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RESEARCH REPORT

Delivery of anesthesia for children with Mucopolysaccharidosis Type III (Sanfilippo syndrome): a review of 86 anesthetics

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What is already known

- Mucopolysaccharidoses are normally associated with anesthesia complexity and airway difficulty. Very few case series of Mucopolysaccharidosis (MPS) Type III patients have been published.
- A recent report from Minneapolis, USA looked at one of four subtypes of MPS III, namely MPS IIIA. Publications to date suggest that MPS III patients, unlike other MPS groups, have easier airways to manage.

What this article adds

- This is the largest anesthesia case series of MPS III patients published.
- We demonstrate that patients with MPS IIIA, MPS IIIB, and MPS IIIC pose few issues with mask ventilation. Difficult intubations are unlikely although a risk may remain. A significant number of MPS III patients have cardiac involvement.

Keywords
Mucopolysaccharidosis; anesthesia; pediatric; difficult airway; perioperative care; metabolic diseases

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Summary

Background: Sanfilippo syndrome (MPS III) is rare, with 97 cases in the United Kingdom between 1988 and 1998. Mucopolysaccharide infiltration of tissues in mucopolysaccharidosis (MPS) causes multi-systemic pathology including difficult airways and cardiac disease. Published anesthesia case reviews of Sanfilippo syndrome have included limited numbers of patients to date.
Aim: To identify the perioperative management and complications of anesthesia in children with mucopolysaccharidosis Type III at Great Ormond Street Hospital.
Methods: A retrospective case note review of all children with MPS III in our institution was undertaken. All medical notes and anesthetic charts were analyzed, and conduct of anesthesia, airway management, perioperative complications, and associated comorbidities were identified.
Results: There were 43 patients with MPS III, of which 34 required anesthesia, on 86 occasions for 156 procedures between 1993 and 2015. Dental extraction was the likeliest indication for anesthesia (34%) (general surgery [30%]; ear, nose, and throat [26%]; other [10%]). Thirteen of 34 patients had cardiac pathology (valvular [n = 6], functional [n = 6], electrophysiological [n = 1]). Ten of 34 patients had evidence of clotting abnormality (mild prolonged clotting time [n = 5], low von Willebrand factor [n = 2], thrombocytopenia [n = 3]). The majority of intubations were Cormack–Lehane Grade 1 (n = 47) (Grade 2 [n = 14], Grade 3 [n = 1], Grade 4 [n = 1]). In 86 anesthetics, there were 0 cases of difficulty with mask ventilation. There was 1 case of failed intubation. They were subsequently anesthetized by a different

operator uneventfully at a later date. Two perioperative complications occurred: a failed intubation and bleeding during adenoidectomy.
Conclusion: We demonstrate a difficult airway is unlikely when anesthetizing an MPS III patient although a risk does remain. A significant proportion of MPS III have cardiac involvement although no perioperative complications were described. With associated coagulation issues, bleeding tendency, while uncommon, can occur in this group.

Introduction

Mucopolysaccharidosis Type III or Sanfilippo syndrome is a lysosomal storage disorder caused by impaired degradation and subsequent accumulation of heparan sulfate in cells and tissues. It is the most common of the mucopolysaccharidoses with estimated prevalences between 1 : 53 000 and 1 : 360 000 (1). In the UK, 97 new cases of MPS III were diagnosed between 1988 and 1998 (2). There are four distinct enzyme defects (MPS IIIA, B, C, and D), all of which have an autosomal recessive inheritance (Table 1) (3). Symptoms and disease progression are most severe in MPS IIIA where life expectancy is shorter. The phenotypic spectrum is wide, and the clinical progression can be described in phases.

Initially, children with MPS III will show mild developmental regression after a period of normal development. Between 2 and 6 years, this becomes more marked and is characterized by severe behavioral disorders, hyperkinesia, aggressiveness, and intellectual deterioration, progressing to severe dementia. Sleep disorders and sleep disordered breathing may be a feature. Mild facial dysmorphism will become apparent. Around 10 years of age, behavioral problems are superseded by progressive neurological deterioration, motor regression, spasticity, communication problems, seizures, dysphagia, and swallowing difficulties (1). Death usually occurs at the end of the second decade in MPS IIIA. It may be delayed until 30–40 years for types B to D (1).

The challenges and complications associated with anesthesia for children with MPS are well documented in the literature and include difficulty or failure to intubate related to a morphologically abnormal airway and short unstable necks, associated cardiovascular and respiratory disease, and obstructive sleep apnea. Each MPS are however distinct clinical diseases with different clinical courses and individual anesthetic risks and complications.

The evidence base for the perioperative care of children with MPS III in the medical literature is limited and until recently consisted of case reports and small case series. In our series, we sought to retrospectively review the perioperative care, anesthetic management, and complications of children with MPS III treated by our anesthetic team. We aimed to primarily identify if the difficult airway management that is a feature of other MPS types was present in all subtypes of MPS III. We sought to review systemic involvement and organ dysfunction in MPS III and how this progressed with age, in order to better define recommendations for the preoperative assessment and optimization of these children. We also evaluated perioperative complications to allow for improved and informed consenting and planning for intraoperative management and postoperative care.

The recent review by Cingi *et al*. (4) analyzed the anesthetic care and perioperative complications of 25 children with MPS III type A undergoing 94 general anesthetics. This study concluded that compared to children with other MPS types, those with MPS IIIA were likely to experience no intubation difficulties and fewer respiratory complications allowing for safe anesthesia by an experienced team. Our case series comparatively included all MPS III subtypes over a far greater patient age range, and is the largest cohort to date with 43 patients reviewed, 34 of whom required general anesthesia. The study by Cingi *et al*.

Table 1 Phenotype-gene relationships (1–3)

MPS subtype	Prevalence	MIM number	Gene locus	Defective enzyme
MPS IIIA	1–9/1 000 000	252 900	17q25.3	Heparan N-Sulfate
MPS IIIB	<1/1 000 000	252 920	17q21.2	Alpha-N acetylglucosaminidase
MPS IIIC	–	252 930	8p11.2-p11.1	Acetyl CoA:alphaglucosaminide acyltransferase
MPS IIID	–	252 940	12q14.3	N-Acetylglucosidase

MIM, Mendelian inheritance in man.

was prospective and had a relatively consistent study protocol for anesthesia which was implemented by three anesthesiologists experienced in the delivery of anesthesia for children with MPS. Comparatively our design was retrospective and included a greater range of induction, maintenance, airway management, and surgical techniques all administered by staff of varying experience. We would propose that this reflects a more realistic view of how anesthesia for these children would routinely be delivered, and consequently the reported perioperative experience and complications in our review bears a closer resemblance to normal outcomes for these children.

Methods

Local audit and ethics committee approval was requested and granted to undertake a retrospective case note review of all patients with MPS III who required a general anesthetic at Great Ormond Street Hospital, London, U.K.

A hospital information request was used to identify all patients with MPS treated at our institution from January 2000 until January 2015. Those with a confirmed diagnosis of MPS III were selected and all case notes including anesthetic charts, in-patient documentation, clinic letters, correspondence, and nursing charts were analyzed. Where identified patients had received anesthetic treatment prior to January 2000, these episodes were included. Our primary endpoint was identification of a difficult airway. Secondary endpoints included organ dysfunction and perioperative complications.

Results

Demographics

We identified 43 patients with MPS III at GOSH between 2000 and 2015. Of these, 34 required anesthesia, on 86 occasions for 156 procedures between 1993 and 2015. Boys with MPS III represented 65% of cases (male [n = 22], female [n = 12]). All children were graded as ASA (American Society of Anesthesiologists) physical status III. The age of the patient at each anesthetic ranged between 1 and 21 years (median age 8 years [IQR 6–12]). MPS IIIA was the commonest subtype identified in our population (MPS IIIA [n = 14]; MPS IIIB [n = 13]; MPS IIIC [n = 5]; MPS IIID [n = 0], unknown [n = 2]).

The median number of anesthetics required by each child was 2 (IQR [1–4], range [1–7]). Of the 86 anesthetics delivered, 22 were to facilitate diagnostic imaging or sampling, e.g., magnetic resonance imaging (MRI), evoked auditory brainstem responses (EABR), cerebrospinal fluid (CSF) sampling. The most frequent indication for anesthesia was dental surgery (Table 2), typically for examination under anesthesia (EUA) followed by extractions (n = 29). Other indications for anesthesia included insertion of, or change of percutaneous endoscopic gastrostomy (PEG) (n = 24), EABR (n = 18), or adeno-tonsillectomy (n = 10). Median duration of anesthesia was 55 min (IQR [35–90 min], range [10–240 min]).

Disease involvement

All children had neurological involvement in keeping with the disease process (Table 3). A significant number of the 34 patients requiring anesthesia demonstrated evidence of swallowing problems (n = 20), hearing loss (n = 20), epilepsy (n = 20), recurrent lower respiratory tract infections (n = 15), and obstructive sleep apnea (n = 13) of which two required home continuous positive pressure ventilation (Table 4).

More than one in three children (n = 13) demonstrated a structural or functional cardiac abnormality on routine transthoracic echocardiography. One child exhibited prolonged QT interval on their

Table 2 Indication for general anesthesia

Type of surgery	Number of cases
Dental	29
General	26
ENT	22
Radiology/investigations	20
Evoked auditory brainstem response	18
Intravenous access	4

Some children had multiple procedures under each anesthetic and indications would be recorded independently.

Table 3 System or region involved in disease process

System/region	Number of patients
Neurology	34
Gastrointestinal	25
Ear, nose, and throat (ENT)	24
Respiratory	23
Cardiovascular	13
Hematological	11
Orthopedic	10
Musculoskeletal	5
Renal	3
Dermatological	2

Table 4 Spectrum of abnormalities

Abnormality	Number of Patients
Neurological	
Developmental delay	34
Epilepsy	20
Sleep disturbance	15
Wheelchair use	13
Oppositional defiant syndrome	6
Autistic spectrum disorder	6
Attention deficit hyperactivity disorder	6
Gastrointestinal	
Swallowing difficulties	20
Chronic diarrhea	7
Chronic constipation	5
ENT	
Hearing loss – sensorineural/conductive	20
Adeno-tonsillar hypertrophy	15
Respiratory	
Recurrent respiratory tract infections	15
Obstructive sleep apnea (OSA)	13
Home continuous positive pressure ventilation (CPAP)	2
Cardiovascular	
Mild aortic valve regurgitation	4
Mild mitral valve regurgitation	2
Moderate aortic valve regurgitation	1
Mild left ventricular hypertrophy	3
Mild left ventricular diastolic dysfunction	2
Prolonged QT interval	1
Orthopedic	
Scoliosis	9
Cervical spine instability	3
Avascular necrosis femoral head	2
Hematological	
Mild clotting derangement	5
Thrombocytopenia	3
Low von Willebrand factor	2

electrocardiogram (Table 4). No evidence of complications from cardiac pathology was seen perioperatively. Ten children had clotting abnormalities on routine and advanced laboratory investigations (mild prolonged prothrombin time (PT) or activated partial thromboplastin time (APTT) [$n = 5$], thrombocytopenia [$n = 3$], low von Willebrand factor [$n = 2$]). Scoliosis was seen in nine children and cervical spine pathology described in a further three patients. This included one case of atlanto-axial instability in a child with MPS IIIA, and two cases of hypoplastic odontoid PEG (MPS IIIB [$n = 1$], MPS IIIC [$n = 1$]).

Anesthetic technique

Premedication

Premedication was administered in 22 of 86 anesthetics (25%). A variety of premedications were prescribed over a 23-year period (midazolam [$n = 12$], temazepam [$n = 4$], diazepam [$n = 1$], atropine [$n = 4$], chloral hydrate [$n = 1$]).

Table 5 Induction of anesthesia

Drug(s)	Number of patients
Inhalational	
Sevoflurane, nitrous oxide, oxygen	51
Sevoflurane, oxygen	13
Halothane, nitrous oxide, oxygen	2
Intravenous	
Fentanyl, propofol	15
Propofol	3
Thiopentone	1
Thiopentone, fentanyl	1

Induction

Inhalational induction was the preferred technique of choice in 66 cases (77%), the remainder receiving intravenous inductions (Table 5). Inhalational induction with nitrous oxide (N_20), sevoflurane, and oxygen (O_2) was the commonest practice [$n = 51$] (sevoflurane/O_2 [$n = 13$]; halothane/N_2O/O_2 [$n = 2$]). Induction of anesthesia with fentanyl and propofol was the most popular technique for intravenous inductions [$n = 15$] (propofol [$n = 3$], thiopentone [$n = 1$], fentanyl and thiopentone [$n = 1$]).

Maintenance

In all cases, anesthesia was maintained with inhalational agents (sevoflurane [$n = 47$], isoflurane [$n = 14$], N_20 and isoflurane [$n = 14$], N_20 and sevoflurane [$n = 5$], desflurane [$n = 5$], halothane [$n = 1$]).

Airway

Following induction of anesthesia, there were zero cases documented of difficulty with mask ventilation (easy [$n = 54$], difficult [$n = 0$], easy with adjunct [$n = 2$], no comment [$n = 30$]). An endotracheal tube (ETT) was used to secure the airway in 73% [$n = 63$] of cases and a supraglottic airway in 27% [$n = 23$]. Cormack–Lehane (CL) classification for intubated patients was as follows: Grade 1 [$n = 47$], Grade 2 [$n = 14$], Grade 3 [$n = 1$], and Grade 4 [$n = 1$].

There was one case of failed intubation in an 11-year old (MPS IIIA) with atlanto-axial instability undergoing anesthesia for adenoidectomy, dental extractions, and gastrostomy insertion. Following inhalational induction, manual in-line stabilization was maintained to ensure cervical spine protection. Mask ventilation was described as easy. A Grade 4 CL view was obtained with direct laryngoscopy and blind intubation was attempted. With failure to intubate, a supraglottic airway was

inserted with success. Subsequently, a videolaryngoscope was used, together with a preloaded ETT on a fibreoptic endoscope, to facilitate intubation. The arytenoids were noted to be swollen and a decision was made to abandon the procedure and the patient was woken up. This patient was anesthetized on first attempt using direct laryngoscopy by a different operator 4 weeks later.

In total, four episodes of airway obstruction following induction of anesthesia were documented on anesthesia charts (MPS IIIA [$n = 2$], MPS IIIB [$n = 2$]). Two of these patients had a formal diagnosis of OSA. All cases were easy to mask ventilate, one of which required an oropharyngeal airway to assist ventilation. All four patients were intubated with a Grade 1 CL view. Other airway incidences documented from 86 anesthetics include severe laryngospasm ($n = 1$) and bronchospasm ($n = 1$) requiring intravenous salbutamol.

Fluids

Intraoperative intravenous fluids were administered in 54 of 86 cases (Hartmann's solution [$n = 53$], Platelet transfusion [$n = 1$]). There was only one documented case of intraoperative transfusion. A 5-year old undergoing dental extractions with borderline thrombocytopenia received a platelet transfusion postinduction of anesthesia. No documented bleeding was recorded during this case.

Bleeding

There was one case of intraoperative bleeding during an adenoidectomy in a patient (MPS IIIA) with known thrombocytopenia. The bleeding was managed surgically and no transfusion was required. In addition, a 2-year old (MPS IIIA) with a borderline high normal PT and APTT underwent a tonsillectomy and a constant 'ooze' noted postoperatively. They were investigated and diagnosed with low levels of von Willebrand factor. This child was managed medically and did not require further surgical intervention.

Other complications

There was one episode of vomiting at extubation in a 2-year old (MPS IIIA) with abdominal distension undergoing anesthesia for an MRI of their brain and abdomen. This patient recovered uneventfully with no clinical or radiological evidence of aspiration and was discharged the same day.

Discussion

This study was a retrospective case note review of patients with a known diagnosis of MPS III receiving anesthesia in a single UK tertiary pediatric center. The majority of information was dependent on documentation of the perioperative care during this time. We are confident that we identified all MPS III patients managed at Great Ormond Street Hospital between 2000 and 2015.

MPS III children suffer from an accumulation of glycosaminoglycan throughout their tissues, with devastating multi-systemic effects. They suffer from global developmental delay, speech regression, seizures, adeno-tonsillar hypertrophy, sleep disturbance, loss of mobility, poor swallow and dental issues, all of which was evident in our population (1,2,5).

There is good evidence that other mucopolysaccharidoses, namely MPS I (Hurler) and MPS II (Hunter), are a high risk for airway difficulty (6). Our ultimate question was to assess airway complexity among all subtypes of MPS III patients. Our study found that while there is evidence of airway obstruction in some children following induction of anesthesia, the airway of an MPS III patient is easy to manage. In particular, they pose little issue with oxygenation and mask ventilation, and any overwhelming obstruction can be easily overcome with an airway adjunct. The significant majority of MPS III children in this study were easy to intubate (Grade 1 or 2 CL view). Of the 34 patients, two MPS III children had a difficult airway (Grade 3–4 CL view) of which both were easy to mask ventilate. The Grade 3 airway (MPS IIIB patient) was successfully intubated with a videolaryngoscope on first attempt. The Grade 4 airway (MPS IIIA patient), following failed intubation on direct laryngoscopy had a clear glottis view with a videolaryngoscope, and several weeks later, demonstrated a Grade 1 CL view with cricoid pressure (Sellick's maneuver) on direct laryngoscopy by a different operator. Interestingly, the majority of the complexity in this case revolved around concern of cervical spine instability as seen on X-ray images preoperatively. Potentially, the strict positioning of the neck led to difficult laryngoscopy views and the question of whether we should use alternative methods to intubate in the first incidence could possibly be debated.

Multiple cases in historical series support the assertion that the airways of children with MPS III are less challenging than those of other children with MPS. Baines and Keneally reviewed a cohort of 28 patients with MPS in 1983. In this group, two patients had MPS III and no complications or difficult airways were described in these children (7). In 1988, Herrick and Rhine reported their experience of anesthesia for 12 patients with MPS. This group included three patients with MPS III who had 16 anesthetics between them. No difficult airways were reported. Two children received

sedation, one with intramuscular ketamine, and the second with nitrous oxide and diazepam. The latter patient, who had a history of dysphagia and aspiration died suddenly of a respiratory arrest 1 week after anesthesia at home (8).

In 1994, Walker *et al*. (9) reviewed the perioperative care of 34 patients with MPS. These patients had 89 anesthetics for 110 procedures. Four of these children had MPS III, and there were no reports of difficult or failed intubations, or cardiac anomalies among them. In 2012, Frawley *et al*. (6) described a second case series that included one child with MPS III who had eight anesthetics. This child demonstrated no difficulty with facemask ventilation or intubation and all anesthetics were uncomplicated.

Moores *et al*. (10) described a case series of 28 patients with MPS of which eight had MPS III and required anesthesia for 33 procedures including myringotomies, tonsillectomies, adenoidectomies, dental surgery, neurosurgery, radiological, and diagnostic procedures. As noted in our cohort, Moores' patients with MPS III had significantly easier airways in comparison to the other MPS groups. They reported no difficulties with mask ventilation, and of the 17 intubations, 2 presented difficulty. The first required a stylet in order to intubate, but was noted to be a Grade 1 CL view on subsequent attempts. The second was classed as moderately difficult due to difficulty in extending the patients neck.

The prospective review published in 2016 of MPS IIIA patients by Cingi *et al*. (4) assessed airway management and associated perioperative airway complications in 25 patients undergoing a total of 94 anesthetics. They similarly found that facemask ventilation was easy for all patients. The three expert anesthesiologists who delivered the anesthetic care, found all intubations to be easy. Of our 34 patients, we found difficulty with intubation in one patient with a Grade 4 view by direct laryngoscopy in a case with known cervical instability and when extra caution was taken not to disturb the cervical spine. Interestingly, Cingi *et al*. described that video laryngoscopy was the preferred method of choice for intubation in their study. This difficult view and intubation may have also gone unnoticed today with the availability of modern techniques for intubation in our institution. In the Cingi study, postoperative airway complications were described in 24% of patients, including wheeze, croup, and laryngospasm. Only two similar events (6%) were described in our 34 patients (laryngospasm [$n = 1$] and bronchospasm [$n = 1$]). This difference might reflect the limitations of a retrospective review rather than a true lower incidence. The Cingi research intubated all patients in their study to assess for airway complexity. While the majority of patients (73%) were intubated in our center, the remainder had a supraglottic airway device.

Mucopolysaccharide infiltration of the airway, tongue, and temporo-mandibular joint may lead to difficult mask ventilation, poor mouth opening, and impair our ability to intubate by conventional techniques (1,6–8). It would also appear from our population that the airway concerns, often seen in MPS I and II, are less likely to occur and we feel encouraged that unexpected difficult airways are unlikely with MPS III patients. In particular, all patients were oxygenated without concern. We remain aware however, based on 2 of our 34 patients that a difficult view was obtained and that vigilance remains essential during ETT placement in MPS III patients.

We add to recent published work, by additionally observing for nonairway perioperative complications and organ involvement in our MPS III cohort. Despite considerable tissue and organ involvement, there are very few perioperative complications in MPS III children.

Thirteen of 34 patients had evidence of cardiac pathology. It is very difficult to retrospectively assess with confidence when our patients were first investigated for evidence of cardiovascular involvement, particularly as the case notes stretched back to 1988. What was clear was that none of these children demonstrated any signs or symptoms of cardiac disease or failure. Initial echocardiography (ECHO) began at a median of 12 years of age [IQR 5.5–15.5]. In the last 15 years, an ECHO is routinely performed following diagnosis of MPS III (Median age at ECHO 5 years [IQR 1–6, $n = 5$]). Interestingly, 12 of the 13 cases had pathology which affected the left side of the heart (mitral valve, aortic valve, and left ventricle). Why the deposited glycosaminoglycans have a predilection for the left side may warrant further questioning. All children received a standard anesthetic, and importantly, no perioperative cardiac complications were seen.

In 1992, Mahoney *et al*. described a group of 35 patients with MPS treated by bone marrow transplantation (BMT). Of this cohort, four patients had MPS III and underwent 12 general anesthetics. One patient with MPS III died due to failure of the BMT and was noted on autopsy to have biventricular dilatation with thickening of all valve cusps, particularly the aortic and mitral valves (11). Misumi *et al*. (12) described a 39-year-old woman with MPS IIIC in 2010. This patient was found to have a second-degree atrioventricular block and required a pacemaker implantation under general anesthesia. Echocardiography revealed mitral valve prolapse with moderate mitral regurgitation and left ventricular

diastolic dysfunction. Anesthesia and surgery proceeded uneventfully.

Three children demonstrated an abnormality on routine preoperative cervical spine flexion and extension X-rays. In each case, neurosurgical review deemed the pathology mild or insignificant requiring no further management. These investigations are no longer part of the normal investigative process of MPS III patients at GOSH. It has been shown that concerning odontoid abnormalities are mainly found in children with MPS I, IV, and VI (13).

In our study, 13 patients had obstructive sleep apnea (OSA) diagnosed on sleep study. It is difficult retrospectively to quantify or comment on the postoperative length of stay (LOS) for these children with OSA. LOS following an anesthetic has changed considerably over the last few decades and as such we did not attempt to examine this in further detail.

Of the 34 children, 10 had abnormal clotting results and bleeding was seen in 1 patient with thrombocytopenia undergoing a tonsillectomy and in 1 patient with low von Willebrand factor post-tonsillectomy. Specifically, no child required transfusion with red blood cells as a result of bleeding, although no major surgery was performed in any of the 86 anesthetics. Comparison cannot be made to the recent work by Cingi *et al*. as their study patients received anesthesia for noninvasive investigations and lumbar punctures, and bleeding tendency was not discussed in this review. In 1989, Myles and Westhorpe described the case of a 9-year-old child with MPS III having an elective tonsillectomy and adenoidectomy for sleep disordered breathing. This case was complicated by a post-tonsillectomy hemorrhage, a complication reported in our series of patients where there appears to be an increased incidence of coagulation anomalies (14).

Great Ormond Street Hospital is one of only three centers commissioned to provide care for children with lysosomal storage diseases in the UK. We are aware that children with life-limiting diseases such as MPS III suffer from frequent episodes of ill health and may present to their local hospital emergency department between regular follow-up appointments or planned anesthetics. This work not only adds information to specialist anesthesiologists involved in the care of patients with MPS III but also to clinicians and healthcare workers in local hospitals where instant attention may be required and transfer to a specialist center is not immediately possible. This work, together with previous case series, should reassure clinicians that inability to oxygenate, bleeding, and cardiovascular complications are uncommon when anesthetizing a patient with MPS III.

Ethics Approval

This study was approved by the local audit and ethics committee at Great Ormond Street Hospital, U.K.

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Conflict of Interest

The authors report no conflict of interest.

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