. Anesthesia was maintained with volatile anesthetics with the exception of a propofol infusion used in 2 patients. Patients' intraoperative temperatures were maintained using a forced air warming blanket and/or increasing the ambient temperature, and no significant hypothermia or hyperthermia was recorded. Three patients developed postoperative shivering, which resolved after the application of warm blankets. No prolonged apnea, cyanosis, aspiration, or generalized tonic spasm was noted in any of the anesthesia records. Nine anesthetics required boluses of phenylephrine and/or ephedrine for transient hypotension and 2 required infusion of dopamine (Table 1). One patient died within 30 postoperative days after evacuation of a large subdural hematoma.

A comprehensive literature search revealed 23 English-language case reports of general anesthesia in patients with HD who had received a total of 29

Table 1. Continued

Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
None	Central, arterial	None	None	None	None
Ephedrine	Ephedrine	Ephedrine	None	1. PHE, ephedrine 2. None	None
None	Dopamine	None	None	None	None
35.1	38.3	35.9	36.0	1. 35.4 2. 36.2	36.2
None	Yes	None	None	None	None
None	None	None	None	None	None
None No	None No	None No	None No	None No	None No

anesthetics from 1960 to the present (Table 2).[6,12,17,27] In addition, 2 non-English case reports were included because they had English abstracts.[21,23] The literature search produced an additional 20 articles that were excluded for the following reasons: 3 case reports were not in English,[28–30] 2 case reports described the anesthetic management of juvenile HD, which is considered a separate clinical entity,[31,32] 2 case reports of regional anesthesia,[33,34] 1 case of sedation,[35] and 12 review articles.[36–47] Of the included case reports, 10 reported complications including prolonged apnea,[3,8] generalized tonic spasms,[3] postoperative fever,[5] prolonged recovery,[8] increased sensitivity to benzodiazepines,[4] moderate hypertonia,[24] and postoperative shivering.[4,19,26] STP was used most often for induction of anesthesia, as well as propofol and midazolam. A variety of inhalation anesthetics were used including nitrous oxide, trichloroethylene, halothane, ether, isoflurane, desflurane, and sevoflurane. Succinylcholine was used 6 times and a variety of nondepolarizing muscle relaxants included gallamine, pancuronium, atracurium, mivacurium, rocuronium, cisatracurium, and vecuronium, all without incident.

DISCUSSION

HD is a rare neurodegenerative disorder that prior case reports suggest may have implications for the anesthesiologist. HD has an autosomal dominant inheritance that is caused by an expansion of the CAG repetition in the *IT15* gene, resulting in increased production of a mutant protein, huntingtin. This protein initially leads to cell loss and atrophy, mainly of GABAergic striatal medium spinal output neurons of the caudate, putamen, and cortex.[1] Degeneration throughout the cortex and abnormalities of the dopaminergic substantia nigra pars compacta can occur.[48] Widespread dysregulation of glutamatergic and dopaminergic signaling systems results.[49,50] As the disease progresses, patients develop worsening ataxia resulting in falls and trauma, pharyngeal dysfunction and poor nutrition requiring feeding tube placement, and poor oral hygiene requiring dental procedures, all of which may result in the need for procedures that require anesthesia. Several case reports describe idiosyncratic reactions to frequently used anesthetics.[2–4,8] Our study is the largest review of patients with HD undergoing anesthesia to date. Overall, our patients had unremarkable anesthetic courses without signs of excessive hemodynamic instability or temperature dysregulation. Our patients also exhibited normal responses to frequently used anesthetics including a variety of muscle relaxants, anesthetic induction drugs, volatile anesthetics, benzodiazepines, and opioids. The postanesthesia recovery time was also unremarkable without respiratory complications or psychotic episodes requiring treatment.

Psychotropic medications are frequently used for symptom management in this incurable condition.[1]

Table 2. Summary of Published Reports of Patients with Huntington's Disease Who Underwent General Anesthesia

Report	No. of operations: type of operation	Symptoms	Type of anesthesia induction
1[3]	1. Hand	Chorea, memory loss	Thiopental
	2. Hand		Thiopental
	3. Hand		Ether
2[5]	Dental	Chorea, dementia	Thiopental
	General surgery	Chorea, dysarthria	Diazepam
3[6]	Dental	Chorea, dysarthria	N_2O, diazepam, and halothane
4[7]	Orthopedic	Chorea, memory impairment	Thiopental
5[8]	General surgery	Chorea, dementia	Thiopental
6[9]	Thoracic	Chorea, dementia, and dysarthria	Thiopental
	Thoracic	Chorea, ataxia	Thiopental
7[10]	Tracheostomy	Unknown	Thiopental
8[11]	General surgery	Chorea, dementia, and dysphagia	Thiopental
9[12]	Otolaryngology	Chorea, dysphasia	Althesin, alfentanil
10[4]	Dental	Chorea, dysarthria	Midazolam
11[13]	Orthopedic	Chorea, dementia, and dysarthria	Propofol
12[14]	Ophthalmology	Unknown	Thiopental
13[15]	Dental	Unknown	Propofol, alfentanil
14[16]	Dental	Chorea, dementia	Sevoflurane, propofol
15[17]	Dental	Chorea, dementia	Sevoflurane
16[18]	1. Unknown	Chorea, ataxia	Midazolam
	2. Unknown		Propofol
	3. Unknown		Propofol
17[19]	Dental	Dysphagia	Propofol, Remifentanil
18[20]	General surgery	Chorea	Propofol
19[21]	General surgery	Chorea, dysphasia, and dementia	Thiopental
20[22]	Ophthalmology	Chorea, ataxia, dementia	Propofol
21[23]	General surgery	Chorea, dysarthria, dementia, and ataxia	Thiopental
22[24]	Dental	Chorea, dysphagia	Propofol
23[25]	Neurosurgery	Chorea, depression	Propofol
24[26]	Dental	Chorea, dysarthria, and ataxia	Unknown
25[27]	Dental	Chorea, dysarthria	Isoflurane

N_2O = nitrous oxide.

The majority of our patients were prescribed antipsychotics, antidepressants, benzodiazepines, and antiepileptic medications. The anesthesiologist should be aware of potential interactions of these medications with frequently used anesthetic drugs. Although not observed in our patients, theoretically, general anesthesia could exacerbate psychiatric symptoms resulting in postoperative agitation, chorea, and psychosis. It is probably prudent for patients to continue the use of psychotropic medications until the day of surgery.

Increased sensitivity to barbiturates and benzodiazepines among patients with HD has been reported.[3,4,8] Davies[3] reported a patient who had prolonged recovery and generalized tonic spasms after the administration of 600 mg STP for 2 general anesthetics. There is another case report of prolonged apnea and recovery from 7.5 mg/kg STP for induction of anesthesia.[8] In retrospect, these doses were likely excessive for sick and debilitated patients, and the prolonged effects of STP should not be surprising. Others described normal responses to both STP[5,7,9–11,14,21,23] and propofol.[13,15,16,18–20,22,24,25] In our series, normal responses to both induction drugs were also observed. "Increased sensitivity" to benzodiazepines was reported in a patient who underwent a dental procedure with general anesthesia. He received 10 mg oral diazepam preoperatively (5 mg evening before, and 5 mg morning of, the procedure) and an induction dose of 5 mg midazolam IV, followed by a short anesthetic consisting of halothane and nitrous oxide.[4] The patient had an uneventful recovery but was amnestic for the remainder of the day. Such an amnesic response to a large amount of benzodiazepines is probably not unusual or unexpected, particularly if patients are debilitated or demented from HD. In our series, the majority of patients were taking benzodiazepines chronically to control psychiatric symptoms, and midazolam was used intraoperatively in 10 cases without incident.

In 1968, Gualandi and Bonfanti[2] described a patient with HD who had an apneic response that lasted >120 minutes after the administration of 50 mg succinylcholine. She was subsequently found to have a low plasma cholinesterase level. Of note, although widely cited, the case report by Gualandi and Bonfanti[2] was in Italian, and thus, it is not summarized in Table 2. There are mechanisms that might increase the risk of patients with HD to have prolonged apnea after

Table 2. Continued

Muscle relaxant	Inhalation anesthetic	Opioid	Complications
Gallamine	N_2O, trichloroethylene	Papaveretum	Apnea, tonic spasms
None	N_2O, trichloroethylene	Papaveretum	Apnea, tonic spasms
None	N_2O, ether	Papaveretum	None
Pancuronium	N_2O, halothane	Fentanyl	None
Pancuronium	N_2O	Fentanyl	Postoperative fever
None	N_2O, halothane	None	None
Succinylcholine	N_2O, halothane	Fentanyl	None
Pancuronium			
Succinylcholine	N_2O	Dextromoramide	Prolonged apnea, and prolonged recovery
Succinylcholine	N_2O	Papaveretum	None
Pancuronium			
Succinylcholine	N_2O	Papaveretum	None
Pancuronium			
Atracurium	N_2O, halothane	Fentanyl	None
Succinylcholine	N_2O, isoflurane	Fentanyl	None
Atracurium	N_2O, althesin	Alfentanil	None
Alcuronium	N_2O, halothane	Fentanyl	Sensitivity to midazolam, postoperative shivering
Atracurium	None	Fentanyl	None
Atracurium	N_2O, isoflurane	Fentanyl	None
Atracurium	N_2O	Alfentanil	None
None	Desflurane, N_2O	Morphine	None
Rocuronium	N_2O, sevoflurane	Fentanyl	None
None	N_2O, isoflurane	Morphine	None
Atracurium	N_2O, isoflurane	Morphine	None
Atracurium	Sevoflurane	Fentanyl	None
None	None	Remifentanil	Shivering
Cisatracurium	N_2O, isoflurane	Fentanyl	None
Vecuronium	Sevoflurane	Fentanyl	None
Rocuronium	Sevoflurane, N_2O	Morphine	None
Pancuronium	N_2O, halothane	None	None
Atracurium	N_2O, isoflurane	Sufentanil	Moderate hypertonia treated with clonidine
None	N_2O, propofol	Butorphanol	None
Succinylcholine, mivacurium	N_2O, isoflurane	Unknown	Shivering
Unknown	Unknown	Unknown	None

receiving succinylcholine. Genetic variation of plasma cholinesterase is a potential cause of prolonged muscle paralysis after receiving succinylcholine. Population studies on the incidence of atypical pseudocholinesterase genotypes in patients with HD have been contradictory. A regional study from England found that 6 of 28 subjects with HD possessed the rare plasma cholinesterase fluoride-resistant allele ($E_I^U E_I^F$ plasma cholinesterase genotype in 6 subjects).[51] This study also cited an unpublished study from the Danish Cholinesterase Research Unit in which 4 of 13 Danish patients with HD were reported to also possess this fluoride-resistant allele.[51] The possibility that this frequent incidence of the fluoride-resistant allele in those 2 studies might be attributable to a shared common ancestry was suggested by the contrasting results of an Australian study, which documented that 73 nonrelated patients with HD had a similar distribution of pseudocholinesterase genotypes as a control sample of healthy subjects.[52] The Australian study did find reduced levels of plasma pseudocholinesterase among subjects with HD compared with a sample of healthy controls.[52] Unfortunately, this study did not provide the actual pseudocholinesterase level, so the clinical significance of this lower level cannot be determined. Also, the study did not provide information regarding the general state of health of the patients with HD to determine whether there was an obvious explanation for the low levels, such as a severely deconditioned state.[53,54] Clinically, case reports in the English language have not documented an abnormal response to succinylcholine in patients with HD.[7–9,11,26] One report also documented that the time to motor strength recovery after succinylcholine administration was normal in a patient with HD as measured by ulnar nerve stimulation.[11]

Six of our 11 patients received succinylcholine, 1 on more than 1 occasion, and in all of them the responses were normal. Despite this, it remains a possibility that muscle paralysis after succinylcholine may be prolonged in patients with HD, and caution must be exercised when using this drug. It should be noted that the dibucaine number can be normal in a patient with fluoride-resistant atypical pseudocholinesterase, as the activity of this variant is inhibited almost normally by dibucaine.[55] This is important in this patient population because upper airway dysfunction is common, and postoperative muscle weakness may

increase the theoretical risk of pulmonary aspiration. Our case series and our review of the literature found no cases of unusual or prolonged responses to nondepolarizing neuromuscular blocking drugs.

Neither hemodynamic instability nor autonomic dysfunction has been described in patients with HD undergoing anesthesia. Postoperative shivering has been reported, and 2 of our patients developed this complication, which responded to application of warm blankets.[4,19,26] It does not seem that this patient population has significant problems with thermoregulation.

Because patients with HD have bulbar muscle dysfunction, there is a theoretical increase in the risk of aspiration. The ideal method for minimizing the risk of aspiration during the perioperative period in patients with HD has not been established, but the use of promotility drugs that act on central dopamine receptors, such as metoclopramide, should be avoided because these drugs can aggravate chorea symptoms in patients with HD.[56]

Because HD is a very rare disorder, we are dependent on case reports to assess the safety of general anesthesia. Our case series has all the inherent limitations of a retrospective observational study. All 11 patients in our series had genetically confirmed HD and they all underwent general anesthesia safely with no obvious deleterious effects. These results mirrored those found in our review of the literature. There are a few case reports of prolonged recovery after anesthesia, but these observations could be explained by the large doses of anesthetics used based on current practice guidelines. Despite normal responses to succinylcholine observed in our series and in the English literature, the question of whether HD is associated with low levels of atypical pseudocholinesterases remains unanswered. Therefore, succinylcholine should be used with caution. Given these findings, the anesthesia provider should remain vigilant because these patients are often debilitated, frequently take psychotropic medications, and may be at increased risk of pulmonary aspiration.

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