Prolonged Sedation in Infants: Is There a Correlation Between the Amount of Sedation and Negative Neuroradiological Outcomes?

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In partial fulfillment of the requirement for the degree of Bachelor of Science

by

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ABSTRACT

**Background.** Infants routinely undergo prolonged sedation with opioids and benzodiazepines for proper clinical management, as part of the standard of care. Recent evidence suggests that prolonged exposure to pain medication may have negative effects on infant brain development. The clinical impact of such treatment on the full-term infants is largely unknown.

**Hypothesis.** Prolonged sedation with opioids and benzodiazepines in full-term patients is associated with increased incidence of brain abnormalities as per brain MRI scan in comparison to healthy controls.

**Methods.** We compared full-term patients less than 12 months of age with healthy controls as per IRB approval at Boston Children’s Hospital. We quantified the amounts of drugs used for prolonged sedation management that included *opioids* (fentanyl, morphine, methadone) and *benzodiazepines* (midazolam, lorazepam). End-point analyzes included: (1) length of sedation and weaning (days), (2) total treatment doses per patient (mg/kg/day), (3) average daily doses during sedation and weaning (mg/kg/day ± SD), (4) number of anesthesia events. To correlate these values with neurological outcomes, we further quantified (5) number of incidental findings on brain MRI reports, and (6) estimated cerebrospinal and brain volumes using MANTiS segmentation. Pearson’s correlation coefficient was used to measure the linear relations between the different variables analyzed.

**Results.** Morphine and midazolam were the two drugs used the most frequently for prolonged sedation and were administered at the highest doses. Neuroradiology reports showed abnormalities in extra-axial space, parenchyma, and/or white matter structures that were not present in the controls. Our data show significant positive linear relationships for the average daily dose of administered morphine (r=0.933, p=0.002) and midazolam (r=0.810, p=0.03) with
the number of neuroradiological abnormalities. Although there is a positive trend between the average daily dose of morphine \((r=0.573, p=0.18)\) and midazolam \((r=0.548, p=0.20)\) with the amount of cerebrospinal fluid, as well as a negative trend between the average daily dose of morphine \((r=-0.561, p=0.19)\) and midazolam \((r=-0.521, r=0.23)\) with the brain volume, none were significant. Additional factors such as the number of anesthesia events \((r=0.398, p=0.37)\) and days of sedation \((r=0.397, p=0.37)\) are not significantly correlated to the number of neuroradiological abnormalities. The number of anesthesia events \((r=-0.040, r=0.93)\) and days of sedation \((r=0.189, p=0.69)\) have no relationship to the amount of cerebrospinal fluid. Similary, the number of anesthesia events \((r=0.065, p=0.89)\) and days of sedation \((r=-0.186, p=0.69)\) have no relationship to brain volume.

**Conclusions.** Prolonged sedation with morphine and midazolam is significantly associated with an increased incidence of incidental neuroimaging findings. In contrast, there is no correlation to increased cerebrospinal fluid and decreased brain volumes in full-term infants. Given the current standard of care using these drugs, further studies should investigate how prolonged sedation with opioids and benzodiazepines can affect brain development and its long-term sequelae.
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Days of Sedation and Number of Anesthesia Events Correlation to Measures of Brain Volumes

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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>EA</td>
<td>Esophageal atresia</td>
</tr>
<tr>
<td>LGEA</td>
<td>Long-gap esophageal atresia</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>ICV</td>
<td>Intracranial volume</td>
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I. INTRODUCTION

Infants routinely undergo prolonged sedation with opioids and benzodiazepines for proper clinical management, as part of the standard of care (Anand et al., 2010). Current sedation management in the intensive care units during mechanical ventilation uses a combination of opioids and benzodiazepines as a gold standard of sedation, even though morphine is considered safer than midazolam for prolonged administration (Shaprio et al., 2007; Bellu et al., 2008). Unfortunately, such prolonged sedation treatment is associated with a high incidence of analgesic tolerance and drug dependence (Anand et al., 2010). Furthermore, recent evidence in preterm infants suggests that such treatment may have negative effects on infant brain development (Anand et al., 2010). Despite the common clinical pairing of opioids with benzodiazepines, no studies to date have evaluated the effects of their simultaneous administration on longitudinal development. Additionally, studies of long-term safety following exposure to prolonged sedation are limited to investigations in premature infants. Our lack of clear understanding regarding potential negative neurobehavioral outcomes in full-term children exposed to prolonged sedation in infancy should be investigated in studies that minimize potential biases (e.g. prematurity and cardiopulmonary bypass surgery). Since there is a gap in the literature regarding the neurodevelopmental effects of such combined treatment when applied to full-term infants, the main objective of this study was to identify correlations between the amount of sedation and neuroradiological findings associated with opioid and benzodiazepine dependence.

Full-term infants who receive prolonged sedation are intubated and on mechanical ventilation for either (1) treatment for lung disease (without confounds of surgery and anesthesia), or (2) following major cardiothoracic or thoracic surgery (Bajic et al., unpublished
We focused our investigations of the population of infants with gastrointestinal anomalies requiring surgical repair (without confound of cardiopulmonary bypass). Specifically, we identified a population of infants born with the gastrointestinal condition long-gap esophageal atresia (LGEA), a congenital anomaly in which the esophagus does not properly connect to the stomach. As part of their surgical management, they undergo thoracotomy and Foker Procedure (see below) that entails prolonged postoperative intubation and sedation (several weeks long) during which patients develop opioid and benzodiazepine dependence.

There is much to learn about the relationship between LGEA treatment, namely prolonged sedation, and infant brain development. Therefore, this study aims to determine the extent of associations between amount of sedation associated with LGEA postoperative treatment and neuroradiological findings, as per brain MRI. Specifically, we hypothesized that infants with prolonged sedation associated with drug dependence will have pathological findings on brain MRI reports. We correlated (1) the amount of sedation, (2) the length of sedation, and (3) the number of anesthetic events to MRI findings.

**Characteristics of The Specific Surgical Population: Infants with Esophageal Atresia**

Esophageal atresia (EA) occurs in 1 in 2500-3000 live births. There are several types depending on the location of the gap. EA with distal tracheoesophageal fistula is the most common type (86% of diagnoses (Spitz, 2007)). EA with distal tracheoesophageal fistula is characterized by a dilated proximal esophagus with a thickened muscular wall that ends blindly at about the third or fourth thoracic vertebra. The thinner, narrower distal esophagus enters the wall of the trachea, forming the distal tracheoesophageal fistula. The distance between the proximal esophagus and the distal fistula can vary from overlapping to a wide gap, which is
known as LGEA (Spitz, 2007). The two other less common type of EA are: (1) isolated EA without fistula, and (2) tracheoesophageal fistula without atresia. The first is characterized by the proximal and distal esophagus ending blindly with no connection to the trachea. The second has an intact esophagus but a fistula between the esophagus and trachea (Spitz, 2007). These three most common types of EA are illustrated in Figure 1.

**Figure 1. Types of Esophageal Atresia.** Schematic illustration show esophageal atresia (EA) with distal tracheoesophageal fistula (A), isolated EA without fistula (B), and tracheoesophageal fistula without atresia (C). Illustration from textbook (Spitz, 2007).

Diagnosis of EA can be suspected prenatally by ultrasound documentation of polyhydramnios (accumulation of amniotic fluid as a result of fetal inability to swallow; Hamza et al., 2013). Furthermore, respiratory complications (e.g. desaturations with feeding), and inability to pass the nasogastric tube (catheter) immediately following birth leads to high suspicion of EA. If the catheter cannot be inserted beyond 11 or 12 centimeters, finding the coiled catheter in the upper esophageal pouch with lack of air bubble in the stomach, as per chest
x-ray, confirms the diagnosis of EA (Pinheiro et al., 2012). It is also known that 65% of infants with EA have other associated anomalies that may contribute to symptoms found in VACTERL syndrome. The latter is comprised of vertebral, anorectal and intestinal malformations, cardiac, tracheo-esophageal fistula, renal, as well as limb abnormalities (Pinheiro et al., 2012).

Infants with complex surgical disease must be transferred to a regional pediatric surgical center (Pinheiro et al., 2012). In addition to infants admitted for the initial surgical treatment, a great number of infants with failed primary treatment elsewhere are referred for a complex surgical repair at the premier Esophageal Atresia Treatment Center at Boston Children’s Hospital, which is considered the World’s foremost leader in pediatric esophageal and airway repair and treatment center. The total number of surgeries is expected to nearly double from 388 in fiscal year 2013 to 754 in fiscal year 2018 (personal communication with Dr. R.W. Jennings, Director of Esophageal Atresia Treatment Center at Boston Children’s Hospital). Prior to surgical treatment, doctors can determine the patient’s prognosis via one of three different classification systems: Waterston, Montreal, or Spitz (Pinheiro et al., 2012). The most recent system, created by Spitz in 1994, separates patients by birth weight and cardiac condition. *Group 1* includes patients with a birth weight greater than or equal to 1500 g without major cardiac disease; they have a survival rate of 97%. *Group 2* includes patients with a birth weight of less than 1500 g or major cardiac disease; they have a survival rate of 59%. *Group 3* includes patients with a birth weight of less than 1500 g and a major cardiac disease; they have a survival rate of 22% (Spitz, 1994). However, some authors no longer consider birth weight a factor that influences prognoses (Pinheiro et al., 2012). Most infants with EA are premature; however, some are born full-term (37-42 weeks).
Surgical Repair of EA

The only way to repair EA is through surgical intervention. For most infants with short-gap EA (approximately 80% of patients), the two esophageal ends are directly approximated for the final repair. In other words, these infants undergo a primary repair that is defined as a direct anastomosis, or connection, of the two esophageal ends.

However, for infants with long-gap EA, (e.g. a gap of 2-3 cm or longer that is too large for direct anastomosis), the surgery results are historically less satisfactory (Foker et al., 2007) when bridging tubes from the stomach or the colon tissue are used. The difficulty of the primary repair is generally proportional to the length of the gap. It is therefore important to understand the surgical approaches for treating LGEA. To overcome the difficulties that surgeons face with LGEA, Foker et al. (2007) presented a novel approach in treating LGEA. This approach is based on the primary repair but expands its application, aims to avoid complications and highlights the importance of customizing the surgery to each individual patient. This approach has two major principles: that a well-done anastomosis will be able to withstand considerable tension; and, that if the gap is too long, growth can be induced, eliminating the need to interposition with other tissues (e.g. stomach or colon).

Specifically, as described by Foker et al. (2007), surgical repair for LGEA uses a thoracotomy approach; for very long gaps, two intercostal entries are made. In all cases, sutures are placed at the ends of the proximal and distal esophageal pouches, which allows an assessment of anastomotic tension. If the two ends can be easily brought together, direct anastomosis is performed. Generally, with gaps of 2.6 cm or larger, other steps must be taken to solve the problem of the gap length. The first technique, referred to as “Traction in the OR,” is used when there is moderate tension between two esophageal ends. In such cases, the ends of the
esophageal segments are dissected and sutures are preplaced and tagged. Steady traction is then applied until the ends are in position and tied off without tension. The second technique, or “Internal Traction,” is used when the tension is too great for an immediate anastomosis but the ends are relatively close. The segment ends are not dissected but sutures are placed around the ends. The sutures are placed in the prevertebral fascia and tied down in order to pull the ends close while under tension. The chest is closed and after a few days the surgeons go back in to find the two ends more lax and thicker, indicating growth. Direct anastomosis can now proceed as described above. The third technique is used with very long gap cases where the pulling described in the second technique is not enough and can be called “External Traction.” In the third technique, the sutures in the ends of the segments are brought out of the incision and tied over silastic buttons. Each day, the tension is increased to continue to stimulate growth. This is continued, until the two ends are approximately 1 cm apart, when direct anastomosis repair can be achieved (Foker et al., 2007). Of the 63 patients with LGEA that Foker et al. (2007) studied, 61 had satisfactory primary repairs. The two cases with unsatisfactory outcome include a patient who had a previously failed colon interposition and a patient who passed away before the scheduled primary repair due to a subdural hematoma. All three techniques, including combinations of techniques, yielded rapid esophageal growth response; in fact, some patients had spectacular growth of almost the entire intrathoracic esophagus (Foker et al., 2007).

Surgical repair of EA can increase a child’s life span by 70 years or more. Successful treatment allows for normal growth of the child; in other words: ability to eat a normal, regular diet, minimal negative psychological sequelae, and no adverse pathological events due to the surgical repair. Indeed, such complex surgical repair is not without major surgical complications that may include (but are not limited to): leak and stenosis of the anastomosis, gastro-esophageal
reflux, esophageal dysmotility, fistula recurrence, scoliosis, and deformities of the thoracic wall. Furthermore, for the esophageal growth during “External Traction,” patients need to be intubated and sedated for a prolonged period of time, which places them at risk for development of drug dependence (Pinheiro et al., 2012).

**Standard of Care: Sedation Management**

Historically, it was the initial study by Anand and Hickey (1987) that showed infants’ increased stress response to surgery in the absence or pain and anesthesia administration. Over the past 2 ½ decades, our better understanding of the negative implications of untreated pain in infants and children has shifted the management of pain towards the use of analgesic agents to relieve pain and discomfort in the pediatric population (Fitzgerald and Walker, 2009; Fitzgerald et al., 1989; Fitzgerald, 1991). Pain management in neonates and children has been shown to decrease stress, morbidity and mortality rates, and recovery times after surgery or disease (Dilworth and Mackellar, 1987). Even without a source of surgical pain, critically ill infants and children receive sedation to reduce anxiety, agitation, stress responses, and to facilitate ventilation (Berde and Sentha, 2002). Sedation is currently considered a component of safe and compassionate care of critically ill infants and children. Original studies with increased dosing and prolonged administration of opioids during neonatal and pediatric intensive care demonstrate that neonates, infants, and children rapidly develop analgesic tolerance (defined as escalating drug dosage to achieve the same level of pain relief achieved initially, Table 1) and drug dependence (defined as an adaptive state that develops from repeated drug administration and results in withdrawal upon cessation of drug use, Table 1; Arnold et al., 1991; Anand et al., 2010).
Drugs Used for Pain Management Following LGEA Repair

As previously mentioned, patients undergoing LGEA repair often receive prolonged sedation as safety and comfort measures during the period of endotracheal intubation of “External Traction” management that provides time for esophageal growth. Current clinical practice includes administration of opioids and benzodiazepines for sedation (Table 2 and Figure 2).

**Opioids.** Opioids are analgesics that block endocrine stress responses and prevent stress-induced increases in pulmonary vascular resistance that might, otherwise, jeopardize respiratory functions during controlled ventilation. Most commonly used opioids for sedation include fentanyl, morphine, alfentanil, and methadone. Fentanyl is a lipophilic synthetic opioid with fast onset and short duration of effect, which acts on μ1- and δ-opioid receptors. However, opioid tolerance and dependence occurs more rapidly following prolonged intravenous infusions of short-acting opioids such as fentanyl (Anand et al. 2005). Morphine, is a hydrophilic opioid that is longer acting and binds to μ1- and μ2-opioid receptors to reduce behavioral and hormonal responses, improve ventilator synchrony, and alleviate post-operative pain. Opiates as a group are associated with adverse effects that include paralytic ileus in mechanically ventilated preterm infants, retention of urine in the bladder, and (with higher doses) hypotension and bradycardia.

**Benzodiazepines.** Benzodiazepines, which can also be referred to as sedative-hypnotics, are different from opioids in that they do not directly treat pain. Benzodiazepines act as allosteric modulators on the gamma amino butyric acid (GABA)-A receptor, thereby allowing for inhibitory neurotransmitter GABAergic effects to occur. GABA is an inhibitor and reduces the excitability of neurons in the brain, leading to a sedating effect on patients (Griffin et al. 2013).
Common benzodiazepines used for sedation include midazolam and lorazepam. Both drugs produce sedation, hypnosis, anxiolysis, muscle relaxation, and antiepileptic effects. Midazolam is considered an adjunct to opioids for sedation during prolonged ventilation for neonates even though there is limited data to support this practice (Anand et al., 2005). It is mostly given in the form of infusion. In fact, a meta-analysis performed by Aranda et al. (2015) suggests that there is insufficient data to support the use of continuous midazolam infusions. Lorazepam is a longer acting benzodiazepine that, like midazolam, is also used to augment sedation for patients undergoing prolonged mechanical ventilation. It is never used in the form of infusions, but only in individual intravenous boluses over time intervals. As a group, benzodiazepines, specifically midazolam, may put the infant at a higher risk of adverse neurologic events such as death, intraventricular hemorrhage grade III/IV, and periventricular leukomalacia (Arvada et al. 2005).

**Prolonged Sedation and Tolerance**

As of now, we know that opioid tolerance and dependence occurs more rapidly in younger age groups, develops more commonly during critical illness, and results more frequently from prolonged intravenous infusions of short-acting opioids such as fentanyl (Anand et al. 2005; 2010). Prolonged sedation is defined as more than 72 hours of continuous sedation, since tolerance and physical dependence rarely occurs before this point (Anand et al., 1999; Dewey, 1984). Once a tolerance develops and the drug begins to be weaned, withdrawal symptoms (ranging from diarrhea and vomiting to tremors and increased muscle tone) must be prevented and treated (Franck et al., 2009). Tolerance, dependence, and withdrawal are defined in Table 1.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Tolerance</td>
<td>Decreasing clinical effects of a drug after prolonged</td>
</tr>
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</table>
Dependence  
Physiological and biochemical adaptation of neurons such that removing a drug leads to withdrawal or abstinence syndrome.

Withdrawal  
Clinical syndrome that manifests after stopping or reversing a drug after prolonged exposure.

Table 1. Definition of terms: as defined in Anand et al. (2010).

In fact, reports indicate that opioid dependence occurs in 37-57% patients in Pediatric Intensive Care Units patients (Anand et al., 2010). To prevent withdrawal, physicians determine the best course of weaning treatment, which commonly includes methadone, buprenorphine, clonidine, dexmedetomidine, gabapentin, propofol, and propoxyphene (Anand et al., 2010).

Drug Dosing

Pharmacokinetics of opioids are different in the neonatal population due to immaturity of liver and kidney for metabolism and elimination, respectively. Furthermore, neonates (newborn infants less than four weeks old) tend to have a lower plasma clearance, higher volume of distribution, decreased protein binding, and decreased renal clearance, which all lead to decreased clearance and longer elimination half-life when compared to adult populations. In addition, they also have immature blood-brain barriers. This immaturity impacts the potential effects of more water-soluble opioids (e.g. morphine), which can lead to respiratory depression (Bhalla et al., 2014).

While there exist explicit clinical practice guidelines for pain management in adult intensive care units (such as the Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium set forth by the Society of Critical Care Medicine; Barr et al., 2013), the same cannot be said of pediatric or neonatal guidelines. In fact, there is much variation in the
field of pediatric critical care (Playfor et al., 2006). Anand et al. provides five guidelines to provide safe and effective opioid analgesia without inducing tolerance or withdrawal, as summarized in Table 2 (from Anand et al., 2010).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Details</th>
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<tr>
<td>1</td>
<td>Opioid dose should match the intensity and frequency of pain, be titrated initially to achieve adequate analgesia, and be adjusted to find the minimum effective dose for each patient. Increased opioid requirements may be dictated by opioid tolerance or opioid-induced hyperalgesia or worsening pain states, each of which are treated differently.</td>
</tr>
<tr>
<td>2</td>
<td>Short-acting opioids can be used for procedural or breakthrough pain, whereas longer-acting opioids can be used for established, prolonged, or chronic pain. Avoid using opioids if only sedation or motion control are required. Scheduled intermittent doses of longer acting opioids may substitute for opioid infusions to reduce tolerance.</td>
</tr>
<tr>
<td>3</td>
<td>Opioid withdrawal can be assessed by using various methods (MNAS, Sedation Withdrawal Score, Sophia Observation Withdrawal Symptoms Scale, Opioid and Benzodiazepine Withdrawal Scale). Currently, however, the WAT-1 scale seems to show the greatest promise for efficient assessment of opioid withdrawal in PICU patients.</td>
</tr>
<tr>
<td>4</td>
<td>Management of opioid withdrawal includes gradual opioid weaning (see Table 5), environmental and nursing supportive measures, and treatment with methadone, clonidine, or both or alternative therapies such as buprenorphine, dexmedetomidine, propofol, or gabapentin.</td>
</tr>
<tr>
<td>5</td>
<td>Prevention of opioid tolerance may include practical approaches such as nurse-controlled sedation or sequential rotation of analgesics, although promising experimental therapies include opioids combined with low-dose ketamine or naloxone or other classes of drugs</td>
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</table>

Table 2: Opioid analgesia recommendations set forward by Anand et al. (2010) to safely administer opioid analgesia in infants and to minimize potential development of analgesic
Considering this study involved patients from the Boston Children’s Hospital, we also provide a copy of the hospital’s guidelines for postoperative pain management implicated for prolonged sedation, as displayed in Figure 2. All the patients in this study underwent the sedation protocol that involved combination of opioid (e.g. fentanyl and/or morphine) and the midazolam infusions that were supplemented by additional intravenous boluses if needed. Note that guidelines provide suggested starting doses for fentanyl and morphine and suggestions for when to increase the dosage, but not the upper limit of the dose (Boston Children’s Hospital, 2009).
**Figure 2. Guidelines for pain and sedation management.** Flow chart illustrates recommended practices for drug selection for pain and sedation treatment in Neonatal Intensive Care Units (NICU). Care should be individualized for each patient depending on prior history and anticipated length of intubation (Boston Children’s Hospital, 2009).
II. SPECIFIC AIMS

The main objectives of the following thesis include:

1. A detailed background on the current knowledge of state of the art clinical practice of sedation.

2. We hypothesized that patients with prolonged sedation (associated with development of opioid and benzodiazepine dependence) will have abnormal findings on the brain magnetic resonance imaging (MRI).

3. We hypothesized that there is a correlation between the average daily dose of drug of sedation (morphine and midazolam) with the number of neuroradiological findings, the cerebrospinal fluid volume, and brain volume as per MRI scans.
III. MATERIALS and METHODS

Patient Population

The study method was reviewed and approved by the Boston Children’s Hospital Institutional Review Board (Protocol Number IRB-P000007855) and classified as a no more than minimal risk study. Inclusion criteria included full-term infants less than one year old with history of LGEA and no known neurological disease or any magnetic resonance imaging (MRI) incompatible implants who received sedation for more than 72 hours. Before 72 hours, tolerance and physical dependence to pain medication is rare (Dewey, 1984). The parents of each infant enrolled signed informed consent documents before participation began. In total, 7 patients (all less than 12 months old) were identified through chart review as meeting the aforementioned requirements. Additionally, 6 controls (all less than 12 months old) were identified; all were healthy babies who received no anesthesia. A retrospective patient chart review documented the following data for all patients: baseline demographics (gender, race, ethnicity), pregnancy and birth details (gestational age at birth, weight at birth, multiple births, birth by cesarean section), clinical info (initial admission service, procedure type, number of anesthesia events, intraventricular hemorrhage (IVH) grade), and scan info (chronological age at scan, corrected age at scan, weight at scan), as seen in Table 3. To note, the presence of IVH was grounds for exclusion from the study. The demographics and clinical information for the patients and controls are presented in Table 3.
<table>
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<th>Controls (N=6)</th>
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<td>0</td>
</tr>
<tr>
<td>Asian Indian</td>
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<td>0</td>
</tr>
<tr>
<td>Japanese</td>
<td>0</td>
<td>1 (17)</td>
</tr>
<tr>
<td>American</td>
<td>4 (57)</td>
<td>0</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (14)</td>
<td>5 (83)</td>
</tr>
<tr>
<td><strong>Pregnancy and Birth Details</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>38.57 ± 1.51</td>
<td>39.7 ± 0.82</td>
</tr>
<tr>
<td>Weight at birth (kg)</td>
<td>2.92 ± 0.55</td>
<td>3.5 ± 0.14*</td>
</tr>
<tr>
<td>Multiple births</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Birth by C/S</td>
<td>2 (29)</td>
<td>1 (17)</td>
</tr>
<tr>
<td><strong>Clinical Info</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial admission service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU</td>
<td>4 (57)</td>
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</tr>
<tr>
<td>MSICU</td>
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<td>CICU</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Primary surgery</td>
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<td></td>
</tr>
<tr>
<td>General Surgery</td>
<td>6 (86)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac Surgery</td>
<td>2 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Days of sedation</td>
<td>16.71 ± 6.26</td>
<td>0</td>
</tr>
<tr>
<td>Days of weaning</td>
<td>11.43 ± 8.68</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total number of anesthesia events</strong></td>
<td>7 ± 6.68</td>
<td>0</td>
</tr>
<tr>
<td><strong>Scan Info</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at scan</td>
<td>5 ± 3.42</td>
<td>6.17 ± 4.58</td>
</tr>
<tr>
<td>Weight at scan (kg)</td>
<td>6.42 ± 2.14</td>
<td>4.1*</td>
</tr>
</tbody>
</table>
Table 3. Baseline demographics and clinical information: displays demographics and clinical characteristics for patients (N=7) and controls (N=6). Data are presented as either n (%) or mean ± SD. The total number of anesthesia events include all events documented in Boston Children’s Hospital Anesthesia reports, admission notes, and outside medical records. Outside medical records were reviewed to identify operating room reports, summary of hospital stay, and summary of hospital procedures. The initial admission service is defined as the clinical unit where the patient was first admitted: neonatal intensive care unit (NICU); medical-surgical intensive care unit (MSICU); cardiac intensive care unit (CICU). Inconclusive ultrasounds are due to poor technique. Additionally, since the control infants were otherwise healthy, and were never admitted to the hospital they do not have any applicable clinical info. Asterisks (*) denote control demographics and info where data were available for less than 3 controls.

Magnetic Resonance Imaging (MRI)

The MRI scans were completed at night, allowing for non-sedated imaging (imaging under natural sleep is also referred to as feel and wrap approach). Infants were continuously monitored throughout the scan for stable heart rate and oxygenation by the study PI (Dr. Bajic), while MRI sequences were collected by the MRI technologist on call. The MRI was performed with a 3Tesla scanner (Siemens Medical Solutions, USA, Inc., Malven, PA) equipped with a 32-channel head coil. The scans produced T1-weighted, T2-weighted anatomical images that were evaluated by the neuroradiologist on call. These MRI images are characterized by different tissue contrasts most easily distinguished by contrast of the cerebrospinal fluid (CSF) such that it is characteristically darker (black) in T-1 weighted images, and lighter (white) in T-2 weighted images in comparison to brain tissue (scales of gray). Scanning parameters were as follows for the T-1 weighted scans: 5.02min MPRAGE sagittal sequence; TR 2520ms; TE 1.75ms; field of
T2-weighted images were analyzed in the current research (3:33 min axial sequence; TR 12430ms; TE 110ms; field of view 180x180; slice thickness 2mm and 63 slices; voxel size 0.35x0.35x2.0 mm).

Neuroradiology reports were reviewed from patient charts reported by neuroradiology physician staff. In addition, neonatal neurologist blinded to the subjects’ history or study group, reviewed all research MRI scans to confirm accuracy of the clinical reports. Any pertinent findings for clinical care were immediately communicated to the primary surgical team. Noted MRI abnormalities ranged from changes in (1) shape of the head (e.g. brachycephaly, microcephaly), (2) extra-axial space (e.g. accumulation of CSF, subdural hematoma), (2) grey matter parenchyma (e.g. tissue loss, delayed cortical gyration, hemorrhages), (3) white matter tracks (e.g. thinning of the corpus callosum), and (4) other incidental findings (e.g. enlarged ventricles) It is significant to note that both white and gray matter abnormalities are associated with neurological sequelae (Woodward et al., 2006). Abnormalities in the amount of CSF or its makeup can have significant clinical implications as well. For example, accumulation of extra-axial fluid (fluid surrounding the brain) in the brain during infancy is associated with an increased risk of autism (Shen et al., 2013).

**Brain Tissue Segmentation (T2-Weighted Images Analysis)**

Brain tissue segmentation allowed for quantitative analysis that included estimation of: (1) total intracranial space volume (ICV), brain volume, and cerebrospinal fluid (CSF) volume. The latter is a biologic fluid secreted by the choroid plexuses that fills the ventricular system and the subarachnoid space within the central nervous system. CSF serves to protect the brain and plays an important role in homeostasis by supplying nutrients and removing waste products.
(Sakka et al., 2011). To efficiently estimate listed brain volumes 3D T2-weighted MRI images were analyzed with *Morphologically Adaptive Neonate Tissue Segmentation* (MANTiS) in Matlab (Beare et al. 2016), a novel technique specifically designed for infant brain segmentation analyses. MANTiS allowed for quantification of estimated ICV and CSV volumes. Automated ICVs masks were manually edited for accuracy. Similarly, the threshold used for CSV estimation was set at 0.2 (20% certainty), which was the best number based on previous visual inspection. Total brain volume was calculated as follows: ICV – CSV volume for each individual brain. In addition to total volume values, normative values (as a % of ICV for each individual subject) were calculated. Data were presented as normalized brain and CSF volumes as the % of the estimated ICV.

**Quantification of Anesthesia during Sedation and Weaning Protocol**

Sedation encompassed the time during which the infant was intubated. Weaning was defined as the period following extubation during which patients continued to receive medications (to prevent occurrence of withdrawal syndrome). Drugs used for prolonged sedation included opioids (fentanyl, morphine, methadone), and benzodiazepines (midazolam, lorazepam). To quantify drugs’ exposure, the following end-point analyses were collected: (1) length of sedation (days); (2) total treatment of all drugs per patient (mg/kg/day); and, (3) average daily doses during sedation and weaning (mg/kg/day ± SD).

To effectively compare the amount of medication administered to infants of varying weights; average daily dose during sedation (mg/kg/day), average daily dose during weaning (mg/kg/day), and individual total treatment dose (mg/kg/day) were calculated using the following formulas:
Average daily dose during sedation:

\[
\text{Infusion (mg)} = \text{dose (mg/kg/hr)} \times \text{weight (kg)} \times \text{time (hrs)}
\]

\[
\text{Average Dose (mg/kg)} = \frac{\text{infusion (mg)} + \text{boluses (mg) during sedation}}{\text{average weight during sedation (kg)}}
\]

\[
\text{Average Daily Dose (mg/kg/day)} = \frac{\text{average dose (mg/kg)}}{\text{sedation length (days)}}
\]

Average daily dose during weaning:

\[
\text{Infusion (mg)} = \text{dose (mg/kg/hr)} \times \text{weight (kg)} \times \text{time (hrs)}
\]

\[
\text{Average Dose (mg/kg)} = \frac{\text{infusion (mg)} + \text{boluses (mg) during weaning}}{\text{average weight during weaning (kg)}}
\]

\[
\text{Average Daily Dose (mg/kg/day)} = \frac{\text{average dose (mg/kg)}}{\text{weaning length (days)}}
\]

Individual total treatment daily dose:

\[
\text{Infusion (mg)} = \text{dose (mg/kg/hr)} \times \text{weight (kg)} \times \text{time (hrs)}
\]

\[
\text{Total Treatment Dose (mg/kg)} = \frac{\text{infusion (mg)} + \text{boluses (mg) during total treatment}}{\text{average weight during total treatment (kg)}}
\]

\[
\text{Total Treatment Daily Dose (mg/kg/day)} = \frac{\text{total treatment dose (mg/kg)}}{\text{total treatment length (days)}}
\]

To compare drugs in the same units, fentanyl (which is administered in mcg) was converted to equivalent mg morphine (10 mcg fentanyl = 1 mg morphine, 10mcg/kg/day fentanyl = 1 mg/kg/day morphine). Data such as treatment duration (days) and average daily dose (mg/kg/day) were analyzed by calculating mean, range, and standard deviation (SD).

The number of anesthesia events was also determined and included all events documented in Boston Children’s Hospital Anesthesia reports, admission notes, and outside medical records. Outside medical records were reviewed to identify operating room reports,
summary of hospital stay, and summary of hospital procedures. Outside anesthesia events often included g-tube insertions and PICC placements.

**Correlation Analysis**

With the assumption that the relationships between the examined variables (amount of morphine, amount of midazolam, length of sedation, number of anesthesia events) and the outcomes (number of neuroradiological abnormalities, normalized ICV and CSF volumes) were linear, Pearson correlation coefficients were determined using R for each combination of variable and outcome. Positive/negative correlations were considered if they had a high r-value (closer to ±1): r±0.7 represents a strong linear relationship; r±0.5 represents a moderate linear relationship; and, r±0.3 represents a weak linear relationship. Statistically significant correlations had a p-value of less than 0.05.
RESULTS

To test the hypothesis that prolonged sedation with opioids and benzodiazepines (including the amount of drugs received, the length of sedation, and the number of anesthesia events) is associated with increased incidence of abnormalities (either neuroradiological abnormalities, increased CSF per ICV, or decreased brain volume per ICV) in full-term patients as per brain MRI scan, we analyzed the amount of pain medication each patient received, reviewed MRI reports, and determined the Pearson correlation coefficient for each combination of variable and outcome, as summarized in Supplemental Table 1.

Neuroradiological Abnormalities as Per MRI Findings

A total of 7 patients exposed to prolonged sedation (associated with development of drug dependence) and 6 healthy controls under the age of 12 months underwent brain MRI scans. Clinical MRI reports for all control subjects were within normal limits. In contrast, reports for nearly all patients, with the exception of one (1/7), had incidental neuroradiological findings as per neuroradiological reports. Incidental findings ranged from abnormalities inclusive of all intracranial spaces and structures (viz. extra-axial space, parenchyma, white matter tracts, ventricular system). Individual incidental findings of all patients are illustrated in a detailed list in Table 4.
<table>
<thead>
<tr>
<th>Number of Abnormalities</th>
<th>Other Abnormalities</th>
<th>Parenchymal (Grey Matter)</th>
<th>Tracts (White Matter)</th>
<th>Extra-axial Space (m)</th>
<th>Age (m)</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td></td>
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<td></td>
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</tr>
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<td>7</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Summary of individual neuroradiological findings for patients (N=7) analyzed that included changes in (1) the extra-axial space, (2) parenchyma, (3) tracts, (4) other incidental findings that were not present in the controls (N=6; not shown), and (5) the tallied number of neuroradiological abnormalities. Age at scan is given in months (m). Only one patient (#2) had no pathological findings on the brain MRI report. Findings were obtained from clinical MRI reports by staff neuroradiologist and confirmed by blinded 2nd evaluation by neonatal neurologist at Boston Children’s Hospital.

Morphine and Midazolam Correlation to Number of Neuroradiological Abnormalities

Patients received several medications during post-surgical treatment that covered two periods: the period of intubation and mechanical ventilation (period of sedation) and subsequent period following extubation (period of drug weaning). In accordance with guidelines for sedation (Figure 2; Table 2), morphine and midazolam were the two drugs used the most frequently and were administered at the highest doses (Figure 3 and 4). Individual total treatment dose, the total amount of each drug that each patient received over the course of treatment, is summarized in Figure 3, while the average daily dose of drugs for all patients is shown in Figure 4.
Figure 3. Individual total treatment dose (sedation and weaning) (mg/kg/day) of each drug for each patient (N=7). Total treatment period is defined as the total number of days that a patient received one particular drug. It included periods of both sedation and weaning. Fentanyl is shown in morphine equivalents (10 mcg fentanyl = 1 mg morphine). As a highly liposoluble drug, fentanyl was used only during first few days of sedation and subsequently switched to longer-acting hydrosoluble morphine for longer sedation (time courses not shown).
Figure 4. Average daily dose of drugs used for sedation and weaning: opioids (fentanyl, morphine, and methadone) and benzodiazepines (midazolam and lorazepam) in full-term patients (N=7). Average daily dose (mg/kg/day ± SD) is shown separately for sedation treatment and weaning periods. Fentanyl is presented in morphine equivalents (10 mcg fentanyl = 1 mg morphine).

Despite the small sample size of this pilot study, reported preliminary data show significant correlation between the amount of drugs received during sedation and the total number of neuroradiological findings. Specifically, there is a strong positive linear relationship between both morphine (r=0.933, p=0.0021; Figure 5A) and the midazolam (r=0.810, p=0.027; Figure 5B) with the number of MRI incidental findings.
**Figure 5. Correlation of drugs of sedation to neuroradiological abnormalities:** illustrate the positive linear relationship between (A) the average daily dose of morphine \((r=0.933, p=0.002)\) and (B) midazolam \((r=0.810, p=0.03)\) during sedation with the total number of neuroradiological abnormalities \((N=7)\).

**Morphine and Midazolam Correlation to Measures of Brain Volume**

For each patient, the normalized estimated CSF and brain volumes are reported in **Table 5** (with permission from Dr. Bajic).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Normalized CSF Volume (% ICV)</th>
<th>Normalized Brain volume (% ICV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.64</td>
<td>83.98</td>
</tr>
<tr>
<td>2</td>
<td>26.13</td>
<td>73.86</td>
</tr>
<tr>
<td>3</td>
<td>19.34</td>
<td>80.85</td>
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<tr>
<td>4</td>
<td>14.83</td>
<td>84.89</td>
</tr>
<tr>
<td>5</td>
<td>16.55</td>
<td>83.45</td>
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<tr>
<td>6</td>
<td>19.39</td>
<td>80.61</td>
</tr>
<tr>
<td>7</td>
<td>20.41</td>
<td>79.59</td>
</tr>
</tbody>
</table>
Table 5. Normalized of CSF and brain volumes. Estimated intracranial volume (ICV) and CSF volume were determined using the segmentation tool, MANTiS. Subsequently, estimated brain volume was calculated by subtracting the percent brain volume from the total ICV (mm3; raw data not shown). Normalized values of CSF and brain volumes were presented as % of ICV (100%).

When analyzing the correlation between the average daily dose of morphine or midazolam with normalized CSF volume (as a % ICV), we did not find any significant relationship (Figure 6A). In other words, despite moderate positive linear correlation between increase in drug dose and the CSF volume, it was not significant for either morphine (r=0.573, p=0.18) or midazolam (r=0.548, p=0.20). Similarly, we report moderate negative linear correlation between increases in drug doses and a decrease in normalized brain volume (as a % of ICV) for both morphine (r= -0.560, p=0.19) and midazolam (r= -0.521, p=0.23; Figure 6B). These relationships are also not statistically significant.
Figure 6. Correlation of drugs of sedation to normalized CSF and brain volume (% of intracranial volume): illustrates the relationship between the average daily dose of morphine or midazolam during sedation with (A) the %CSF per intracranial volume and (B) the % brain volume.
volume per intracranial volume. In both graphs, morphine is represented by white circles and midazolam by black squares. All data are presented with their corresponding linear trend lines.

**Days of Sedation and Number of Anesthesia Events Correlation to Number of Neuroradiological Abnormalities**

Length of sedation and number of anesthesia events are presented in **Table 6**. We report a weak, linear correlation between the days of sedation \((r=0.397, p=0.38)\) and the number of anesthesia events \((r=0.398, p=0.38)\) to the number of neuroradiological abnormalities. Neither of these trends is statistically significant (**Supplemental Table 1**).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Length of sedation (days)</th>
<th>Anesthesia events (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
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<td>17</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 6. Days of sedation and number of anesthesia events** for each patient. The total days of sedation only includes days that the patient was intubated. The number of anesthesia events includes all events during which patients received anesthesia either for different surgeries (e.g. EA repair, g-tube placements) or procedures (e.g. PICC line placements, imaging studies) as per documentation from medical records from BCH and/or outside hospitals.
Days of Sedation and Number of Anesthesia Events Correlation to Measures of Brain Volumes

We did not find any significant relationships between the days of sedation ($r=0.189$, $p=0.69$) and the number of anesthesia events ($r=-0.040$, $p=0.93$) to the percent CSF. Additionally, no relationship was found between the days of sedation ($r=-0.186$, $p=0.69$) and the number of anesthesia events ($r=0.065$, $p=0.89$) to brain volume (Supplemental Table 1).
DISCUSSION

We demonstrate that full-term infants with LGEA, gastro-intestinal disease requiring Foker surgical repair with ‘external traction,’ undergo very long periods of sedation. Such treatment is uniformly associated with development of drug dependence to both opioids and benzodiazepines. This is the result of administration of morphine and midazolam, the two drugs used the most frequently and administered at the highest doses during periods of post-operative sedation. Our preliminary data also show significant positive correlation between received daily doses of morphine and midazolam with an increased number of neuroradiological abnormalities, as per MRI reports. In contrast, days of sedation and the number of anesthesia events show no correlation to neuroimaging outcomes. Despite demonstrated trends between increased amount of administered drugs and increased normalized CSF volume, as well as decreased estimated normalized brain volume, these were not found to be significant.

Limitations of the Study

The largest limitation of the presented findings is the small sample size of this pilot study. Therefore, any generalization of presented preliminary findings should be avoided until further research has been completed. Sample size of minimum 10 subjects/group per variable has been reported in the literature for infant imaging; ideally N=17 would implicate statistical significance that could likely be true and make inferences about population of infants with LGEA. Major challenge of the study relates to difficulty of recruitment, given the sensitive nature of the health conditions of the subject population (viz. critical illness, protracted clinical course with possible surgical complications). Furthermore, although there was no evidence of any neurological abnormalities prior to Foker procedure (e.g. absence of any findings per head ultrasounds as per
routine clinical care), it is not known if any of the neuroradiological findings identified had already been present prior to the surgical treatment or not. There are many factors that dictate the health of these patients and it is possible that other factors (e.g. exposure to anesthetic drugs, hemodynamic instability during anesthesia and/or sedation, symptoms of withdrawal, failure to thrive, and/or combinations listed) influenced their neurological outcomes and should be taken into considerations as confounders in addition to drugs of sedation. Finally, the use of surgical controls, infants who receive pain control and/or sedation for less than 5 days (that do not develop analgesic tolerance or drug dependence), could help to clarify the relationship between prolonged sedation and neurological outcomes.

**Prolonged Sedation and Brain Injury**

The average daily doses of morphine and midazolam in the selected group of full-term infants with LGEA (N=7) are significantly positively correlated with incidental brain MRI findings as outlined in Figure 5 and 6. Such findings implicate possible immediate and long-term correlation between sedation and brain injury. Literature shows similar MRI findings in infants following cardiac surgeries undergoing repair of cardiac anomalies. Specifically, a study by Andropoulus et al. (2013) evaluated 57 neonates following aortic arch reconstruction surgery. Of the 57 participants, 40% had new postoperative MRI brain injuries. Although all of these children also underwent thoracotomy and were exposed to prolonged sedation associated with physical dependence to drugs of sedation, abnormal brain MRI findings were attributed primarily to the fact that these infants underwent extracorporeal circulation (by-pass) for the repair of heart abnormalities (as the major confounding factor). Other major difference is that they were premature infants, in contrast to full-term infants in our study. Since our study avoids confounds
of prematurity and cardiopulmonary bypass, it implicates drugs of sedation (associated with development of drug dependence) as having a possible role in increased incidence of brain injury.

**Long-Term Implications of Administered Drugs**

Demonstrated incidental findings as per brain MRI reports in described group of infants undergoing LGEA repair with prolonged sedation raises concern for possible long-term neurodevelopmental outcomes. Furthermore, described quantification of volumes shows trends of increased CSF and decreased brain volumes following such treatment. The current literature is sparse regarding long-term implications following prolonged sedation in infancy (with both opioids and benzodiazepines), especially among full-term infants. The Neurologic Outcomes and Pre-emptive Analgesia in Neonates (NEOPAIN) trial, by Anand et al. (2005), found evidence of long-lasting negative effects in premature infants following preemptive treatment with morphine, specifically: diminished body weight and head circumference, social problems, and short-term memory task delays (Ferguson et al., 2012). This study focused on premature infants and could therefore not exclude prematurity as a confounding factor. Another study by Guerra et al. (2014) found a small but significant association between benzodiazepine cumulative dose following neonatal cardiac repair for arterial switch operation and a lower Visual Motor Integration score at 12 months of age, indicating some negative neurodevelopmental outcomes. In contrast, morphine was found not to have any significant influence on outcome variables by age 8-9 following neonatal participation in a morphine-placebo controlled trial (de Graaf et al., 2013). In fact, de Graaf et al. (2013) concluded that morphine during the neonatal period may even have a positive influence on executive functions. These three studies are difficult to compare to our study given
differences in gestational age (premature vs. full-term) and the type of infant populations (medical treatment and cardiac surgery with cardiopulmonary bypass vs. thoracotomy without extra-corporeal circulation in our case). However, all studies agree in their suggestion as to use caution when administering morphine and midazolam for prolonged periods of time in the youngest of patients.

**Long-Term Implications of MRI Findings**

In addition to the lack of literature on long-term outcomes following prolonged sedation, literature on long-term outcomes associated to brain abnormalities as per MRI reports in full-term infants in the perioperative settings is limited. This contrasts with the number of studies demonstrating several neuroradiological abnormalities associated with prematurity. Specifically, a prospective longitudinal study by Woodward et al., (2006) reported associations between white and gray matter abnormalities at term equivalent age (as per MRI findings) to neurodevelopmental outcomes at 2-years of age. This study found that severe **white matter abnormalities** were associated with poorer performance on cognitive and psychomotor assessments, increased risk of severe cognitive delay, motor delay, cerebral palsy, and risk of severe cognitive delay. Additionally, **gray matter abnormalities** were associated with poor scores on the cognitive and psychomotor tests, severe cognitive delay, motor delay, and cerebral palsy. Mathur et al. (2010) reported that specific white matter injuries are associated with loss of brain volume and increased CSF volume. Interestingly, these altered volumes are associated with verbal and performance IQ scores. Similarly, Andropoulos et al. (2013) found that following cardiac surgery in infancy, language and motor outcomes were lower by 12 months of age. All together, these reports suggest that brain abnormalities (as per MRI reports) are associated with
long-term neurodevelopmental outcomes. Further research must be completed to fully appreciate any differences between long-term outcomes in preterm versus term patients. Future studies in infants with LGEA should also include long-term neurobehavioral evaluations that can give insight into potential long-term sequelae from identified brain structure abnormalities.

**Additional Considerations: Total Parenteral Nutrition**

Nutrition is vital for brain development during pre and postnatal life. Certain nutrients that are especially important during the late fetal and neonatal stages include protein, iron, zinc, selenium, iodine, folate, vitamin A, choline, and long-chain polyunsaturated fatty acids. Aspects of brain development that are susceptible to nutrient deficiency include myelination of neurons, glial cell proliferation, neurotransmitter synthesis, receptor synthesis, neurotransmitter reuptake mechanisms, metabolism, and signal propagation (Georgieff, 2007). Both critically ill preterm and full-term infants often receive total parenteral nutrition (TPN), which is designed to substitute daily nutritional requirements, and is administered either via Central Venous Line (CVL) or Peripherally Inserted Central Catheter (PICC). It provides glucose for energy, amino acids (both essential and non-essential), lipids, vitamins, and trace elements such as zinc. TPN is administered to critically ill children during prolonged sedation or in cases where infants cannot feed (e.g. due to gastrointestinal tract anomalies, muscular and neurological immaturity, or various chronic illnesses). Unfortunately, TPN can lead to side effects such as a decrease in the function and structure of the gastrointestinal mucous membrane, a decrease in the secretion of gastrointestinal hormones, and can result in intolerance to enteral (via the mouth) nutrition. Additionally, long-term overall growth retardation has been observed. It is therefore recommended that TPN be replaced by enteral nutrition (with or without partial PN) as soon as
possible (Fusch et al. 2009). Although our quantification of drugs of sedation and the MRI reports are regenerated at the end of the weaning treatment, infants may undergo feeding challenges for a protracted period. Lack of regular nutrition may have consequences that are still not known (e.g. TPN as a confounder). Future studies should also elucidate the role of prolonged TPN on the brain development.

**Implications**

Given the risks associated with both extremes of pain treatment: (1) withholding the treatment, and (2) administering sedation medication for prolonged time that would lead to drug dependence, clinicians must take the utmost of care to personalize each patient’s treatment plan to avoid under treatment or over sedation (Anand et al., 2010; Anand and Hickey, 1987). This is made particularly difficult given the lack of knowledge around how much is too much. Additionally, it is imperative that parents and guardians of infants who undergo such extensive sedation be well informed of all the potential risks that come with such treatment on brain structure and possibly brain development.

**Future Directions**

The first step to further our research is to increase the sample size of participants in order to have meaningful statistical power that will allow for more definite conclusions to be made. In general, as research in the field of sedation management continues, researchers need to turn their attention to the full-term neonatal population. Given the ethical considerations, conducting more retrospective studies to evaluate the safety of specific sedation medication on the neonatal population may be the place to start. Although valuable, retrospective analysis is vulnerable to
incomplete or missing documentation, poorly recorded or absent chart information (e.g. apparent lack of sedation scales), as well as difficulty in identification of desired patients (e.g. possible underestimation of total number of patients). Our overarching goal should also be to better understand the underlying mechanisms of potential brain injuries that could pave the way to finding better treatments for prolonged sedation. Furthermore, long-term neurobehavioral studies should also be investigated to augment the data presented in this report. Last, but not least, surgeons should continue to look into best outcomes of different and novel surgical techniques with the goal of shortening the exposure of infants younger than 12 months of age to drugs of sedation and possibly avoiding development of iatrogenic drug dependence.
CONCLUSIONS

In conclusion, our preliminary data in selected group of full-term LGEA infants shows that the average daily dose of morphine and midazolam is significantly associated with an increased incidence of abnormal neuroradiological findings. Such treatment also shows moderate correlation to increased CSF and decreased brain volumes. Completion of the study by increasing the sample size would confirm if such correlation could be significant. Moving forward, future research should also explore the impact of opioids and benzodiazepines on neurocognitive outcomes in the absence of prematurity and cardiopulmonary bypass confounds. This study raises many questions and concerns, all in benefit of the infant and pediatric care.
**SUPPLEMENTAL MATERIAL**

<table>
<thead>
<tr>
<th># of Neuroradiological Abnormalities</th>
<th>Amount of Morphine</th>
<th>Amount of Midazolam</th>
<th>Length of Sedation</th>
<th># of Anesthesia Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Cerebrospinal Fluid per ICV</td>
<td>0.933*</td>
<td>0.810*</td>
<td>0.397</td>
<td>0.398</td>
</tr>
<tr>
<td>% Brain Volume per ICV</td>
<td>0.573</td>
<td>0.548</td>
<td>0.189</td>
<td>-0.040</td>
</tr>
<tr>
<td></td>
<td>-0.560</td>
<td>-0.521</td>
<td>-0.186</td>
<td>0.065</td>
</tr>
</tbody>
</table>

* *p<0.01

**Supplemental Table 1. Pearson Correlation Coefficient matrix.** Table summarizes different correlations that were analyzed as part of the study. Specifically, r±0.7 represents a strong linear relationship; r±0.5 represents a moderate linear relationship; and, r±0.3 represents a weak linear relationship. Asterisks identifies the level of significance (p<0.01).
REFERENCES


Analgesia and sedation during mechanical ventilation in neonates. *Clin Ther* 27(6), 877-899.


