Evaluating the Effects of General Anesthesia on Sleep in Children Undergoing Elective Surgery

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

Institute of Medical Science
University of Toronto

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Abstract

Background: There is increasing interest towards factors that may contribute to impaired sleep following surgery, but there remains a gap in knowledge regarding the impact of general anesthesia on sleep. The objective of this study was to identify potential effects of a general anesthetic on sleep and related behavioural consequences. Methods: Children, aged 18 months to 8 years, wore an actigraph to estimate sleep-wake patterns for 7 consecutive nights prior to and after surgery. Data regarding baseline behaviour patterns were collected using behavioural assessments. One and three months after surgery, the actigraph was worn again for 7 nights with completion of behavioural assessments. Sleep and behavioural patterns were compared with a control group of healthy children. Results: No significant differences were found in preoperative and postoperative sleep and behavioural patterns. Overall, general anesthesia did not cause sleep disturbance or negative behaviour changes. These findings are reassuring to physicians and parents.
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and close friends. Despite the hardships during this journey, your patience and support provided the motivation to push through and successfully complete my thesis.

Contributions

A number of investigators contributed to the research work presented in this thesis. Dr. Sharon Cushing, Dr. Evan Propst and Dr. Armando Lorenzo were the staff surgeons who assisted in the screening of eligible patients to take part in the research study. Dr. Jason Maynes and Dr. Conor McDonnell were the staff anesthesiologists who coordinated anesthesiologists for the subjects’ surgical procedures, and ensured that medical records were updated appropriately with details relating to the procedure, anesthetics and pain management. Dr. Lisa Meltzer and Dr. Andrew Lim assisted in the analysis of the actigraphy data. Zihang Lu was the biostatistician that provided assistance with the statistical analysis for this thesis. Additional funding for equipment needed for this research work was provided by the SickKids Perioperative Services Innovation Program. Additional funding sources for Sarah Selvadurai included the Institute of Medical Science Entrance and Open Awards, and Dalton Whitebread Scholarship Fund from University of Toronto as well as research travel grants from the Canadian Sleep and Circadian Network, and School of Graduate Studies at University of Toronto.
List of Abbreviations

ADHD  attention-deficit hyperactivity disorder
BMI  body mass index
BRIEF  Behaviour Rating Inventory of Executive Function
CSHQ  Children’s Sleep Habits Questionnaire
CBCL  Child Behaviour Checklist
DR  dorsal raphe
EEG  electroencephalogram
EMG  electromyogram
ENT  ear-nose-throat
GABA  γ-aminobutyric acid type A
GAS  General Anesthesia compared to Spinal Anesthesia
LC  locus coeruleus
NMDA  N-methyl-D-aspartate
NREM  non-rapid eye movement
PANDA  Pediatric Anesthesia Neurodevelopment Assessment
PHBQ  Post-Hospitalization Behavioural Questionnaire
PPT/LDT  pedunculopontine and laterodorsal tegmental nuclei
PSQI  Pittsburgh Sleep Quality Index
REM  rapid eye movement
STAI  State-Trait Anxiety Inventory
SWS  slow-wave sleep
TIVA  total intravenous anesthesia
<table>
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<tr>
<td>TMN</td>
<td>tuberomammillary nucleus</td>
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<tr>
<td>VLPO</td>
<td>ventrolateral preoptic nucleus</td>
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Chapter One: General Introduction

1.1. Overview

Sleep is essential in promoting physical, mental and socio-emotional health (Reimer & Flemons, 2003). Especially during early development, achieving a sufficient amount as well as good quality sleep is necessary for brain and cognitive development (Dahl, 1996). Thus, sleep disturbances, including frequent nocturnal awakenings, restlessness and an inability to fall asleep, during critical periods of development can lead to cognitive impairment, behavioural disorders and emotional dysregulation (Dahl, 1996). Approximately 20 to 30 percent of infants and toddlers experience disturbed sleep and the frequency of such disturbances remains high in school-aged children (Sadeh, Raviv, & Gruber, 2000). If left untreated, one in three children can experience persistent sleep disturbances and overall poor sleep quality during adolescence (Sivertsen, Harvey, Pallesen, & Hysing, 2017). As such, sleep disturbances in young children is an important, under-addressed public health concern. Increasing efforts in improving sleep quality during early childhood is potentially important for the prevention of related health complications.

There has been concern regarding disturbed sleep following elective surgery in children (Kain & Caldwell-Andrews, 2003; Kain et al., 2005). Several factors can contribute to poor postoperative sleep including the nature of the surgery, child’s preoperative anxiety, parental anxiety, increased and prolonged pain as well as the impact of an overnight hospital stay (Caldwell-Andrews & Kain, 2006; Dolan, Huh, Tiwari, Sproat, & Camilleri-Brennan, 2016; Kain, Mayes, Caldwell-Andrews, Karas, & McClain, 2006). Of emerging interest is the impact of general anesthesia on postoperative sleep disturbances in otherwise healthy children. Data from animal and human research have suggested that anesthetics can disturb postoperative sleep
patterns by affecting the circadian rhythm and sleep-wake cycle (Aurell & Elmqvist, 1985; Poulsen, Warman, Sleigh, Ludin, & Cheeseman, 2016). In adults, altered sleep architecture has been observed following exposure to specific anesthetics, where individuals experience suppressed slow-wave sleep (SWS) and rapid eye movement (REM) sleep followed by a rebound reaction (Knill, Moote, Skinner, & Rose, 1990; Lehmkuhl, Prass, & Pichlmayr, 1987). These changes may result in short-term sleep fragmentation and poor postoperative sleep quality (Aurell & Elmqvist, 1985; Kain et al., 2005). This is relevant in the context that more than two million children undergo elective surgery and receive general anesthesia each year in North America (Rabbitts, Groenewald, Moriarty, & Flick, 2010; Sun et al., 2016).

To date, the impact of anesthetic exposure on the developing brain has been a major concern, where research has specifically focused on the neurotoxic properties of general anesthesia in young children (Creeley, 2016; Sun, 2010). For example, several animal studies found that anesthetics can trigger apoptotic mechanisms. Such neurodegenerative activity can interfere with peak synaptic growth, which primarily occurs between birth and 36 months of age (Jevtovic-Todorovic et al., 2003; Sun, 2010; Yon, Daniel-Johnson, Carter, & Jevtovic-Todorovic, 2005). Although the clinical relevance of such neurotoxic effects remains inconclusive, the U.S. Food and Drug Administration have placed compulsory warnings to be added to labels of general anesthetics. This is due to the potential harm that general anesthesia may cause on the brain development of young children ("FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women," 2016). It is clear that further research is necessary to provide additional information regarding the use of general anesthesia and whether such anesthetics are safe to administer to a pediatric population. Moreover, there remains a lack of research that
assesses sleep quality before and after anesthesia using objective sleep measures. This is particularly important as sleep disturbances have modifiable risk factors, which can be attenuated by targeted intervention strategies. Thus, this thesis will identify and discuss short and long-term sleep disturbances using objective sleep measurements following anesthetic exposure in a pediatric population.

1.2. Thesis Structure

Chapter 2 consists of a literature review, which outlines several concepts that are important for gaining an understanding of this thesis. Firstly, in this chapter, the physiology of sleep is described. Next, the components of the sleep-wake neural circuitry are defined. A brief description of general anesthesia, including its various types and its molecular mechanism of action is provided. Preclinical and clinical findings relating to the effects of general anesthesia on neurocognitive and behavioural development are also reviewed. Lastly, the impact of general anesthesia on sleep will be explained as introduced by previous animal and adult studies. Chapter 3 presents the rationale for this thesis based on the gaps in knowledge that currently exist in the field. Additionally, the research objectives and study hypotheses are described. Chapter 4 outlines the methodology, including the eligibility criteria for the study population and study design. The study measures are also described in detail, which included actigraphy (used as a means to estimate sleep-wake patterns based on gross motor activity), and validated behavioural assessments. Chapter 5 summarizes the results, where sleep and behaviour patterns were compared before and after surgery, and between a group of surgical patients and healthy children from the community. Parental sleep and anxiety were also compared in a similar manner. Lastly, chapter 6 provides a discussion regarding the significance of the findings and how these findings
compare to previous research. Additionally, this chapter will describe the strengths and limitations, while providing possible avenues for future research related to this thesis.
Chapter Two: Literature Review

2.1. Sleep

Sleep is generally defined as a reversible behavioural state of prolonged periods of quiescence and reduced responsiveness to the environment (Carskadon & Dement, 2011). Sleep is crucial for daily functions such as memory consolidation (Stickgold & Walker, 2007) as well as cardiovascular (Grandner, Sands-Lincoln, Pak, & Garland, 2013), immune (Krueger, 2008), endocrine and metabolic function (Spiegel, Leproult, & Van Cauter, 1999). The quality of sleep is linked to quality of life, which is generally defined as the overall state of an individual’s well-being. Specifically, domains of quality of life, including physical function, social function, emotional or mental health and general health, are negatively impacted by persistent poor sleep quality (Reimer & Flemons, 2003).

2.1.1. Stages of the Sleep Cycle

Across the sleep-wake cycle, three distinct states occur: wakefulness, REM sleep, and non-rapid eye movement (NREM) sleep. A period of NREM sleep is divided into three stages: NREM-1, NREM-2, and NREM-3. A typical night of sleep involves alternating cycles of NREM and REM sleep. The length of human sleep cycles changes throughout development: adult sleep cycles last for about 90 minutes (Hartmann, 1968) and infant cycles last for about 45 minutes (Stern, Parmelee, Akiyama, Schultz, & Wenner, 1969). A hypnogram of a human adult sleep cycle is shown in Figure 1.

In adults, a sleep cycle generally begins in NREM sleep, where each stage progresses into more synchronous brain activity and deeper sleep (Carskadon & Dement, 2011). The first stage of NREM sleep, NREM-1, occurs for a relatively short period, which typically lasts for less than
10 minutes. Subsequently, the second stage, NREM-2, begins. NREM-2 sleep constitutes the largest proportion of total sleep time, ranging between 45 to 55%. The last stage of NREM sleep, also referred to as SWS, is the deepest stage of the sleep cycle and constitutes 15-20% of the total sleep time. During the first cycle of the night, the NREM sleep period lasts for about 80 minutes, and is followed by a 10-minute period of REM sleep. REM sleep typically represents 20-25% of total sleep time. During the first half of the night, the amount of SWS tends to be greater. As the night progresses, periods of REM sleep lengthen and REM sleep dominates the second half of the night.

Newborns and infants typically enter REM sleep before NREM sleep, where their sleep cycle is comprised of approximately 50% REM sleep. By the age of 3 months, sleep cycles are similar to those in adults, where the child enters NREM sleep followed by REM sleep (Stern et al., 1969). As a child develops, the amount NREM sleep increases while the amount of REM sleep is reduced to approximately 20-25% of the sleep cycle (Carskadon & Dement, 2011).
A typical night of sleep involves several cycles of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, beginning with NREM stage 1 sleep through stage 3, followed by REM sleep. During the first half of the night, NREM-3 sleep is greater; however, REM sleep dominates the second half of the night as periods of REM sleep lengthen. Adapted from Carskadon and Dement, 2011.

2.1.2. Neurophysiology of Sleep Stages

In order to differentiate sleep-wake states, behavioural and electrophysiological criteria are used (AASM, 2007; Carskadon & Dement, 2011). In humans, a polysomnogram is utilized as the gold standard for the diagnosis of sleep-related disorders. Polysomnography incorporates an electroencephalogram (EEG) as the measure of cortical activity (Carskadon & Dement, 2011). Changes in EEG frequency are ultimately caused by changes in neuronal activity in brain regions such as the brainstem, hypothalamus and basal forebrain, which project to the hippocampus, thalamus and neocortex (Steriade & McCarley, 2005). Additionally, polysomnography includes recordings of heart rhythms, ocular movements, and muscle activity of the face and legs using an electromyogram (EMG) (AASM, 2007). NREM-1 sleep is characterized by a hypnogogic transition of wake-like alpha waves (8-13 Hz) to theta waves (4-7 Hz) (Spencer, 2013). NREM-2
sleep is characterized by K-complexes that are measured in the cortex (Cash et al., 2009). A K-complex is composed of a brief negative sharp wave that is immediately followed by a positive inflection (AASM, 2007). In addition to K-complexes, sleep spindles appear during NREM-2 sleep, where both K-complexes and sleep spindles promote sleep maintenance by preventing the brain from awakening during sleep (Dang-Vu et al., 2011; Nicholas, Trinder, & Colrain, 2002). Specifically, activity of \( \gamma \)-aminobutyric acid type A (GABA\(_\text{A} \)) receptors in the reticular nucleus of the thalamus generates sleep spindles, which then spread to the thalamocortical system (De Gennaro & Ferrara, 2003). Sleep spindles are brief bursts of high frequency waves that are identified as either fast (13-16 Hz) or slow spindles (11-13 Hz) (Schabus et al., 2007). The majority of the spindles that occur during NREM-2 sleep are fast spindles; however slow spindles primarily occur during SWS. SWS spindles occur within slow oscillations that are represented by an alternation between depolarized and hyperpolarized states (Steriade, 2006). Additionally, SWS is characterized by delta waves (0.5-2 Hz) (AASM, 2007). As its name indicates, REM sleep is characterized by rapid ocular saccades. Additionally, muscle atonia and high frequency EEG activity occurs. EEG activity during REM sleep is desynchronized and is nearly identical to that observed during wakefulness, including theta (4-7 Hz), alpha (8-13 Hz) and beta waves (13-30 Hz) (AASM, 2007).

2.1.3. Neural Correlates for Wakefulness and Sleep

2.1.3.1. Wakefulness

During the First World War, an outbreak of encephalitis lethargica occurred, which was a disease characterized by a high fever, delayed physical and mental responses, and lethargy. After seeing patients with encephalitis lethargica, Von Economo was the first to identify areas of the
brain in which lesions caused specific changes in sleep-wake regulation. Majority of his patients slept excessively, and had lesions at the junction of the midbrain and the diencephalon. Following this observation, he proposed the existence of the ascending arousal system, which contains a heterogeneous population of neurons with neurotransmitters that promote wakefulness (von Economo, 1930). The ascending pathway originates in the rostral pons and continues through the midbrain reticular formation, which spans from the brainstem towards the thalamus (Moruzzi & Magoun, 1949). The pathway has two major branches (Figure 2A). The dorsal branch originates in the cholinergic pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), and extends to the thalamus. Cholinergic input from the PPT/LDT neurons activates the thalamocortical neurons, which in turn stimulates cortical activity (McCormick, 1989). PPT/LDT neurons are active during wakefulness and REM sleep, but are less active during NREM sleep (Strecker et al., 2000). The ventral branch bypasses the thalamus and originates from monoaminergic neurons in the upper brainstem and caudal hypothalamus. Monoaminergic neurons release neurotransmitters such as noradrenaline, serotonin, dopamine and histamine. Specifically, the noradrenergic locus coeruleus (LC), serotonergic dorsal raphe (DR), dopaminergic ventral periaqueductal grey matter and histaminergic tuberomamillary neurons (TMN) project to the lateral hypothalamus, basal forebrain and cerebral cortex (Saper, Chou, & Scammell, 2001). Monoaminergic activity is highest during wakefulness, decreases during NREM sleep and is minimal during REM sleep (Aston-Jones & Bloom, 1981; Fornal, Auerbach, & Jacobs, 1985; Steininger, Alam, Gong, Szymusiak, & McGinty, 1999). This pathway also receives input from additional lateral hypothalamic peptidergic neurons, which contain melanin-concentrating hormone and orexin, and basal forebrain neurons containing acetylcholine (Saper, Scammell, & Lu, 2005).
2.1.3.2. Sleep

In addition to discovering the ascending arousal system, von Economo found that, rather than being sleepy, some patients with encephalitis lethargica became insomniac and slept for only a few hours a day. These patients were tired, but had difficulty falling or remaining asleep, and had specific lesions in regions of the basal ganglia and anterior hypothalamus (von Economo, 1930). Further experiments in animals revealed that lesions of sleep-promoting neurons within the ventrolateral preoptic area (VLPO) may have caused insomniac symptoms seen in von Economo’s patients (Sherin, Shiromani, McCarley, & Saper, 1996). These sleep-promoting neurons send inhibitory GABAergic and galaninergic projections to major arousal-promoting cells located in the hypothalamus and brainstem (Figure 2B) (Sherin, Elmquist, Torrealba, & Saper, 1998). The VLPO neurons form a dense cluster as well as an extended portion of the nucleus, where cell-specific lesions of the VLPO in animals have shown a reduction of both NREM and REM sleep. Specifically, lesions of the VLPO cluster primarily reduces NREM sleep, and lesions of the extended VLPO mainly reduces REM sleep (Lu, Greco, Shiromani, & Saper, 2000). Additionally, the VLPO receives projections from monoaminergic cells, including noradrenergic neurons in the LC, serotonergic neurons in the DR and GABAergic neurons in the TMN (Chou et al., 2002). Activity of VLPO neurons inhibits monoaminergic cells during sleep, while activity of the monoaminergic neurons inhibits the VLPO during wakefulness, where orexin neurons reinforce the monoaminergic tone and prevent unwanted transitions into sleep (Saper et al., 2005).
A.

Ascending Arousal System

Pedunculopontine Tegmental Nucleus (PPT) – cholinergic
Laterodorsal Tegmental Nucleus (LDT) – cholinergic
Basal Forebrain – cholinergic
Tuberomammilary Nucleus (TMN) - histaminergic
Lateral Hypothalamus (LH) – orexinergic
Dorsal Raphe – serotonergic
Locus Coeruleus (LC) – noradrenergic
B. 

**Figure 2** A schematic drawing of the neural circuitry controlling wakefulness and sleep (A) shows components of the ascending arousal system that produce arousal and wakefulness. The dorsal pathway (highlighted in orange) originates in the cholinergic pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), and extends to the thalamus. Firing of PPT/LDT neurons stimulates thalamocortical transmission. The ventral pathway (highlighted in red) bypasses the thalamus and involves activity of monoaminergic neurons, providing the main input to the cerebral cortex. Monoaminergic neurons include the noradrenergic locus coeruleus (LC), serotonergic dorsal raphe (DR) and histaminergic tuberomammillary neurons (TMN). Additional excitatory inputs originate in the peptidergic neurons of the lateral hypothalamus (LH) and cholinergic neurons in the basal forebrain. (B) shows the inhibitory projections of the ventrolateral preoptic nucleus (VLPO) neurons (highlighted in blue) on cells in the ascending arousal system. Activity of GABAergic and galaninergic neurons in the VLPO prevents arousal and generates sleep. Adapted from Saper et al (2005).
2.1.4. Cognitive and Behavioural Consequences of Disturbed Sleep

Sleep is particularly important during early brain development, where a child spends a large amount of time sleeping. In fact, by the age of 5, a child has spent a greater portion of his or her life sleeping compared to being awake (Dahl, 1996). If a child experiences disturbed sleep and is unable to achieve a sufficient amount of sleep at a young age, behavioural or cognitive problems can develop (Dahl, 1996). Sleep disturbances encompass a group of problems that interfere with the initiation and maintenance of sleep during the night. The prevalence of sleep disturbances in children ranges between 20 to 30%, where common disturbances include frequent nocturnal awakenings, difficulties falling asleep and bedtime refusal (Sadeh et al., 2000). Such sleep disturbances can result in shorter sleep durations, daytime sleepiness and overall poor sleep quality (Fallone, Owens, & Deane, 2002). Because the prefrontal cortex is particularly sensitive to sleep, sleep disturbances can impair related functions including executive functioning, impulse control, attention and emotional regulation (Horne, 1993), as shown by several studies. For example, Steenari and colleagues assessed the effects of actigraphy-measured sleep duration and sleep quality on working memory and executive functioning in school-aged children. Using several memory tasks, the investigators found that difficulty falling asleep and lower sleep efficiency were associated with a greater number of errors in such tasks (Steenari et al., 2003). Shorter sleep durations are also associated with behavioural consequences. Based on parent-reported sleep and behavioural measures, Lavigne and colleagues found that preschool-aged children who slept less during the night were more likely to display behavioural problems, especially externalizing problems (Lavigne et al., 1999). Similar findings were also observed in a group of children, aged 7 to 12 years, where sleep patterns were measured using actigraphy for 5 week nights (Sadeh, Gruber, & Raviv, 2002). Behaviour was assessed using parent-reported questionnaires and cognitive tests. Based on their
sleep patterns, children were categorized into two groups: good sleepers and poor sleepers. Poor sleepers were defined as those who either experienced at least 3 night awakenings per night, where each awakening lasted for 5 minutes, or those who spent at least 10% of the night in wakefulness. Poor sleepers showed slower reaction times, indicating inattention and difficulties in behavioural inhibition. Such findings were more significant in younger children, particularly those aged 7 and 8 years. Parent-reported behavioural problems, such as delinquency and thought disorders, were also more evident in poor sleepers. While these studies demonstrate the relationship between disturbed sleep and poor behavioural outcomes in children, the studies do not elaborate on the long-term effects of poor sleep. In order to evaluate such a relationship, Touchette and colleagues conducted a longitudinal study that identified the effects of shorter sleep durations on long-term behaviour and cognitive functioning in children. In their study, sleep duration was measured in children aged 2 years, where parents reported their child’s sleep duration on a yearly basis until the child turned 6 years old. Additionally, the child’s cognitive functioning and behaviour was assessed at the age of 6 years. The investigators found that shortened sleep duration, specifically before the age of 41 months, was significantly associated with a higher incidence of externalizing behaviours, such as hyperactivity and impulsivity, at the age of 6 despite an improvement in sleep duration that was observed at 3 years old. Shorter sleep durations were also associated with poor cognitive performance relating to language acquisition and consolidation (Touchette et al., 2007). This study highlights the importance of sufficient sleep as a lack of sleep at a young age can be detrimental for a child’s cognitive and behavioural development. Moreover, inattention and hyperactivity are behaviours of particular interest as these behaviours are key features of attention-deficit hyperactivity disorder (ADHD), suggesting a possible link between sleep disturbance and ADHD-like symptoms (Paavonen et al., 2009). A
study by Peppers and colleagues provided further support for the relationship between poor sleep and ADHD symptoms. Their findings showed that children with ADHD, aged 5 to 11 years, showed significant improvement in sleep quality and an associated reduction in ADHD symptoms following an intervention that focused on the development of a proper sleep hygiene routine (Peppers, Eisbach, Atkins, Poole, & Derouin, 2016).

Further experimental studies incorporated a sleep deprivation paradigm in order to investigate the causal impact of disturbed sleep on cognitive and behavioural functioning in healthy children. Typically, a sleep deprivation paradigm involves chronic or acute sleep restriction. Fallone and colleagues used a sleep deprivation paradigm in order to evaluate the effects of experimental sleep restriction on teacher ratings of academic performance and behaviour in children aged 6 to 12 years. Children followed a 3-week long sleep schedule. The sleep schedule consisted of one week in each of the following sleep conditions: baseline sleep, 10-hour optimized sleep and restricted sleep. The restricted sleep condition varied depending on the age group, where children in first and second grade slept for 8 hours, and those in third grade and higher slept for 6.5 hours. Based on actigraphy-based sleep monitoring and teacher-reported surveys, restricted sleep in school-aged children resulted in poorer academic performance, increased sleepiness and inattention (Fallone, Acebo, Seifer, & Carskadon, 2005). In another study by Randazzo and colleagues, the impact of sleep deprivation in young adolescents was assessed, where participants were randomized to either a control group or an experimental 5-hour sleep restriction group. Nocturnal sleep was recorded using a polysomnogram for one night, and cognitive tests were conducted several times the following day. Compared to the control group, the sleep restriction group performed poorly on several cognitive tasks throughout the day. Specifically, a single night of restricted sleep resulted in impairment of higher cognitive
functions, including abstract thinking and verbal creativity (Randazzo, Muehlbach, Schweitzer, & Walsh, 1998). A modest degree of sleep restriction can also result in poor cognitive and behavioural functioning. In a study by Sadeh and colleagues, sleep patterns were monitored using actigraphy for one week in children aged 9 to 12 years. Baseline sleep was measured for the first three nights. For the following three nights, children were either told to go to sleep an hour earlier or an hour later. Cognitive and behavioural tests were conducted during the baseline period and following the sleep alteration period. Compared to baseline, cognitive and behavioural performance did not change significantly in the sleep restriction group; however, the sleep extension group showed improved performance in tasks involving working memory and reaction time (Sadeh, Gruber, & Raviv, 2003). Such experimental studies provide causal evidence for the negative impact of sleep disturbances towards cognitive and behavioural development, and may encourage implementing interventions that improve sleep quality as a strategy to improve associated cognitive performance and behaviour.

There have been some studies that showed improvement in behaviour following early intervention programs that focus on reducing sleep disturbances. For example, sleep-disturbed children, aged 12 to 36 months, showed improvement in their sleep patterns, daytime behaviour and feeding interactions with mothers following a brief behavioural intervention. The intervention used an extinction protocol, where parents would ignore the child’s crying or tantrums while staying in the child’s room at bedtime (Minde, Faucon, & Falkner, 1994). Similarly, Gruber and colleagues showed improvement in sleep quality and academic performance among children aged 7 to 11 years following a school-based intervention that promoted proper sleep hygiene, and emphasized the importance and benefits of sleep. Specifically, children received improved grades in physical education, mathematics and language
arts (Gruber, Somerville, Bergmame, Fontil, & Paquin, 2016). Additionally, sleep disturbances during early childhood can predict poor sleep at a later age. Using a population-based longitudinal design, Siversten and colleagues found that school-aged children that experienced difficulties with initiating or maintaining sleep were more likely to experience similar problems during late adolescence. Specifically, the investigators estimated that one in three children can continue to experience difficulties in falling or maintaining sleep during adolescence if left untreated. Early sleep disturbances were also found to be an important predictor for insomnia during adolescence (Sivertsen et al., 2017). These findings thus demonstrate the potential importance for early interventions that treat sleep disturbances.

2.1.5. Postoperative Changes in Sleep

2.1.5.1. Factors Associated with Postoperative Sleep Disturbances

Because achieving a sufficient amount of sleep is important for the growth and healthy development of young children (Dahl, 1996), increasing concern has been directed towards the onset of sleep disturbances following elective surgery (Kain & Caldwell-Andrews, 2003; Kain et al., 2005). Kain and colleagues, for example, found a high prevalence of postoperative sleep disturbances among pediatric patients. The study population consisted of 92 children aged 3 to 9 years who were undergoing outpatient elective surgeries including minor general surgeries, ear tube placement, tonsillectomies and adenoidectomies. Approximately 47% of the population experienced postoperative sleep disturbances during the first postoperative week as determined by either actigraphy or subjective assessments (Kain et al., 2002). A drawback with this study is that the investigators did not specify the observed sleep disturbances, nor did they discriminate between actigraphy- or subjectively-assessed sleep disturbances. In contrast, our study compares
preoperative and postoperative sleep patterns in order to determine specific sleep disturbances, including shorter sleep durations or sleep fragmentation, using actigraphy as the primary method to estimate sleep-wake patterns. Additionally, preoperative and postoperative sleep patterns are compared according to duration of anesthetic exposure.

It is likely that several factors may affect sleep patterns after a procedure. For example, prolonged postoperative pain can affect sleep quality (Kain et al., 2002). However, Cronin and colleagues found that postoperative sleep quality remains poor despite sufficient pain control (Cronin, Keifer, Davies, King, & Bixler, 2001). Likewise, in a subsequent study by Kain and colleagues, a portion of adult patients who underwent outpatient surgeries experienced clinically significant sleeping problems despite low levels of pain (Kain & Caldwell-Andrews, 2003). Thus, these findings suggest that postoperative sleep may be influenced by additional factors. Other factors may include the hospital environment as surgical patients who stay overnight may encounter greater noise and interruptions (Dolan et al., 2016). In the case of individuals who undergo outpatient surgeries and do not require an overnight hospital stay, psychological factors such as the temperament of the parent as well as the child can influence postoperative sleep patterns. Using actigraphy and parent-reported measures in a sample of children aged 4 to 10 years who were undergoing outpatient elective surgeries, Caldwell-Andrews and colleagues identified parental neuroticism and the child’s aggressive behaviour as predictors of poor postoperative sleep in children (Caldwell-Andrews & Kain, 2006). Additionally, parents who experience poor sleep tend to perceive a greater degree of sleep problems in their children (Ronnlund, Elovainio, Virtanen, Matomaki, & Lapinleimu, 2016). Thus the potential influence of parental sleep on child’s postoperative sleep quality should be considered. Min and colleagues further investigated the association between preoperative anxiety and postoperative sleep
patterns by conducting a randomized controlled trial involving midazolam, which is a common premedication that is administered to reduce preoperative anxiety. The study population consisted of 70 children aged 3 to 12 years undergoing elective outpatient tonsillectomy and adenoidectomy procedures. Actigraphy and parent-reported assessments were used to measure postoperative sleep patterns and temperament in children. The investigators found that a greater proportion of children who were given midazolam experienced slightly improved postoperative sleep quality compared to the control group, where the midazolam group had shorter wake episodes and slept an average of 20 minutes longer (Min, Kain, Stevenson, Jenkins, & Fortier, 2016). Nonetheless, no statistically or clinically significant differences were observed between the control group and midazolam group for total sleep time or sleep efficiency, which may suggest that postoperative sleep disturbances can occur due to factors other than preoperative anxiety. General anesthesia, for example, has been linked to sleep disturbances as shown by studies with animals and human adults. In these studies, altered sleep architecture was observed following exposure to specific anesthetics, resulting in fragmented postoperative sleep patterns (Aurell & Elmqvist, 1985; Knill et al., 1990; Kushikata et al., 2016; Lehmkuhl et al., 1987). Despite the amount of literature that focuses on postoperative sleep patterns in children, there is a gap in knowledge that addresses the potential detrimental impact of general anesthesia on a child’s sleep. This may be particularly important given the cognitive and behavioural impairment that can arise following a period of disturbed sleep and that millions of children receive general anesthesia annually.
2.2. General Anesthesia

According to the American Society of Anesthesiologists, general anesthesia is a drug-induced reversible loss of consciousness during which patients are not arousable, and ventilatory and cardiovascular function may be impaired (“American Society of Anesthesiologists,” 2014). An ideal general anesthetic agent for surgical procedures is associated with rapid induction, adequate analgesia and amnesia, depression of the autonomic nervous system, muscle relaxation, rapid emergence and avoidance of undesirable side effects (Jordan & Wright, 2010). General anesthesia is commonly administered via inhalational or intravenous methods.

2.2.1. Types of General Anesthesia

2.2.1.1. Inhaled or Volatile General Anesthesia

During the beginning of the 20th century, chloroform and nitrous oxide were administered to provide general anesthesia; however, chloroform was discovered to have adverse risks such as severe depression of the respiratory rate, possible heart failure and damage to other organs including the liver, pancreas and kidneys (Wawersik, 1997). Additionally, a large mixture of nitrous oxide was required to provide adequate anesthesia. As such, new inhaled or volatile anesthetics were synthesized, including the halogenated vapours of halothane, isoflurane, desflurane and sevoflurane (Robinson & Toledo, 2012). Recently, xenon has also been favoured as a general anesthetic due to its low blood-gas coefficient, and rapid induction and emergence times (Jordan & Wright, 2010). Table 1 summarizes the properties of common inhaled anesthetic agents.
### Table 1 Summary of properties for common inhaled general anesthetics

<table>
<thead>
<tr>
<th>Common Inhaled Agents</th>
<th>Properties</th>
</tr>
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</table>
| Nitrous Oxide         | • Not generally used alone for general anesthesia due to its weak anesthetic properties (Robinson & Toledo, 2012)  
• Used as a carrier gas (with oxygen) for stronger anesthetic agents (Robinson & Toledo, 2012) |
| Halothane             | • Higher potency (Robinson & Toledo, 2012)  
• No longer clinically used due to an increased onset of hepatic necrosis and failure following halothane exposure (Safari, Motavaf, Seyed Siamdoust, & Alavian, 2014) |
| Desflurane & Isoflurane | • Was increasingly used as a substitute for halothane (Robinson & Toledo, 2012)  
• Associated with rapid emergence from anesthesia, but poorer induction due to higher pungency and risk for airway irritation (Robinson & Toledo, 2012) |
| Sevoflurane           | • One of the last inhaled anesthetics to be introduced and remains extensively used (Robinson & Toledo, 2012)  
• Associated with fast and well-tolerated induction, hemodynamic stability, rapid emergence from anesthesia, low hepatotoxicity, and reduced airway irritation (Lerman et al., 1996; Singhal, Gray, Guzman, Verma, & Anand, 2010; Welborn, Hannallah, Norden, Ruttimann, & Callan, 1996) |
| Xenon                 | • Recently favoured as a gaseous general anesthetic (Jordan & Wright, 2010)  
• Associated with low blood-gas coefficient, and rapid induction and emergence times (Jordan & Wright, 2010)  
• Use of xenon remains minimal compared to sevoflurane due to limited availability and high cost (Jordan & Wright, 2010) |
2.2.1.2. Intravenous General Anesthesia

In 1872, intravenous general anesthetics were introduced, where chloral hydrate was the first intravenous anesthetic. Following chloral hydrate, the use of barbiturates, such as sodium thiopental, increased. Because barbiturates were associated with significant cardiovascular and respiratory depressant risks, more suitable intravenous anesthetics were sought and etomidate gained popularity due to its minimal cardiovascular depressant effects (Robinson & Toledo, 2012). Similarly, benzodiazepines, such as diazepam and midazolam, replaced barbiturates for sedative purposes (Guerrini & Ciciani, 2013; Wick, 2013). Ketamine is also commonly used as an induction agent (Powers, Gancsos, Finn, Morgan, & Corlett, 2015). In recent years, propofol has been increasingly used as a substitute for etomidate due to concerns about postoperative nausea and adrenal toxicity following exposure to etomidate (Allolio, Stuttmann, Leonhard, Fischer, & Winkelmann, 1984; St Pierre, Dunkel, Rutherford, & Hering, 2000). The effectiveness of propofol led to a new method of general anesthesia termed total intravenous anesthesia (TIVA). Essentially, TIVA does not require the use of inhaled agents, but is combined with intravenous opioids to provide successful sedation and analgesia (Robinson & Toledo, 2012). Table 2 summarizes the properties of common intravenous anesthetic agents.
<table>
<thead>
<tr>
<th>Common Intravenous Agents</th>
<th>Properties</th>
</tr>
</thead>
</table>
| **Barbiturates**          | • Provides rapid anesthesia but associated with significant cardiovascular and respiratory depressant risks (Robinson & Toledo, 2012)  
• Narrow therapeutic window between the dose required for sedation and the dose that will cause coma and death (Coupey, 1997) |
| **Benzodiazepines**       | • Increasingly used as a substitute for barbiturates (Wick, 2013)  
• Sedative properties and ability to induce a state of unconsciousness (Wick, 2013)  
• Used as an induction agent or as an anesthesia adjunct (Wick, 2013) |
| **Etomidate**             | • Used as an induction and sedative agent (Robinson & Toledo, 2012)  
• Potent amnesic properties and an ability to induce a state of unconsciousness, but lacks analgesic effects (Forman, 2011)  
• Well-tolerated with minimal cardiovascular depressant effects (Forman, 2011)  
• Associated with postoperative nausea and adrenal toxicity (Forman, 2011) |
| **Ketamine**              | • Used as an induction agent (Powers et al., 2015)  
• Associated with a higher incidence of hallucinations (Powers et al., 2015)  
• Used in smaller doses in combination with additional agents to prevent hallucinations (Robinson & Toledo, 2012) |
| **Propofol**              | • Increasingly used as a substitute for etomidate (Robinson & Toledo, 2012)  
• Associated with anti-emetic properties, resulting in fewer incidences of postoperative nausea (St Pierre et al., 2000)  
• Can be combined with intravenous opioids to provide total intravenous anesthesia (TIVA) (Robinson & Toledo, 2012) |
2.2.2. Molecular Targets

All general anesthetics act as either positive or negative allosteric modulators of ligand-gated ion channels at clinically effective concentrations (Hemmings et al., 2005). Examples of such molecular targets include glycine receptors, N-methyl-D-aspartate (NMDA) receptors, potassium channels and voltage-gated sodium channels (Franks, 2006; Rudolph & Antkowiak, 2004). The molecular targets of several general anesthetics are shown in Table 3. The molecular target for many inhaled and intravenous anesthetics is the GABA\textsubscript{A} receptors (Hemmings et al., 2005).

<table>
<thead>
<tr>
<th></th>
<th>GABA\textsubscript{A} receptor</th>
<th>Glycine receptor</th>
<th>nAch (muscle) receptor</th>
<th>nAch (neuro) receptor</th>
<th>5-HT\textsubscript{3} receptor</th>
<th>AMPA receptor</th>
<th>Kainate receptor</th>
<th>NMDA receptor</th>
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<tbody>
<tr>
<td>Etomidate</td>
<td>A</td>
<td>B</td>
<td>D</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Propofol</td>
<td>A</td>
<td>A</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>A</td>
<td></td>
<td>D</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>A</td>
<td>B</td>
<td>D</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>B</td>
<td></td>
<td>D</td>
<td>C</td>
<td>B</td>
<td></td>
<td></td>
<td>C</td>
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<tr>
<td>Isoflurane</td>
<td>A</td>
<td>A</td>
<td>D</td>
<td>C</td>
<td>A</td>
<td>C</td>
<td>A</td>
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<tr>
<td>Sevoflurane</td>
<td>A</td>
<td>A</td>
<td>D</td>
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<tr>
<td>Nitrous Oxide</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>D</td>
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**Table 3 Molecular targets of general anesthetics**

General anesthetics act on multiple ligand-gated ion channels. For example, the majority of general anesthetics enhance inhibitory currents that are generated by GABA\textsubscript{A} receptors and glycine receptors. Certain anesthetics can also depress excitatory currents that are generated by nicotinic acetylcholine (nAch) muscle and neuronal receptors, 5-HT\textsubscript{3} (serotonin) receptors, AMPA receptors, kainate receptors, and NMDA receptors. Green areas indicate the degree of potentiation, where dark green (labelled A) represent significant potentiation and light green (labelled B) represents little potentiation. Pink areas indicate degree of inhibition, where dark pink (labelled C) represent significant inhibition and light pink (labelled D) represents little inhibition. White areas indicate that the anesthetic does not have a known effect on the receptor. Adapted from Rudolph and Antkowiak, 2004.
2.2.2.1. \textbf{GABA}_A Receptors

In the mammalian brain, GABA is the major inhibitory neurotransmitter with almost one third of all synapses being GABAergic (Bloom & Iversen, 1971). Most inhibition is mediated by \textbf{GABA}_A receptors, which are chloride-permeable ligand-gated ion channels. Following activation of \textbf{GABA}_A receptors, an influx of chloride occurs, leading to hyperpolarization of the membrane and reduced excitability of neurons (Bonin & Orser, 2008). The \textbf{GABA}_A receptor is composed of five different subunits. Approximately 19 mammalian genes encode for different subunits such as $\alpha_{1-6}$, $\beta_{1-3}$, $\gamma_{1-3}$, $\delta$, $\varepsilon$, $\varphi$, $\pi$, and $\rho_{1-3}$ (Macdonald & Olsen, 1994). The common combination of subunits is $\alpha$, $\beta$, and $\gamma$ in a 2:2:1 ratio (Bonin & Orser, 2008) (Figure 3). Many general anesthetics act as \textbf{GABA}_A receptor agonists. For example, higher concentrations of intravenous anesthetics, such as propofol and etomidate, can open \textbf{GABA}_A receptors in the absence of GABA (Hales & Lambert, 1991; Tomlin, Jenkins, Lieb, & Franks, 1998). Additionally, most inhaled anesthetics increase the opening of synaptic and extrasynaptic \textbf{GABA}_A receptors to enhance inhibition (Krasowski & Harrison, 1999).

\textbf{GABA}_A receptors were originally recognized as synaptic receptors that mediate fast inhibition by generating transient miniature inhibitory postsynaptic currents. Such phasic receptors are activated by higher, near-saturating concentrations of GABA (Maconochie, Zempel, & Steinbach, 1994). An additional class of \textbf{GABA}_A receptors includes extrasynaptic \textbf{GABA}_A receptors, which generate tonic inhibitory currents and may contribute to the depressive properties of general anesthetics (Hemmings et al., 2005; Semyanov, Walker, Kullmann, & Silver, 2004). Extrasynaptic receptors respond to low GABA concentrations as the receptors have a high affinity for GABA and show slow desensitization (Hemmings et al., 2005) (Figure 4).
GABA receptors are composed of five subunits, which can consist of various combinations of at least 19 different subunits. The common combination of subunits is α, β and γ in a 2:2:1 ratio. GABA binds onto the receptor, causing an influx of chloride ions and resulting in hyperpolarization. Several binding sites exist for different anesthetics. For example, volatile anesthetics, propofol and etomidate typically interact with a binding pocket located on the α and β subunits. Anesthetic action on specific receptor isoforms can produce various behavioural endpoints such as amnesia or a loss of consciousness. Adapted from Wang and Orser, 2011.

Figure 3 A schematic diagram of a GABA<sub>A</sub> receptor
**Figure 4** Currents from synaptic and extrasynaptic GABA_A receptors

Synaptic GABA_A receptors mediate fast inhibition by producing inhibitory post-synaptic currents. An action potential causes the release of vesicular GABA into the synaptic cleft, activating synaptic GABA_A receptors on the postsynaptic membrane. Synaptic GABA_A receptors are activated by near-saturating concentrations of GABA. Extrasynaptic GABA_A receptors are activated by low GABA concentrations and exhibit slow desensitization. As such, extrasynaptic GABA_A receptors generate persistent tonic inhibitory currents despite the application of a GABA_A antagonist. Most anesthetics bind onto GABA_A receptors and enhance the tonic current. Adapted from Bonin and Orser, 2008.
2.2.3. Neurocognitive and Behavioural Development Following Anesthesia Exposure

2.2.3.1. Anesthetic-Induced Neurotoxicity

Several experimental studies have documented plausible neurotoxic effects of general anesthetics on the mammalian brain. Mechanisms of neurotoxicity, such as neuroapoptosis, reduced neurogenesis, altered dendritic architecture and disrupted synaptogenesis, are of great concern in the young mammalian brain (Briner et al., 2010; Head et al., 2009; Pearn et al., 2012; Sun, 2010), especially up to 36 months of age. As such, the suggested period of anesthetic-induced vulnerability is from birth and up to 3 years of age in humans (Casey, Giedd, & Thomas, 2000; Sun, 2010). Because the majority of general anesthetics act as either a GABA_A receptor agonist or a NMDA receptor antagonist, excessive apoptosis and neurodegeneration can occur as demonstrated by a rat study conducted by Jevtovic-Todorovic and colleagues. Postnatal day 7 rats were exposed to a cocktail consisting of isoflurane, midazolam and nitrous oxide. The rat pups displayed excessive neuronal apoptosis in areas of the hippocampus and cerebral cortex, resulting in impaired long-term potentiation and coinciding memory impairment (Jevtovic-Todorovic et al., 2003). However, conflicting evidence exists, showing that anesthetics do not cause long-term adverse effects. In a study by Drobish and colleagues, postnatal day 2 rats were divided into a control group or treatment groups, where rats received a single 2-hour exposure to either sevoflurane, isoflurane or desflurane anesthesia. The investigators found a reduced number of hippocampal cells at postnatal day 7 following exposure to isoflurane and desflurane, but the number of cells following sevoflurane anesthesia were similar to those observed in the control group. Additionally, behavioural impairment was observed in rats exposed to isoflurane and desflurane at 6 weeks following exposure, but not at 6 months following exposure. Thus, isoflurane and desflurane, but not sevoflurane, caused a transient disruption in brain development.
with no evidence for long-term effects on learning and memory (Drobish, Gan, Cornfeld, & Eckenhoff, 2016). Similar findings were observed in another study involving postnatal day 10 mice that were injected with either etomidate, propofol, ketamine or a placebo (Nyman, Fredriksson, Lonnqvist, & Viberg, 2016). No significant differences were found in activated caspase-3 concentrations among the study groups, suggesting that exposure to etomidate, propofol or ketamine did not induce cerebral apoptosis. Mice that were given ketamine showed a significant change in spontaneous behaviour; however, mice that were given etomidate or propofol did not exhibit long-term behavioural effects. Although these results may suggest a reversibility or an absence of cognitive and behavioural consequences following exposure to various general anesthetics, conducting further studies is necessary in order to confirm the clinical relevance of such findings, while determining the dosages and durations for each anesthetic at which neuronal impairment may no longer be reversible.

General anesthesia can trigger apoptosis by damaging neuronal organelles. For example, anesthesia can initiate a downregulation of the bcl-xL anti-apoptotic protein via an intrinsic mitochondrial-dependent pathway. Subsequently, mitochondrial membrane permeability increases, resulting in an increase of cytochrome c release into the cytoplasm that activates caspase proteins, initiating apoptosis (Yon et al., 2005). Anesthetics can damage the structural properties of mitochondria by affecting GTPase proteins and increasing production of excessive reactive oxygen species (Zorzano, Liesa, Sebastian, Segales, & Palacin, 2010), causing overall neuronal damage and behavioural impairment (Jevtovic-Todorovic, Boscolo, Sanchez, & Lunardi, 2012). Early exposure to anesthetics can also inhibit neurogenesis, as shown by postnatal days 7 and 14 rats exposed to isoflurane, where these rats exhibited decreased neurogenesis within the hippocampus (Stratmann et al., 2009; Zhu et al., 2010). One proposed
mechanism for neurogenesis and alteration of dendritic architecture involves inhibition of brain-derived neurotrophic factor signaling pathways (Lu, Yon, Carter, & Jevtovic-Todorovic, 2006). Concomitant administration of specific neuroprotective drugs can alleviate such pro-apoptotic effects of anesthetics. For example, dexmedetomidine, which is an intravenous sedative agent, increases the expression of anti-apoptotic proteins and brain-derived neurotrophic factors through activation of α2-adrenoceptors (Dahmani et al., 2008). Sauders and colleagues also demonstrated the neuroprotective properties of dexmedetomidine in postnatal day 7 rats, where dexmedetomidine reduced isoflurane-induced neuroapoptosis in a dose-dependent manner by activating anti-apoptotic mechanisms (Sanders et al., 2009). Additionally, xenon may prevent isoflurane-induced neuronal apoptosis in a dose-dependent manner as shown with postnatal day 7 rats that were randomly exposed to eight gas mixtures, including air and various combinations of isoflurane, xenon and nitrous oxide. As expected, isoflurane enhanced neuronal apoptosis, which significantly increased when combined with nitrous oxide. However, xenon significantly reduced the degree of apoptosis, similar to that observed in the group exposed to air (Ma et al., 2007). Thus, these findings provide evidence towards the use of neuroprotective drugs as a means to mitigate anesthetic-induced apoptosis, but additional clinical research is beneficial to determine the applicability of these results.

2.2.3.2. Clinical Studies Evaluating Neurocognitive Consequences of General Anesthesia

While numerous in vitro and animal studies have investigated the neurotoxic effects of general anesthesia on the developing mammalian brain, the translational relevance of such findings remains uncertain. Recent data from two large-scale prospective studies did not provide evidence for cognitive and behavioural effects following early anesthetic exposure in humans. One randomized controlled trial, known as the General Anesthesia compared to Spinal
Anesthesia (GAS) trial, involved infants that were younger than 60-weeks postmenstrual age who underwent inguinal hernia surgery (Davidson et al., 2016). Two hundred thirty-eight infants were randomized to an awake-regional group and 294 infants were randomized to a general anesthetic group. The Bayley-III was administered to participants to assess neurodevelopment at the age of 2 years. The investigators found no significant differences in scores for several neurodevelopmental domains including overall cognitive performance, motor ability, language and adaptive behaviour. Such preliminary findings suggest exposure of sevoflurane anesthesia for a duration of an hour or less during infancy does not increase the risk of adverse neurodevelopmental outcomes at 2 years of age. However, further assessment at 5 years will be completed to confirm the results and assess multiple domains of cognition. Additionally, a sibling-matched cohort study, known as the Pediatric Anesthesia and Neurodevelopment Assessment (PANDA) study, was conducted to control for genetic and environmental contributions towards cognitive performance (Sun et al., 2016). The cohort consisted of 105 unexposed and exposed sibling pairs who underwent inguinal hernia surgery prior to the age of 3 years. The mean age of the children at the time of anesthetic exposure was approximately 17 months, and the mean duration of anesthesia exposure was 84 minutes. Approximately 16% of the study population was exposed to a prolonged duration of 120 minutes or longer. A battery of neuropsychological assessments was administered to the subjects during ages 8 and 15 years including the Wechsler Abbreviated Scale of Intelligence, NEPSY-II, Child Behaviour Checklist (CBCL) and Behaviour Rating Inventory of Executive Functioning (BRIEF). There were no statistically significant differences in full-scale IQ between siblings with and without a single anesthesia exposure. Similarly, there were no statistically significant differences in measures of memory, attention, executive function, language and behaviour. Both studies confirmed that
anesthesia exposure prior to 3 years of age does not increase the risk of cognitive and behavioural impairment in children. However, further investigation is required to address the effects of multiple or prolonged exposures to general anesthesia, specifically for a duration greater than 120 minutes.

The GAS trial and PANDA study led to an improved understanding of findings from previous retrospective studies. Although early retrospective studies suggested a probable association between early exposure to anesthesia and an increased risk of behavioural/developmental disorders in children before the age of 3 years (DiMaggio, Sun, Kakavouli, Byrne, & Li, 2009; DiMaggio, Sun, & Li, 2011), findings of subsequent studies were similar to that of the GAS and PANDA studies. Such studies showed no causal association between anesthetic exposure and later onset of cognitive or behavioural impairment during early childhood. For example, using a monozygotic concordant-discordant twin design, Bartels and colleagues analyzed retrospective medical records of 1,143 monozygotic twins, where one twin was exposed to an anesthetic between birth and 12 years of age. At age 12, academic performance and cognitive development were prospectively assessed among unexposed and exposed twins using standardized tests and teacher ratings. Exposed twins from concordant twin pairs, particularly those who were given an anesthetic prior to the age of 3 years, showed lower academic performance and more cognitive problems compared to unexposed twins. However, these measures were not significantly different between the unexposed and exposed twins from discordant twin pairs, suggesting that later learning disabilities were not caused by anesthetic exposure. Rather, the individual’s genetic vulnerability to learning disabilities was correlated with the reason for the surgery for which anesthesia was administered (Bartels, Althoff, & Boomsma, 2009). Similar findings were seen with perinatal exposure to anesthetics, where
likelihood in developing learning disabilities did not significantly differ between children exposed to an anesthetic during cesarean delivery or children who were delivered vaginally (Sprung et al., 2009). Additional studies using birth cohorts also found no evidence of poor academic performance and increased risk of behavioural disorders following anesthetic exposure (Hansen et al., 2011; Ko et al., 2015; Ko et al., 2014).

Despite the significant findings of the GAS trial and PANDA study, further prospective research is required to address the effects of multiple or prolonged exposures to general anesthetics as related retrospective findings are inconsistent. For example, a recent population-based retrospective cohort study showed a statistically significant increase in the rate of early developmental vulnerability in children exposed to surgery, suggesting that children are more likely to experience adverse developmental outcomes following anesthetic exposure. Such adverse developmental outcomes include poor language, cognitive functioning and emotional health. However, the magnitude of the difference was small, and factors such as an age of younger than 2 years at first exposure and multiple exposures were not risk factors for adverse developmental outcomes (O'Leary et al., 2016). Other retrospective cohort studies have rather suggested that multiple, rather than a single, exposures to a general anesthetic can cause the onset of developmental problems including learning disabilities, particularly in speech, language, cognition, and ADHD (Flick et al., 2011; Graham et al., 2016; Sprung et al., 2012; Wilder et al., 2009). Nonetheless, such retrospective analyses are unable to conclude an association between multiple exposures and increased neurocognitive risks due to confounding factors.
2.2.3.3. Negative Postoperative Behavioural Changes

Negative postoperative behavioural changes are reported to occur in up to 50% of children undergoing surgery and anesthesia (Kain, Mayes, O'Connor, & Cicchetti, 1996). Such behavioural changes arise following emergence agitation, which is a state of restlessness and inconsolability that can occur after the termination of general anesthesia (Houck, 2005). Although occurrence of agitation may not differ between an intravenous or inhalational induction method (Kotiniemi & Ryhanen, 1996), the type of anesthesia administered for maintenance can play an important role. Propofol, for example, tends to be associated with a lower incidence of agitation. On the other hand, sevoflurane is frequently associated with emergence agitation (Chandler et al., 2013; Picard, Dumont, & Pellegrini, 2000). Stipic and colleagues also assessed the incidence of negative behavioural changes using a randomized controlled trial in children who underwent adenotonsillectomy. Based on parent-reported behavioural measures, Stipic and colleagues found that the incidence of negative behavioural changes was higher among children who receive sevoflurane in comparison to those who receive propofol. Behavioural changes in the sevoflurane group included increased separation anxiety, general anxiety and withdrawal, which persisted after six months (Stipic et al., 2015). The incidence of negative behavioural changes has also been compared between sevoflurane and halothane. Using a retrospective cohort, Foesel and Reisch found that behavioural changes were more common following sevoflurane anesthesia in a group of children aged 8 years and younger undergoing urological and minor ear-nose-throat (ENT) surgeries (Foesel & Reisch, 2001). However, a randomized-controlled trial by Kain and colleagues found no differences in behaviour among children aged 3 to 10 years who were given sevoflurane and those given halothane (Kain et al., 2005). Thus, the degree of agitation can differ depending on the type of anesthetic. Since sevoflurane is
commonly used in pediatric anesthesia, attempts have been made to identify specific sedative or analgesic drugs that can be administered to reduce the incidence of emergence agitation following sevoflurane anesthesia. One such drug is dexmedetomidine, where less occurrences of agitation are documented among children who receive an intravenous dose of dexmedetomidine. In a group of 90 children aged 1 to 10 years undergoing urological surgeries, Ibacache and colleagues found that a dose of dexmedetomidine administered during sevoflurane anesthesia was associated with a lower score of emergence agitation as reported by nurses (Ibacache, Munoz, Brandes, & Morales, 2004). Boku and colleagues found similar results in 70 infants aged 10 to 14 months undergoing cleft palate surgery, where infants either received dexmedetomidine or saline during sevoflurane anesthesia. Based on an anesthesiologist’s score of emergence agitation and pain, agitation and pain were found to be significantly lower in children who were given dexmedetomidine as compared to those given saline (Boku et al., 2016).

2.3. General Anesthesia and Sleep

2.3.1. Changes in Sleep Following Anesthetic Exposure

General anesthetics can disturb postoperative sleep patterns by disrupting the circadian rhythm. For example, GABA<sub>A</sub> receptor agonists such as isoflurane and sevoflurane may induce phase shifts through sustained activation of GABA<sub>A</sub> receptors. Anesthetics that are NMDA receptor antagonists, such as ketamine, may also affect the circadian rhythm by inhibiting light entrainment of the circadian clock (Poulsen et al., 2016).

Disturbed sleep architecture has also been observed following surgery in young and middle-aged adults. Several clinical studies have documented suppression of REM sleep in human adults following exposure to volatile anesthetics, particularly halothane and isoflurane. In
a study by Lehmkuhl and colleagues, sleep stages were measured using EEG for the first postoperative night in young adults undergoing minor surgeries. The patients either received halothane anesthesia or a combination of fentanyl and halothane anesthesia. Compared to a control group of healthy young adults, patients who received halothane anesthesia showed severely disturbed sleep architecture following surgery. These patients showed an increased amount of NREM-1 and NREM-2 sleep, a reduced amount of SWS and nearly suppressed REM sleep. Such changes were also observed in the group that received halothane and fentanyl anesthesia (Lehmkuhl et al., 1987). Similar results were found in a group of middle-aged adults who received isoflurane and fentanyl anesthesia during abdominal surgery. Sleep was monitored using polysomnography for two nights prior to surgery and five to six nights following surgery. During the first three postoperative nights, patients experienced increased NREM-2 sleep, reduced SWS and a lack of REM sleep. During subsequent nights, a rebound in SWS and REM sleep was observed, where an increased frequency of nightmares tends to occur during this rebound of REM sleep (Brimacombe & Macfie, 1993; Knill et al., 1990). Such changes in sleep architecture results in an overall shortened total sleep time and decreased sleep efficiency, accompanied by frequent arousals and awakenings (Aurell & Elmqvist, 1985). However, these previous studies were unable to conclude whether general anesthesia caused such changes in sleep architecture as additional factors, such as the surgery itself, can contribute to disturbances in sleep architecture. Moote and colleagues attempted to assess the effect of isoflurane anesthesia on nocturnal sleep among healthy young adults that were not undergoing surgery. During the first night following exposure, no change was found in NREM-1 and REM sleep following a 3-hour duration to isoflurane, but a reduction in SWS and an increase in NREM-2 sleep was observed (Moote & Knill, 1988). Altered sleep architecture has also been found in mice models
following exposure to volatile anesthetics. In a study by Pick and colleagues, mice were exposed to a 6-hour duration of either sevoflurane, isoflurane or halothane. Sleep following exposure was monitored using EEG and EMG recordings. For all three groups, a deficiency in REM sleep occurred followed by a large rebound in REM sleep. However, only the halothane group experienced a deficiency in NREM sleep followed by a rebound in NREM sleep (Pick et al., 2011). These findings differ from those found in the study by Moote and colleagues as their study permitted unmonitored daytime napping that may have affected the findings. Further research in mice has also shown that general anesthesia could modulate sleep architecture by influencing endogenous substances that promote sleep or wakefulness. For example, Kushikata and colleagues assessed sleep architecture using EEG and EMG recordings in rats that were either given ketamine or propofol anesthesia. Within the first hour following ketamine anesthesia, rats showed an increase in wakefulness and reduced NREM sleep. At the same time, a restoration of orexin content in the hypothalamus and pons was seen (Kushikata et al., 2016). As orexin stabilizes wakefulness through activation of noradrenergic neurons in the LC, an increase in wakefulness and decrease in NREM sleep was observed following ketamine anesthesia (de Lecea & Huerta, 2014). In contrast, rats showed reduced wakefulness and an increase in NREM sleep following propofol anesthesia. Additionally, propofol had a dominant effect on melanin-concentrating hormone, where an increase in melanin-concentrating hormone was seen in the pons and hypothalamus following propofol anesthesia (Kushikata et al., 2016). Because melanin-concentrating hormone promotes sleep, and propofol reduces noradrenergic activity in the LC, propofol can promote sleep following anesthetic exposure (Kushikata et al., 2002). As such, changes in postanesthetic sleep architecture can be associated with anesthetic-related changes in various endogenous substances that promote sleep or wakefulness (Kushikata
et al., 2016). Overall, data from both animal and adult studies suggest that general anesthesia can play a role in postoperative sleep disturbances, where these disturbances may be agent-specific.

Continuous administration of an intravenous dose of dexmedetomidine has been shown to improve sleep quality in adults. In a group of 13 critically ill patients, Alexapoulou and colleagues found that an infusion of dexmedetomidine increased sleep efficiency and improved sleep architecture by reducing NREM-1 sleep and increasing NREM-2 sleep; however, the amount of SWS and REM sleep remained low. In addition, dexmedetomidine partly restored normal circadian rhythm in the patients by adjusting the 24-h sleep pattern and shifting sleep to the night (Alexopoulou et al., 2014). Wu and colleagues also found similar results among 61 elderly patients who underwent non-cardiac surgery. While receiving an infusion of dexmedetomidine, sleep patterns were recorded on the first postoperative night using a polysomnogram. Compared to a placebo group, the dexmedetomidine group displayed a higher percentage of NREM-2 sleep, increased total sleep time and increased sleep efficiency, but SWS and REM sleep remained absent. Subjects in the dexmedetomidine group also reported improved sleep quality (Wu et al., 2016). In another study, Tan and colleagues examined whether dexmedetomidine could improve postoperative sleep quality when combined with general anesthesia. Sleep quality was assessed in adults who were undergoing elective thoracic surgery using bispectral index, which is commonly used to monitor brain activity in response to various anesthetics. Patients were randomized into groups who either received sevoflurane anesthesia, sevoflurane anesthesia with dexmedetomidine, or sevoflurane anesthesia with an epidural. Those who received sevoflurane anesthesia combined with an epidural during surgery experienced better postoperative sleep quality compared to patients in the other groups. Nonetheless, the investigators acknowledged that more valid measures, such as an EEG, should be used to provide
an accurate assessment for sleep quality (Tan et al., 2016). Overall, these findings suggest that the quality of postoperative sleep may differ depending on the type of anesthesia that is administered. Additionally, specific drugs may be used as an adjunct with general anesthesia to improve sleep quality following surgery.

Sleep disturbances following anesthetic exposure has also been observed in younger children. For example, Steinmetz and colleagues randomized thirty-nine infants, aged 4 to 6 months, to receive either a combination of propofol and remifentanil anesthesia, or sevoflurane and fentanyl anesthesia. Sleep patterns were compared between the two groups using parent-reported sleep diaries. Based on the sleep diary, sleep duration was significantly shorter in the propofol group following surgery, but sleep quality was generally impaired in both the sevoflurane and propofol group following surgery as compared to before surgery (Steinmetz, Holm-Knudsen, Eriksen, Marxen, & Rasmussen, 2007). However, infant sleep patterns were measured using parent reported sleep diaries, which are known to have limited accuracy (Dayyat, Spruyt, Molfese, & Gozal, 2011; Werner, Molinari, Guyer, & Jenni, 2008). Also, it is unknown how these findings may translate to older children as the study population solely consisted of young infants. Steinmetz and colleagues also did not measure additional factors that can contribute to poor postoperative sleep such as preoperative anxiety in the child and parents. In another randomized controlled trial by Kain and colleagues, the potential impact of volatile anesthetics on sleep disturbances were studied. Children, aged 3 to 10 years, either received halothane anesthesia or sevoflurane anesthesia. Using actigraphy as a measure of sleep patterns, Kain and colleagues found that the degree of sleep disturbances did not differ between both groups (Kain et al., 2005). Although no group differences were observed, the findings do not reflect within-individual sleep disturbances that may exist following exposure to a general anesthetic.
Likewise, individual sleep patterns were not measured in a longitudinal manner, rather sleep patterns were solely measured immediately following surgery. As such, this study does not evaluate long-term sleep disturbances that may result from anesthetic exposure. Additionally, the investigators compared postoperative sleep patterns following exposure to two different volatile anesthetics. While neither sevoflurane or halothane anesthesia resulted in an increased risk for sleep disturbances, such findings cannot be generalized towards all types of general anesthetics. Furthermore, a proportion of the study population underwent an adenoidectomy, which is commonly performed to treat sleep disorders such as sleep apnea. Following an adenoidectomy, sleep quality tends to improve. Such improvement in sleep may partially contribute to the lack of sleep disturbances that were observed following surgery. Thus, the investigators did not control for sleep-related problems as a potential confounding variable. The duration of anesthetic exposure was also not considered as a potential predictor of sleep disturbances. Majority of the study population underwent surgeries that lasted for a duration of an hour or less. Further investigation is required in order to determine whether prolonged durations of anesthetic exposure, specifically durations greater than an hour, may result in sleep disturbances.
Chapter Three: Experimental Rationale, Objectives and Hypotheses

3.1. Rationale

The number per year of surgeries and exposure to anesthetics has increased dramatically over the last two decades. In 1996, an estimated 800,000 children in the U.S. received general anesthesia (Rabbitts et al., 2010). Currently, more than two million children receive general anesthesia in North America, where an estimated 46,000 Canadian children, aged 5 years and younger, receive general anesthesia during elective surgeries each year (Barton, 2017; Sun et al., 2016). A substantial amount of research has focused on investigating the detrimental risks associated with general anesthetic exposure at a young age (See Chapter 2, Sections 2.2.3.1 to 2.2.3.3). Although the findings from these studies remain inconclusive, the U.S. Food and Drug Administration has issued a warning regarding the potential adverse impact of general anesthesia on children’s brain development based on previous animal studies that suggest prolonged exposure to anesthetics can cause widespread loss of brain cells and related long-term cognitive deficits ("FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women," 2016). While this warning has led to changes in the labelling of common general anesthetics and sedative agents in the U.S., Health Canada is currently conducting a review to determine whether a similar warning should be implemented in Canadian hospitals. Thus, further research is underway to gather more information regarding the impact of general anesthetics on pediatric health. An important issue that remains to be addressed is the incidence of sleep disturbances following general anesthetic exposure in otherwise healthy children. As many children do not outgrow such problems, poor sleep quality can persist into adolescence, resulting in possible
insomniac-related symptoms (Sivertsen et al., 2017). Increasing efforts should be directed towards treating sleep disturbances at a young age as poor sleep can lead to significant health complications, such as neurocognitive impairment, behavioural disorders, and obesity.

Several studies involving young and middle-aged adults as well as elderly patients suggest an association between general anesthesia and postoperative sleep disturbances, where postoperative sleep patterns deviate from what is typically observed during normal sleep following exposure to volatile anesthetics (Knill et al., 1990; Lehmkuhl et al., 1987). Further evidence shows that continuous administration of a specific agent, like dexmedetomidine, can improve sleep architecture by reducing NREM-1 sleep, increasing NREM-2 sleep and reducing sleep fragmentation (Alexopoulou et al., 2014; Wu et al., 2016). These findings suggest that certain drugs may be used in combination with general anesthesia to improve sleep quality following surgery, but additional research using validated measures for sleep would be useful (Tan et al., 2016). There have been a few studies that have shown poor sleep quality among children following surgery (Kain et al., 2002; Steinmetz et al., 2007). However, findings of such studies do not mention specific changes in sleep patterns that may occur following anesthetic exposure; thus these studies have several limitations that require further research. Specific changes in sleep and the onset of sleep disturbances can only be identified using an objective measure of sleep/wake patterns over an extended period of time. Our study addresses these limitations by using actigraphy as the primary method to estimate sleep-wake patterns in preschool- and school-aged children before and after surgery. By comparing preoperative and postoperative sleep patterns in a longitudinal manner, specific short- or long-term sleep disturbances following surgery can be identified. Moreover, our study compares preoperative and postoperative sleep patterns according to duration of anesthetic exposure in order to
determine whether longer durations of exposure are associated with a greater incidence of postoperative sleep disturbances. As clinicians continue to be concerned about the prevalence of sleep disturbances following surgery, knowledge regarding potential anesthetic-related sleep disturbances would be beneficial in order to provide the appropriate behavioural interventions and anticipatory guidance that can either attenuate or prevent associated risk factors. As such, a comprehensive evaluation of sleep patterns following anesthetic exposure would either suggest an alteration of pediatric anesthetic practice or provide support towards the use of general anesthesia in young children.

3.2. Objectives
Primary objective – To identify the potential effects of general anesthesia on sleep disturbances and overall sleep quality in children undergoing elective surgery by assessing sleep patterns using actigraphy prior to surgery and following surgery, and by comparing with control children who will not undergo surgery.

Secondary objective – To identify behavioural changes that can result from disturbed sleep by assessing behavioral patterns prior to and following surgery.

3.3. Hypotheses
This thesis will investigate the following hypotheses:

1) Children will display increased sleep disturbances following anesthetic exposure, including increased nocturnal awakenings, delayed sleep onset and shorter sleep duration. Specifically, a greater number of children will experience disturbed sleep during the first postoperative week. The incidence of sleep disturbances will decrease overtime, but persistent sleep disturbances will be observed among a proportion of the population
during the 1- and 3-month follow-up. Additionally, sleep disturbances will be more prevalent in the surgical group as compared to a control group across time.

2) Disturbances in sleep will lead to behavioural changes, such as aggression, anxiety and poor attention. Such changes will be evident during the first postoperative week. By the 1- and 3-month follow-up, behavioural patterns will normalize, but there will be a proportion of the population that experiences persistent sleep disturbances and associated behavioural changes. The prevalence of poor behavioural changes will be higher in the surgical group as compared to a control group across time.
Chapter Four: Methodology

4.1. Overview

This is a prospective, observational research study of children receiving general anesthesia during elective surgery at the Hospital for Sick Children. The sleep patterns of children were objectively assessed using actigraphy. Additional information regarding the child’s sleep behavior was obtained using a parent-reported sleep questionnaire. Behaviour patterns were assessed using parent-reported assessments. As an attempt to control for confounding variables, parents completed a daily pain scale following the child’s surgery as well as questionnaires that measured parental sleep quality and anxiety. Sleep and behaviour patterns were also assessed in a control group of age- and gender-matched healthy children, where parents of the control group completed similar parental sleep and anxiety measures.

4.1.1. Ethics

The study protocol was approved by the ethics board at the Hospital for Sick Children (Toronto, Ontario) in November 2015 (REB #1000051065).

4.2. Study Population

The study population consisted of 2 groups, a surgical group and a control group. The surgical group included pediatric patients who received general anesthesia during elective surgery at the Hospital for Sick Children. Patients undergoing urologic and ENT surgical procedures were recruited for the study. Surgical procedures are listed in Appendix 1. A control group was incorporated into the study to better assess the variability of sleep patterns and behavioural development in children. The control group included age- and gender-matched
healthy children who were not undergoing surgery and had not previously received general anesthesia.

4.3. Eligibility Criteria

Eligibility to participate in the study was determined using the following inclusion and exclusion criteria:

4.3.1. Inclusion Criteria

The inclusion criteria included 1) children aged 18 months to 8 years and 2) patients and their parents/guardians who gave informed consent/assent to take part in this research study.

4.3.2. Exclusion Criteria

To avoid potential confounding variables, any history of chronic illnesses, prematurity, developmental delay, brain injuries and sleep-related problems excluded children from participation in the study. As obesity is a known risk factor for sleep disorders such as obstructive sleep apnea, children with significant obesity (BMI > 95th percentile for age and gender) were also excluded.

In addition to satisfying the eligibility criteria listed above, the control group consisted of overall healthy children who had not previously received a general anesthetic.
4.4. Recruitment

4.4.1. Surgical Group

Prior to surgery, patients were reviewed in the urology clinic or ENT clinic at the Hospital for Sick Children. Patients were screened for eligibility by a urologist, Dr. Armando Lorenzo, and otolaryngologists, Dr. Evan Propst and Dr. Sharon Cushing. Eligible patients were contacted and recruited by phone by the graduate student (Sarah Selvadurai). Informed written consent and assent (where appropriate) were obtained from parents and children. Approximately one week prior to surgery, the actigraph, sleep diary and instructions about how to use the actigraph were mailed to the parents.

4.4.2. Control Group

A community control group of age- and gender-matched healthy children was recruited to provide comparative actigraphy and behavioural data from a population of children who had not received general anesthesia. Children were recruited using advertisements that were placed at the Hospital for Sick Children. Additionally, children of co-workers were also asked to take part in the study. Informed written consent and assent (where appropriate) were obtained from parents and children who were interested in participating. Following consent, the actigraph, sleep diary and instructions were mailed to parents.
4.5. Study Design

**Table 4** Summary of study timeline overview

<table>
<thead>
<tr>
<th>Study Measures</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline – One week prior to surgery/Initial Assessment</td>
</tr>
<tr>
<td>Actigraphy + Sleep Diary*</td>
<td>✓</td>
</tr>
<tr>
<td>Children’s Sleep Habits Questionnaire (CSHQ)*</td>
<td>✓</td>
</tr>
<tr>
<td>Child Behaviour Checklist (CBCL)*</td>
<td>✓</td>
</tr>
<tr>
<td>Behaviour Rating Inventory of Executive Function (BRIEF)*</td>
<td>✓</td>
</tr>
<tr>
<td>Conner’s Behaviour Rating Scales*</td>
<td>✓</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index (PSQI)*</td>
<td>✓</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory (STAI)*</td>
<td>✓</td>
</tr>
<tr>
<td>Parental Expectations Regarding Recovery</td>
<td>✓</td>
</tr>
<tr>
<td>Parental Satisfaction</td>
<td></td>
</tr>
<tr>
<td>Post-Hospitalization Behavioural Questionnaire (PHBQ)</td>
<td></td>
</tr>
<tr>
<td>Parents’ Postoperative Pain Measure</td>
<td></td>
</tr>
</tbody>
</table>

* Study measures that are completed by the control group (excluding postoperative 7-day period)
4.5.1. Surgical Group

One week prior to the surgical date, the actigraph (See Section 4.6.3) was mailed to the parents and child. The actigraph was worn for 7 consecutive nights prior to the surgery. The actigraph was removed on the day of surgery, but worn again for 7 consecutive nights following surgery. A parent-reported sleep diary was associated with the actigraph (see Appendix 2). Daily sleep diaries were used to set up parameters for scoring of sleep onset and offset times as well as identifying artifacts, including times during which the actigraph was removed (Meltzer, Montgomery-Downs, Insana, & Walsh, 2012). On the day of the surgical procedure, questionnaires were completed by parents. The questionnaires provided further information regarding the child’s typical sleep patterns and behaviour. Parents also completed a questionnaire that assessed their expectations regarding their child’s recovery from anesthesia. Because parental sleep disturbances and anxiety are potential predictors for poor postoperative sleep in children (Caldwell-Andrews & Kain, 2006; Ronnlund et al., 2016), parents were asked to complete additional questionnaires that assessed sleep quality and anxiety levels in themselves. Since postoperative pain is a potential determinant for poor postoperative sleep, pain scores were collected by having parents complete a daily pain measure for their children during the 7-day postoperative period. Following surgery, parents completed questionnaires that assessed short-term behavioural changes and parental satisfaction. The actigraph, sleep diary and questionnaires were returned by mail.

In order to minimize the influence of confounding factors, such as pain, and to identify long-term sleep disturbances that are associated with anesthetic exposure, the actigraph and sleep diary were additionally mailed to the parents and child at 1- and 3-months after the surgical procedure. The child wore the actigraph for 7 consecutive nights with parents completing the sleep diary. During this time, parents again completed the sleep-, behavioural- and caregiver-
related questionnaires. Following completion of the 7-day period, the actigraph and questionnaires were returned by mail. A detailed timeline of the study components for the surgical group is shown in Table 4.

4.5.2. Control Group

Following informed consent, parents provided their child’s demographic data. The actigraph and sleep diary were also mailed to parents and the child, where the child wore the actigraph for 7 consecutive nights with parents completing the sleep diary. Similar to the surgical group, parents completed questionnaires that assessed their child’s sleep and behaviour as well as parental sleep quality and anxiety levels. The actigraph, sleep diary and questionnaires were returned by mail. One- and three-months after the initial assessment, the actigraph, sleep diary and questionnaires were mailed to the parents and child. The actigraph was worn again for 7 days with parents completing the sleep diary and questionnaires. Following completion of the 7-day period, the actigraph and additional documents were returned by mail.

4.6. Study Measures

4.6.1. Patient Demographics and Medical History

The demographics, including age, height, weight and existing underlying medical problems, were collected using the patient’s chart at the Hospital for Sick Children. Additional medical history was also collected including indications for surgery, history of previous procedures and anesthetic exposure, and associated medications. For the control subjects, parents provided the demographics and medical history for their child.
4.6.2. Anesthesia Protocol

Upon arrival to the operating room, an oxygen saturation probe was placed on the patient’s hand, and a scented anesthesia mask was introduced. Anesthesia was administered according to standard clinical practice and was not influenced in any way by this study. Anesthesia was induced using sevoflurane inhalation with 50:50 oxygen and nitrous oxide. The sevoflurane vapour was introduced with increments of 2% until maximum strength was achieved. Maximum strength for sevoflurane was defined as 8%. Anesthesia was maintained with either sevoflurane or TIVA with a controlled infusion of propofol (10-15 mg/kg/hour) and opioids such as remifentanil (60 μg/kg), fentanyl (1-5 μg/kg) and morphine (50-100 μg/kg). Once the child was induced, an intravenous cannula was inserted. Tracheal intubation was facilitated using a combination of opioids and muscle relaxants. Nausea and vomiting were managed during and following surgery using ondansetron (1-3 mg/kg) and dimenhydrinate (10-15 mg/kg), respectively. Postoperative analgesia was provided using acetaminophen, ketorolac or patient-controlled morphine. Regional anesthesia was performed for some patients undergoing elective scrotal and groin surgery.

4.6.3. Actigraphy Monitoring of Sleep-Wake Cycles

Actigraphy is an objective, non-intrusive method for estimating sleep-wake patterns using activity-based monitoring (Sadeh, 2011). Specifically, actigraphy was obtained using the Mini-Mitter Actiwatch-2 (Philips Respironics, Bend, OR). The Actiwatch-2 is a portable device, similar to a watch, that has an internal sensor that detects gross motor activity. Such information is collected across epoch intervals, which are stored in the internal memory. The Actiwatch-2 utilizes wake sensitivity thresholds to discriminate between sleep and wakefulness. For example, a medium threshold defines an epoch with 40 or more activity counts as wakefulness. A low
threshold defines an epoch with 20 or more activity counts as wakefulness, while a high
treshold defines an epoch with 80 or more activity counts as wakefulness (Meltzer, Walsh,
Traylor, & Westin, 2012). The raw actigraphy data is translated to sleep measures using the
actigraphic scoring analysis software (Philips Actiware Version 6.0.9).

Participants typically wore the Actiwatch on the non-dominant wrist; however, infants
and toddlers wore the watch on the ankle to limit the child’s engagement with the device
(Ancoli-Israel et al., 2015). As a loss of up to 28% of weekly recordings is common, children
were asked to wear the watch for 7 days in order to collect at least 5 nights of actigraph data.
Collection of actigraph data for minimum of 5 nights ensures reliable estimates (≥ 0.70) for sleep
measures including sleep efficiency and wake after sleep onset (Acebo et al., 1999).

Although the polysomnogram is the gold standard for the diagnosis of sleep-related
disorders, the polysomnogram can be burdensome for young children and parents, especially for
children who underwent surgery. Additionally, because polysomnography typically measures
sleep cycles for one night and is held in an unfamiliar environment, the results may not reflect
natural sleep patterns. As such, actigraphy was chosen as a tool for this study to allow for long-
term monitoring of the sleep-wake cycle. A number of studies have demonstrated the feasibility
and practicality of actigraphy in the pediatric population for both clinical and research purposes
(Sadeh, 2011; Sadeh et al., 2000; Werner et al., 2008). For example, actigraphy is a cost-
effective method to objectively assess sleep patterns for children and adults. Compared to
polysomnography, actigraphy demonstrates good sensitivity to detect sleep from limb activity
(89-97%) (Meltzer, Walsh, et al., 2012), especially when a within-subject design is implemented
(Sadeh & Acebo, 2002). Additionally, actigraphy has been shown to be useful for clinical
interventional studies as actigraphy can provide objective data regarding the efficacy of the
intervention (Sadeh, 2011). However, actigraphy has limitations that should be considered. One limitation is its poor specificity, or its ability to detect wakefulness following sleep onset. Actigraphy demonstrates poor specificity compared to polysomnography (54% to 77%) (Meltzer, Walsh, et al., 2012). Another limitation with actigraphy involves data loss. Several reasons can result in data loss including an inability to complete the sleep diary, failure to wear the actigraph, illnesses and technical issues with the actigraph (Sadeh, 2011). Additionally, movement artifacts are common with actigraphy, especially with younger children who may sleep with their parent (Tryon, 2004). Complimentary subjective methods, including sleep diaries and questionnaires, are important for reducing uncertainties associated with actigraphy and obtaining more detailed information regarding an individual’s sleep (Werner et al., 2008). Thus, using subjective measures for sleep with actigraphy can increase its efficiency for detecting sleep as well as recording total sleep time over extended periods of time in the natural sleep setting (Sadeh, 2011).

4.6.3.1. Scoring and Data Analysis

Data were collected in 30-second epochs, where the data were scored using the medium wake sensitivity threshold. Compared to polysomnography, the low threshold tends to have high specificity, while the high threshold has high sensitivity. However, the low and high thresholds have poorer sensitivity and specificity, respectively. Because the medium threshold yields the least overestimation or underestimation of either sleep or wakefulness, the medium threshold is considered as the most accurate in estimating sleep patterns in young children (Meltzer, Walsh, et al., 2012). In order to provide an accurate estimate for sleep onset latency, sleep onset was scored following 10 consecutive minutes of immobility (Meltzer, Walsh, & Peightal, 2015).
An actogram, which is a graphical representation of the sleep-wake cycle that is generated by the actigraphic scoring analysis software, is shown in Figure 5. Bedtime and wake time were scored using event markers or a daily parent-reported sleep diary. In the case where a discrepancy was found between the event markers and the diary, precedence was given to the sleep diary. The sleep diary was a record of the child’s bedtime and wake time each day, the start and end times of any daytime naps, and any sleep interruptions. Any discrepancies between the sleep diary and actigraph data (i.e. diary indicated the child went to bed at 9 PM, but actigraph data showed no movement after 8 PM) were resolved with the parents. Any periods during which the watch was removed were excluded. An additional analysis was performed where nights that were not representative of the child’s typical sleep were removed from the actigraphy record by a trained research student. These nights included those where parents reported that the child was ill as well as the night prior to the day of surgery as some surgeries were scheduled early the following morning. The outcome sleep variables were total sleep time, sleep efficiency, sleep onset latency and wake after sleep onset. Total sleep time and additional sleep variables referred to nocturnal sleep only. Definitions for actigraph sleep measures are shown in Table 5.
### Table 5 Actigraph sleep measures and definitions

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>Scoring Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedtime</td>
<td>Clock time attempted to fall asleep based on diary/event marker</td>
</tr>
<tr>
<td>Sleep Onset</td>
<td>Time of first consecutive minute with decreased activity below the threshold</td>
</tr>
<tr>
<td>Wake Time</td>
<td>Clock time of final awakening in the morning based on diary/event marker</td>
</tr>
<tr>
<td>Sleep Offset</td>
<td>Time of last consecutive minute of sleep</td>
</tr>
<tr>
<td>Time in Bed</td>
<td>Identified by diary - duration between reported bedtime and wake time</td>
</tr>
<tr>
<td>Sleep Onset Latency</td>
<td>Duration between bedtime and sleep onset</td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
<td>Minutes scored as wake during sleep duration period</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>Minutes scored as sleep between sleep onset and final awakening</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>Percentage of time spent asleep during a defined interval (total sleep time divided by time in bed)</td>
</tr>
</tbody>
</table>
Figure 5 Scored actogram for an illustrative male subject aged 7 years
The actogram for a 6-day period is shown for an illustrative patient. Specific sleep measures are obtained from the actogram as shown above.
4.6.3.2. Transition Probabilities

Actigraphy data is commonly analyzed by quantifying amounts or percentages of time spent in wakefulness and sleep, where such actigraphy measures include total sleep time, wake after sleep onset and sleep efficiency. However, an advanced algorithm for analyzing actigraphy data involves the application of a state-transition approach to describe local temporal dynamics of rest-activity patterns. This algorithm provides a detailed means of quantifying fragmentation based on rest-activity data that is generated by an actigraph. Essentially, the algorithm provides an index of fragmentation during sustained activity as well as sleep. Lim and colleagues constructed and implemented the transitions probabilities algorithm in an elderly population; however there remains a lack of normative data for children (Lim et al., 2011). Thus, the application of the transition probabilities algorithm in a pediatric population is new and relevant to this thesis.

The algorithm was implemented using MATLAB. Using the algorithm, each 30-second epoch of the actigraphic record was categorized as either rest or activity based on the number of activity counts. An epoch with a number of counts of 0 was classified as rest, and an epoch with a number of counts greater than 0 was classified as activity. Next, runs of rest were defined as beginning with at least one epoch of rest and ending at the epoch before the first epoch of activity. In other words, each run of rest begins with an A→R transition and ends with an R→A transition. Similarly, runs of activity were defined as beginning with at least one epoch of activity and ending at the epoch before the first epoch of rest. Each run of activity begins with an R→A transition and ends with an A→R transition. Following this, the probabilities of an R→A transition and A→R transition are determined. The probability that an individual will transition to a resting state after being in an active state following a specific amount of time is defined as pAR(t). Likewise, pRA(t) is defined as the probability that an individual will transition to an
active state after being in a resting state following a specific amount of time. Figure 6 illustrates the estimated transition probabilities \( p_{RA}(t) \) and \( p_{AR}(t) \) plotted against the duration of time that is spent in rest or activity, respectively. A LOWESS regression was performed with the \( p_{RA}(t) \) and \( p_{AR}(t) \) plots, where a consistent shape is observed. The plot is generally divided into 3 regions: a falling region where a rapid decline is observed, followed by a constant non-zero probability region, and ending with a rising region where a slow increase occurs at the end of the longest runs. Similar to Lim and colleagues, we found that the rising regions were identified based on a relatively small number of data points and may represent an artifact (Lim et al., 2011). A weighted average value is calculated within the constant region for the \( p_{RA}(t) \) and \( p_{AR}(t) \) plots, known as \( k_{RA} \) and \( k_{AR} \), respectively. The values for \( k_{RA} \) and \( k_{AR} \) indicate degree of fragmentation with the runs of rest and activity, respectively. Higher \( k_{RA} \) values indicate greater fragmentation during sleep, and higher \( k_{AR} \) values indicate greater fragmentation with activity while awake.
Figure 6 Plot of $p_{RA}(t)$ and $p_{AR}(t)$ for an illustrative male patient aged 5 years

(A) and (B) show the plot for $p_{RA}(t)$ and $p_{AR}(t)$, respectively for an illustrative patient. Observed values are indicated as blue dots. The solid line represents the fitted LOWESS curve, and the dashed line represents estimates for $k_{RA}$ and $k_{AR}$. 
4.6.4. Questionnaires

4.6.4.1. Children’s Sleep Habits Questionnaire

The Children’s Sleep Habits Questionnaire (CSHQ) is a 33-item parent-reported sleep screening instrument that is designed for toddlers and school-aged children (Goodlin-Jones, Sitnick, Tang, Liu, & Anders, 2008). The CSHQ is often utilized as a clinical tool for assessing sleep problems in the pediatric population. The items pertain to the frequency of behaviours that are associated with common pediatric sleep difficulties. Parents are asked to rate the frequency of the child’s sleep behaviour during a typical week. Items are rated on a three-point scale: “usually” if the sleep behaviour occurred five to seven times a week, “sometimes” for two to four times a week, and “rarely” for zero to one time a week. Specific items are scored in a reverse order in order to make a higher score indicative of more disturbed sleep. These items are grouped into eight subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Awakenings, Parasomnias, Daytime Sleepiness and Sleep Disordered Breathing. Higher scores indicate greater sleep problems with a maximum total CSHQ score of 97. A total CSHQ score of 41 has been reported to be a sensitive clinical cut off for the identification of probable sleep problems (Owens, Spirito, & McGuinn, 2000).

4.6.4.2. Child Behaviour Checklist (CBCL)

The CBCL is a widely used parent-reported questionnaire to assess behavioural, social and emotional problems in children (Achenbach & Rescorla, 2000). The CBCL is offered for two age groups: 100-item preschool version for 18 months to 5 years of age and 118-item school-aged version for 6 years to 18 years of age. Parents rate the child’s typical behaviour on a three-point scale, ranging from 0 for “Not True” to 2 for “Very True”. Items are grouped into five domain-specific syndrome scales: Anxiety, Somatic Complaints, Withdrawal, Attention
Problems, and Aggressiveness. Based on these scales, the CBCL provides an overall score for internalizing and externalizing behaviour difficulties, and total behavioural problems. The CBCL provides standardized T-scores for each behavioural scale that are age- and gender-adjusted based on normative data. Higher scores are indicative of problematic behaviour. Specifically, T-scores below 65 are within normal range, T-scores ranging between 65 and 69 are within borderline clinical range, and T-scores above 70 indicate behaviours of clinical concern.

4.6.4.3. Behaviour Rating Inventory of Executive Function (BRIEF)

The BRIEF is a parent-reported questionnaire that assesses executive function behaviours in children (Gioia, Espy, & Isquith, 2003). Similar to CBCL, the BRIEF is available for two age groups: a 63-item preschool version for 18 months to 5 years of age, and 86-item school-aged version for 6 years to 18 years of age. Parents rate a series of statements that describe their child’s typical behaviour. The statements are rated on a three-point scale, ranging from 1 for “Never” to 3 for “Always”. Items are grouped into five clinical scales that measure different domains of executive functioning: Inhibit, Shift, Emotional Control, Working Memory and Plan/Organize. The scores of all clinical scales are combined to provide a summary index of executive functioning referred to as the Global Executive Composite. Age- and gender-adjusted standardized T scores are derived from individual scores of a normative sample. Higher scores are indicative of greater executive dysfunction. A clinical scale with a T-score that is greater than 65 is generally considered as clinically significant.
4.6.4.4. Conners Behaviour Rating Scales

The Conners Behaviour Rating Scales assesses a wide range of behavioural, emotional, and social concerns in children (Conners, 2009). The Conner’s is offered for two age groups: a 47-item preschool version for children aged 18 months to 6 years, and a 43-item version for children aged 7 years to 18 years. Parents rate the frequency of a specific behaviour during the past month using a four-point scale, ranging between 0 for “Never” and 3 for “Very Often”. Items are grouped into three behavioural scales: ADHD, Defiance/Aggressiveness and Social Functioning/Peer Relations. Based on normative data, age- and gender-adjusted standardized T scores are available for each behavioural scale. Higher scores indicate problematic behaviour, where T scores greater than 65 are clinically significant.

4.6.4.5. Post-Hospitalization Behavioural Questionnaire (PHBQ)

The PHBQ is a widely recognized parental-reported questionnaire for assessing children’s behavioural adjustment following hospitalization (Thompson & Vernon, 1993). The PHBQ is a 27-item questionnaire, where parents compare the child’s typical behaviour before the surgery with the child’s behaviour following surgery. The frequency of specific postoperative behaviour changes are rated on a 5-point scale, ranging between 1 for “Much Less” and 5 for “Much More”. A score of 3 indicates no change in postoperative behaviour. Items are grouped into six domains: General Anxiety, Separation Anxiety, Sleep Anxiety, Eating Disturbances, Aggression towards Authority, and Apathy-Withdrawal (Power, Howard, Wade, & Franck, 2012).
4.6.4.6. Pittsburgh Sleep Quality Index (PSQI)

The quality of parental sleep can be a potential predictor for poor postoperative sleep quality in children, where parents who sleep poorly tend to overestimate sleeping problems in their children (Ronnlund et al., 2016). As an attempt to control for confounding effects, the PSQI was administered to collect information pertaining to parental sleep quality. The PSQI is a 19-item self-rated questionnaire that assesses sleep quality and disturbances in adolescents and adults (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Parents rate the frequency of several sleep-related problems. Responses range from 0 for “not during the past month” to 3 for “three or more times a week”. The individual items generate 7 subscale scores: Subjective Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleeping Medications and Daytime Dysfunction. The sum of the scores for the seven subscales yields one global score. Higher scores indicate greater sleep disturbances, where a global score greater than 5 suggests poor sleep quality.

4.6.4.7. State-Trait Anxiety Inventory (STAI)

In addition to parental sleep quality, specific psychological aspects of the parent, such as temperament and personality, can influence the quality of postoperative sleep in children (Caldwell-Andrews & Kain, 2006). For example, children of anxious parents tend to experience poor actigraphy-measured postoperative sleep (Caldwell-Andrews & Kain, 2006). In order to control for confounding effects, the STAI was administered to collect information relating to parental anxiety. The STAI contains two separate 20-item self-reported rating scales that measure state and trait anxiety in caregivers (Spielberger, 1989). State and trait anxiety refer to situational-based and long-term anxiety, respectively. Parents rate a series of statements that assess anxious behaviour using a four-point scale, ranging from 1 for “Almost Never” to 4 for
“Almost Always”. Specific items are scored in a reverse order in order to make a higher score indicative of greater anxiety. State and trait anxiety scores typically range between 20 and 80.

4.6.4.8. Parental Satisfaction

Satisfaction questionnaires were completed to assess whether parents receive sufficient information regarding surgical routines as well as their conceptions regarding the child’s recovery from anesthesia. Parents completed a structured questionnaire that was devised by Sikich and colleagues (Sikich, Carr, & Lerman, 1997). The questionnaire consists of items pertaining to the parent’s preferences and expectations on their child’s state during the first 24 hours following surgery. Parents also rate their level of concern for common side effects of anesthesia including vomiting, sleepiness, and pain, as well as share their opinions regarding their child’s discharge after surgery. Additionally, parents completed a second satisfaction questionnaire that was developed by Kain and colleagues (Kain et al., 2000). Satisfaction was assessed based on statements that parents rate using a 5-cm visual analogue scale that is marked as “Strongly Agree” or “Strongly Disagree” on either end. Responses are scored using a 5-point scale, ranging from 1 for “Strongly Disagree” and 5 for “Strongly Agree”. Specific items are scored in a reverse order in order to make a higher score indicative of higher satisfaction.

4.6.4.9. Pain Assessment

Postoperative sleep disturbances may be a consequence of postoperative pain. As such, a daily parent-reported pain measure was used to assess pain throughout the 7-day postoperative period. The Parents’ Postoperative Pain Measure is a 15-item reliable and validated behavioural checklist based on non-verbal pain cues that children display following surgery (Chambers, Reid,
McGrath, & Finley, 1996). Parents select yes or no for each behaviour. Out of the 15 items, a score of 6 or higher indicates clinically significant levels of pain.

4.7. Sample Size Calculation

Because sleep efficiency is an important sleep variable that indicates decreased sleep duration and overall poor sleep quality, the primary measure will be sleep efficiency. Based on the literature, we assume a 5% expected decrease in sleep efficiency after general anesthesia with a standard deviation of 10 (Acebo et al., 1999; Caldwell-Andrews & Kain, 2006; Sadeh, Lavie, Scher, Tirosh, & Epstein, 1991). A paired t test will be conducted to compare sleep efficiency before and after general anesthesia exposure. Given a power of 0.8 and a type-1 error (alpha) of 0.05, a sample size of 34 surgical patients is required.

4.8. Statistical Analyses

Descriptive statistics, including frequencies of percentages, mean, median and/or range values were obtained for all demographics, sleep, behavioural and satisfaction measures. Comparisons between preoperative and postoperative actigraph and behavioural variables, and parental measures were examined using 2-tailed paired t tests, correlation analysis and one-way repeated measures ANOVA. A mixed model ANOVA was used to determine whether actigraph, behavioral and parental measures differed significantly across baseline, 1- and 3-month follow-up between the surgical and control groups. Actigraph and behavioural data were age and gender matched with normative control data. Bonferroni post-hoc testing was performed for statistically significant differences to adjust for multiple comparisons. Analyses were performed using SPSS version 23.0. Statistical significance was indicated by p-value ≤ 0.05.
Chapter Five: Results

5.1. Demographics

From November 2015 to February 2017, a total of 114 surgical patients were eligible for this study based on the inclusion/exclusion criteria. Of these, 58 patients agreed to participate; however, 21 patients were excluded prior to surgery for reasons including the child having difficulty wearing the actigraph, frequent rescheduling/cancellation of surgical procedures, or parents withdrawing their participation prior to the child’s surgery. A total of 37 subjects were successfully recruited to be a part of the study. Of the remaining 37 subjects, three were lost to follow-up. As a result, a total of 34 subjects were recruited who underwent surgery, and wore the actigraph for a 7-day period before surgery (i.e. baseline) and immediately after surgery (i.e. postoperative 7-day period). A discrepancy exists between the number of subjects that completed the 1- and 3-month follow-up because the 1-month follow-up was later added to the study protocol to capture key changes in sleep patterns that may normalize by the 3-month mark. Of the 34 subjects, 22 completed actigraphy monitoring as well as additional sleep and behavioural assessments at all time points, including before and immediately after surgery, and one and three months after surgery. Additionally, three out of the 34 subjects opted out of the 3-month follow-up after completing the 1-month follow-up, resulting in 31 subjects that completed actigraphy monitoring and additional assessments before and immediately after surgery, and three months after surgery (Figure 7). As such, sleep and behavioural patterns were compared separately for 3 groups of data: 1) 34 subjects at baseline and 7-day postoperative period, 2) 22 subjects at baseline, 7-day postoperative period, and 1- and 3-month follow-up, and 3) 31 subjects at baseline, 7-day postoperative period, and 3-month follow-up. The control group consisted of 18
subjects, who completed actigraphy monitoring, and additional sleep and behavioural assessments at baseline, and one and three months after baseline.

The mean age of the 34 subjects at the time of surgery was 4.7±2.0 years and 79% were male. The surgical group consists of a greater number of males as one-third of the cohort underwent urological surgeries. The mean age of 18 subjects in the control group was 5.3±1.9 years and 61% were male. Overall, the surgical group was similar to the control group with regard to age, gender, height and weight; however, a statistically significant difference was observed with body mass index (BMI), where BMI was higher in the surgical group (Table 6).

Table 6 Demographics and anthropometrics of surgical and control groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD) [Range] – Surgery (n=34)</th>
<th>Mean (SD) [Range] – Controls (n=18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>4.7 (2.0) [1.5 – 8.9]</td>
<td>5.3 (1.9) [2.0 – 8.0]</td>
<td>0.38</td>
</tr>
<tr>
<td>Gender, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Male</td>
<td>27 (79.4)</td>
<td>11 (61.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>– Female</td>
<td>7 (20.6)</td>
<td>7 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>103.2 (14.3) (78.0-135.0)</td>
<td>109.4 (13.3) [85.0-130.0]</td>
<td>0.13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>19.5 (6.5) [10.8-35.4]</td>
<td>19.4 (4.8) [13.0-30.0]</td>
<td>0.98</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>18.0 (3.3) [14.0-23.1]</td>
<td>15.9 (1.7) [12.0-19.0]</td>
<td>0.02a</td>
</tr>
</tbody>
</table>

*a p≤0.05 represents a statistically significant difference between the surgical and control groups
Figure 7 Participant flow for surgical patients

Assessed for eligibility (n=475)

Eligible to participate (n=114)

Agreed to participate (n=58)

Underwent Surgery (n=37)

Completed baseline & 7-day F/U = 34

Lost to 1-month F/U (n=9)

Completed 1-month F/U = 25

Lost to 3-month F/U (n=3)

Completed 3-month F/U = 31

Not meeting inclusion criteria (n=351)

Declined to participate (n=56)

Excluded (n=21)
  • Withdrew participation (n=9)
  • Other reasons (i.e. unable to wear watch, parent rescheduled/cancelled surgery) (n=12)

Lost to 7-day F/U (n=3)

Completed both 1- & 3-month F/U = 22
5.2. Surgery Details

Seventy-four percent of the surgical population were classified as ASA physical status 1 at the time of surgery. Of the 34 subjects, 23 (67.6%) underwent ENT surgeries, including myringotomy, mastoidectomy and cochlear implant. Eleven patients (32.4%) underwent urological surgeries including orchiopexy and hypospadias repair. Appendix 3 outlines the specific surgical procedures and the proportion of subjects that underwent each procedure. Table 7 provides details relating to the general anesthetics and medications that were given during the procedure. All patients received sevoflurane as an inhaled anaesthetic agent. Of the 34 subjects, 26 children received both inhaled and intravenous agents (i.e. propofol, dexmedetomidine, ketamine and remifentanil). Seven children received adjunct regional anesthesia (ilioguanal blocks, caudal, pudendal nerve block). All subjects received analgesic drugs including acetaminophen, ketorolac, fentanyl and morphine. As per clinical guidelines and/or indications, nine children received midazolam as a premedication. The mean duration of anesthesia was 131.5±95.2 minutes, ranging from 10 to 358 minutes, with a median duration of 112.5 minutes. Eight children (23.5%) were exposed to an anesthetic that lasted between 60 and 119 minutes, and 17 children (50.0%) were exposed to an anesthetic that lasted more than 120 minutes.
Table 7 Surgery and anesthesia details

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surgery (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA Physical Status, No. (%)</td>
<td></td>
</tr>
<tr>
<td>– 1</td>
<td>25 (73.5)</td>
</tr>
<tr>
<td>– 2</td>
<td>9 (26.5)</td>
</tr>
<tr>
<td>Length of Surgery, mean (SD) [Range], min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>104.0 (85.6)  [5.0-308.0]</td>
</tr>
<tr>
<td>Duration of Anesthesia, mean (SD) [Range], min</td>
<td></td>
</tr>
<tr>
<td>– 0 to 59 (n=9)</td>
<td>24.6 (18.9) [10.0-59.0]</td>
</tr>
<tr>
<td>– 60 to 119 (n=8)</td>
<td>82.1 (17.6) [63.0-104.0]</td>
</tr>
<tr>
<td>– ≥ 120 (n=17)</td>
<td>211.3 (63.0) [121.0-358.0]</td>
</tr>
<tr>
<td>Inhaled Anesthetic, No (%)</td>
<td></td>
</tr>
<tr>
<td>– Sevoflurane</td>
<td>34 (100)</td>
</tr>
<tr>
<td>Intravenous Agents, No (%)</td>
<td></td>
</tr>
<tr>
<td>– Propofol</td>
<td>22 (64.7)</td>
</tr>
<tr>
<td>– Remifentanil</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>– Dexmedetomidine</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>– Ketamine</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Analgesic Drugs, No (%)</td>
<td></td>
</tr>
<tr>
<td>– Acetaminophen</td>
<td>27 (79.4)</td>
</tr>
<tr>
<td>– Ketorolac</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>– Fentanyl</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>– Morphine</td>
<td>13 (38.2)</td>
</tr>
</tbody>
</table>

5.3. Actigraphy Measures

5.3.1. Comparing Sleep Patterns between Surgery and Control Groups

Sleep patterns were compared between control and surgical subjects that completed actigraphy monitoring at baseline, and the 1- and 3-month follow-up (Table 8). No statistically significant differences were found with total sleep time, wake after sleep onset and the transition probabilities between groups across time (total sleep time: p=0.55; wake after sleep onset: p=0.66; kAR: p=0.59; kRA: p=0.73). Statistically significant differences were found for sleep efficiency and sleep onset latency, where sleep efficiency was lower and sleep onset latency was higher in the surgical group across time (sleep efficiency: p=0.04; sleep onset latency: 0.01).
Post-hoc testing was performed using Bonferroni. Corrected p-values indicated non-significant differences between groups for sleep efficiency at different time points (baseline: p=0.09; 1-month follow-up: p=0.10; 3-month follow-up: p=0.06). Statistically significant differences were found between groups for sleep onset latency at different time points (baseline: p=0.01; 1-month follow-up: p=0.05; 3-month follow-up: p=0.001). After adjusting for gender and age, the observed differences in sleep efficiency between both groups were no longer significant (p=0.09); but differences in sleep onset latency remained statistically significant (p=0.01), where the surgical group had a longer sleep onset latency compared to the control group. However, when comparing the change in sleep parameters between baseline and follow-up, the degree of change in sleep onset latency and additional parameters did not significantly differ between both groups (Table 9).
Table 8 Actigraphy results for surgical group and control group across time

<table>
<thead>
<tr>
<th>Measure</th>
<th>Surgery Baseline</th>
<th>Controls Baseline</th>
<th>Surgery 1-month F/U</th>
<th>Controls 1-month F/U</th>
<th>Surgery 3-month F/U</th>
<th>Controls 3-month F/U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Efficiency (%)</td>
<td>79.0b (5.0)</td>
<td>81.9b (3.0)</td>
<td>77.7b (6.4)</td>
<td>81.1b (3.2)</td>
<td>79.6b (4.1)</td>
<td>82.3b (5.4)</td>
<td>0.04a,d</td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>485.7 (26.4)</td>
<td>494.8 (22.0)</td>
<td>497.2 (39.1)</td>
<td>499.0 (30.5)</td>
<td>494.9 (41.7)</td>
<td>501.6 (42.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>43.0c (22.9)</td>
<td>22.3c (10.5)</td>
<td>44.5c (35.0)</td>
<td>22.9c (15.7)</td>
<td>35.8c (18.8)</td>
<td>15.3c (8.0)</td>
<td>0.01a</td>
</tr>
<tr>
<td>Wake After Sleep Onset (min)</td>
<td>57.1 (20.4)</td>
<td>54.2 (8.5)</td>
<td>59.0 (21.1)</td>
<td>54.4 (14.3)</td>
<td>55.4 (16.8)</td>
<td>55.6 (13.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>k_AR (probability)</td>
<td>0.040 (0.04)</td>
<td>0.040 (0.04)</td>
<td>0.039 (0.04)</td>
<td>0.043 (0.05)</td>
<td>0.037 (0.04)</td>
<td>0.064 (0.10)</td>
<td>0.59</td>
</tr>
<tr>
<td>k_RA (probability)</td>
<td>0.047 (0.01)</td>
<td>0.048 (0.02)</td>
<td>0.049 (0.01)</td>
<td>0.050 (0.01)</td>
<td>0.045 (0.01)</td>
<td>0.046 (0.02)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Data presented as mean (SD) unless otherwise indicated

n=22 for surgical group, n=18 for control group

a p≤0.05 represents a statistically significant difference between the surgical and control groups across time

b Post-hoc testing using Bonferroni revealed statistically non-significant differences at baseline (p=0.09), 1-month follow-up (p=0.10) and the 3-month follow-up (p=0.06) between the surgical and control groups

c Post-hoc testing using Bonferroni revealed statistically significant differences at baseline (p=0.01), 1-month follow-up (p=0.05) and the 3-month follow-up (p=0.001) between the surgical and control groups

d After adjusting for age and gender, p=0.09
Table 9 Change in sleep parameters from baseline compared between the surgical group and control group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean Change from Baseline to 1-month F/U</th>
<th>Mean Change from Baseline to 3-month F/U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Controls</td>
<td>Surgery</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>-1.4</td>
<td>-0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>11.5</td>
<td>4.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>1.5</td>
<td>0.6</td>
<td>-7.2</td>
</tr>
<tr>
<td>Wake After Sleep Onset (min)</td>
<td>1.9</td>
<td>0.2</td>
<td>-1.7</td>
</tr>
<tr>
<td>kAR (probability)</td>
<td>-0.0007</td>
<td>0.003</td>
<td>-0.002</td>
</tr>
<tr>
<td>kRA (probability)</td>
<td>0.002</td>
<td>0.002</td>
<td>-0.002</td>
</tr>
</tbody>
</table>

5.3.2. Comparing Preoperative and Postoperative Sleep

Table 10 shows actigraphy results during baseline and the postoperative 7-day period for the surgical group. The mean sleep efficiency prior to surgery and during the postoperative 7-day period was 77.5±6.1% and 76.1±10.2%, respectively. Mean total sleep time prior to surgery and during postoperative 7-day period was 473.4±37.2 minutes and 472.1±67.1 minutes, respectively. Sleep efficiency and total sleep time did not differ significantly prior to and following surgery (sleep efficiency: p=0.51; total sleep time: p=0.92). Similarly, no significant differences were found with wake after sleep onset, sleep onset latency and transition probabilities, kRA and kAR (wake after sleep onset: p=0.22; sleep onset latency: p=0.41, kAR: p=0.13, kRA: p=0.92). Graphical representations of subject data for each actigraphy measure are shown in Appendix 4. Differences remained non-significant after removing nights that would not
be representative of the child’s typical sleep (sleep efficiency: \(p=0.46\); total sleep time: \(p=0.59\); sleep onset latency: \(p=0.78\); wake after sleep onset: \(p=0.48\)). Nights that were removed included those where the child was reported as sick as well as the night prior to the day of surgery since some surgeries were scheduled early the following morning.

Sleep patterns were also compared among the 31 subjects that wore the actigraph during baseline, post 7 days, and the 3-month follow-up. Across time, no significant differences were found for any actigraphy measure (sleep efficiency: \(p=0.13\); total sleep time: \(p=0.36\); sleep onset latency: \(p=0.21\); wake after sleep onset: \(p=0.12\); \(k_{AR}\): \(p=0.94\); \(k_{RA}\): \(p=0.97\)). Similarly, in the 22 subjects who wore the actigraph during baseline, post 7 days, and both the 1- and 3-month follow-up, no significant differences for any actigraphy measure were observed across time (see Figure 8). Differences in actigraphy measures remained non-significant when nights that were not representative of the child’s typical sleep were excluded (see Appendix 5). As shown in Figure 8, a few subjects, for example, the subject highlighted in blue, showed a large difference in sleep efficiency, total sleep time, wake after sleep onset and sleep onset latency as well as more fragmented sleep during the postoperative 7-day period. However, sleep efficiency and additional sleep parameters normalized by either the 1- or 3-month follow-up.

**Table 10** Actigraphy results at baseline and 7-day postoperative period for surgical group

<table>
<thead>
<tr>
<th>Measure (n=34)</th>
<th>Baseline Mean (SD)</th>
<th>Postoperative 7 Days Mean (SD)</th>
<th>Mean Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Efficiency (%)</td>
<td>77.5 (6.1)</td>
<td>76.1 (10.2)</td>
<td>1.4 (-2.8 to 5.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>473.4 (37.2)</td>
<td>472.1 (67.1)</td>
<td>1.3 (-25.6 to 28.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>36.6 (21.7)</td>
<td>42.0 (39.0)</td>
<td>-5.5 (-18.8 to 7.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Wake After Sleep Onset (min)</td>
<td>70.4 (35.5)</td>
<td>61.6 (21.3)</td>
<td>8.8 (-5.4 to 23.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>(k_{AR}) (probability)</td>
<td>0.050 (0.04)</td>
<td>0.059 (0.05)</td>
<td>-0.01 (-0.02 to 0.003)</td>
<td>0.13</td>
</tr>
<tr>
<td>(k_{RA}) (probability)</td>
<td>0.048 (0.02)</td>
<td>0.048 (0.02)</td>
<td>0.0005 (-0.01 to 0.01)</td>
<td>0.92</td>
</tr>
</tbody>
</table>
**Figure 8** Surgical patient data for primary actigraphy outcomes across time

(A-F) shows mean sleep efficiency, total sleep time, wake after sleep onset, sleep onset latency, and transition probabilities (kAR and kRA) for 22 subjects, respectively. Each line represents each patient that completed actigraphy monitoring at baseline, and 7 days, and 1 month and 3 months following surgery. Statistically significant differences were not observed for any actigraphy measure across time.

5.3.3. Interaction between Anesthetic Duration and Sleep Measures

Further analyses were conducted to investigate whether anesthetic duration can affect sleep quality. Table 11 shows the actigraphy results according to duration of general anesthesia exposure. Cut-off points for anesthetic duration were selected based on similar cut-off points used in the PANDA study (Sun et al., 2016). Among the 9 subjects who were exposed to an anesthetic for less than an hour, a statistically significant difference was found with wake after sleep onset between baseline and the postoperative 7-day period, where children spent less time in nocturnal wakefulness during the week after surgery. Eight children were exposed to an anesthetic for a duration between 60 and 119 minutes, where no statistically significant differences were observed with sleep efficiency and additional sleep parameters between baseline and the postoperative 7-day period. Similar findings were found in those who received an anesthetic for a duration of 120 minutes or longer.
### Table 11: Actigraphy measures at baseline and postoperative 7-day period based on anesthetic duration

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline – Mean (SD)</th>
<th>Post 7 days – Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anesthetic Duration between 0 and 59 min (n=9)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>75.2 (4.5)</td>
<td>79.1 (9.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>458.5 (50.2)</td>
<td>480.5 (73.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>37.8 (20.3)</td>
<td>31.2 (24.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Wake After Sleep Onset (min)</td>
<td>72.6 (16.4)</td>
<td>53.7 (15.9)</td>
<td>0.05(^a)</td>
</tr>
<tr>
<td>k&lt;sub&gt;AR&lt;/sub&gt; (probability)</td>
<td>0.038 (0.03)</td>
<td>0.064 (0.07)</td>
<td>0.29</td>
</tr>
<tr>
<td>k&lt;sub&gt;RA&lt;/sub&gt; (probability)</td>
<td>0.051 (0.03)</td>
<td>0.045 (0.01)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Anesthetic Duration between 60 and 119 min (n=8)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>77.5 (8.5)</td>
<td>77.5 (6.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>481.8 (39.0)</td>
<td>473.2 (60.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>30.4 (12.2)</td>
<td>24.3 (16.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Wake After Sleep Onset (min)</td>
<td>75.6 (55.0)</td>
<td>57.0 (15.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>k&lt;sub&gt;AR&lt;/sub&gt; (probability)</td>
<td>0.078 (0.06)</td>
<td>0.092 (0.06)</td>
<td>0.14</td>
</tr>
<tr>
<td>k&lt;sub&gt;RA&lt;/sub&gt; (probability)</td>
<td>0.053 (0.02)</td>
<td>0.043 (0.02)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Anesthetic Duration ≥ 120 min (n=17)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>78.8 (5.0)</td>
<td>73.7 (12.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>476.2 (28.0)</td>
<td>466.8 (72.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>39.7 (27.1)</td>
<td>58.8 (48.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Wake After Sleep Onset (min)</td>
<td>66.1 (29.9)</td>
<td>68.7 (25.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>k&lt;sub&gt;AR&lt;/sub&gt; (probability)</td>
<td>0.038 (0.03)</td>
<td>0.037 (0.03)</td>
<td>0.58</td>
</tr>
<tr>
<td>k&lt;sub&gt;RA&lt;/sub&gt; (probability)</td>
<td>0.044 (0.02)</td>
<td>0.053 (0.03)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

\(^a\) p≤0.05 represents a statistically significant difference between baseline and post 7 days

5.3.4. Impact of Pain on Sleep Quality

During the 7-day postoperative period, children experienced a high level of pain on the first day following surgery, where 16/34 (47.1%) were reported to have a pain score of 6 or higher, which indicates a clinically significant level of pain. Figure 9 shows that the pain score gradually decreased across the postoperative period, where only 4/34 (11.7%) had a reported pain score of 6 or higher on the seventh postoperative day. Figure 10 compares postoperative pain scores between children who experienced a clinically significant decrease in sleep efficiency and those who did not experience such a decrease. Eight out of the 34 children...
(23.5%) experienced a clinically significant decrease in sleep efficiency, of which four children remained at the hospital overnight after the surgery. On the first postoperative day, the mean pain score was slightly higher for children who experienced a clinically significant decrease in sleep efficiency (8.6±2.3) compared to those who did not (7.0±4.8). Throughout the week, a decrease in pain score was observed, but the pain score on the seventh postoperative day for children remained slightly greater for those who did not experience a clinically significant decrease in sleep efficiency (2.3±3.3) compared to the pain score for children who did experience such a decrease (1.2±2.7). A two-way repeated measures ANOVA showed that postoperative pain scores did not differ across groups (F=0.17, p=0.68).

Figure 9 Mean pain scores each day during the 7-day postoperative period
Daily reported mean pain scores are shown. The mean pain score on the first postoperative day was 7.3±4.4. The pain score gradually decreases across the week, where the mean pain score on the seventh postoperative day was 2.1±3.1.
Figure 10 Mean postoperative pain scores for children with and without a clinically significant decrease in postoperative sleep efficiency
Daily reported mean pain scores are shown. Eight out of 34 surgical subjects (23.5%) exhibited a clinically significant decrease of 5% in postoperative sleep efficiency compared to baseline. The mean pain score was slightly higher on the first postoperative day for children with a clinically significant decrease in sleep efficiency compared to those who did not experience such a decrease; however, pain scores gradually decreased for both groups. A two-way ANOVA repeated for postoperative day revealed that postoperative scores did not differ significantly between both groups (F=0.17, p=0.68).

5.4. Parent-Reported Sleep and Behavioural Measures

5.4.1. Comparing Actigraphy-Measured and Parent-Reported Total Sleep Time
Parents were asked to report their child’s total sleep time on a typical day using the CSHQ. Among the 22 surgical subjects that completed all time points, parent-reported total sleep time did not differ significantly across time (p=0.16); however, parent-reported total sleep time was found to be higher compared to actigraphy-measured total sleep time (baseline: 485.7±26.4 vs 633.6±62.9; 1-month follow-up: 497.2±39.1 vs 615.7±63.2; 3-month follow-up: 494.9±41.7 vs. 630.7±52.5 minutes). A similar trend was observed among the 31 surgical subjects who completed baseline and the 3-month follow-up (baseline: 476.1±42.4 vs 628.9±65.4; 3-month
follow-up: 492.8±59.6 vs 627.8±55.9 minutes), where parent-reported total sleep time did not differ significantly between baseline and the 3-month follow-up (p=0.89). Compared to the control group, parent-reported total sleep time was higher in the surgical group at baseline, and the 1- and 3-month follow-up, but no significant differences were found between the surgical and control groups across time (p=0.12).

5.4.2. Comparing Parent-Reported Sleep Quality in Children

Parent-reported sleep quality in children was defined by CSHQ total scores, where higher scores indicate greater sleep problems including shorter sleep duration, frequent nocturnal awakenings and difficulties falling asleep. Among the 22 surgical subjects that completed the CSHQ at all time points, significant differences were found with total scores across time (p=0.05). However, post-hoc testing was performed using Bonferroni. The corrected p-values revealed non-significant differences (baseline vs 1-month follow-up: p=0.17; baseline vs 3-month follow-up: p=0.78; 1-month follow-up vs 3-month follow-up: p=0.14). For the 31 surgical subjects that completed assessments at baseline and the 3-month follow-up, no significant differences were found in CSHQ total scores between both time points (p=0.17). Table 12 shows CSHQ total scores for the control and surgical subjects that completed assessments at baseline, and the 1- and 3-month follow-up. No significant differences were found in total scores between both groups across time (p=0.55).

5.4.3. Comparing Behaviour between Control and Surgical Groups

Table 12 compares behavioural scores between surgical and control subjects that completed assessments at all time points. Higher behavioural scores indicate more problematic behaviour. The surgical group had significantly higher scores in externalizing behaviours and
global executive functioning compared to the control group (externalizing: p=0.04; global executive functioning: p=0.03). Corrected p-values after performing Bonferroni showed statistically significant differences between the surgical and control groups at the 1-month follow-up for both externalizing behaviours and global executive functioning (externalizing: p=0.03; global executive functioning: p=0.01). After adjusting for age and gender, differences for externalizing behaviours and global executive functioning remained statistically significant (externalizing: p=0.03; global executive functioning: p=0.03). Despite such significant differences in scores, the degree of change in scores for all behavioural outcomes was fairly similar between the surgical and control groups (Table 13). Additionally, majority of control and surgical subjects did not have scores greater than the clinical cut-off score of 65 for various behavioural outcomes (see Appendix 6), which indicates that statistically significant differences seen between both groups may not be considered as clinically significant.

5.4.4. Comparing Preoperative and Postoperative Behaviour

Among the 22 surgical subjects that completed behavioural assessments at baseline, and one and three months following surgery, scores for internalizing and externalizing behaviours as well as total problems did not differ significantly across time (internalizing: p=0.16; externalizing: p=0.38; total problems: p=0.14). Scores for domain-specific behaviours, including ADHD, defiance, social functioning, and global executive functioning also did not significantly differ across time (ADHD: p=0.77; defiance: p=0.08; social functioning: p=0.32; global executive functioning: p=0.57). Among the 31 surgical subjects that completed baseline and the 3-month follow-up, no significant differences were found for externalizing behaviours, global executive functioning, ADHD, defiance and social functioning between baseline and the 3-month follow-up (externalizing: p=0.34; global executive functioning: p=0.38; ADHD: p=0.58;
defiance: \( p=0.07 \); social functioning: \( p=0.39 \)). Scores for internalizing behaviours and total problems differed significantly between both time points (internalizing: \( p=0.04 \); total problems: \( p=0.02 \)). Mean scores for these specific subscales were lower during the 3-month follow-up as compared to baseline (internalizing baseline vs 3-month follow-up: 46.4\( \pm \)10.7 vs 43.6\( \pm \)9.4; total problems baseline vs 3-month follow-up: 45.4\( \pm \)10.1 vs 42.6\( \pm \)10.1). Thus, rather than a negative change, positive changes were observed with internalizing behaviours and overall behaviour. Differences in internalizing behaviours and total problems were no longer significant after adjusting for age and gender (internalizing: \( p=0.80 \); total problems: \( p=0.87 \)).
Table 12 Scores for sleep- and behavioural-related measures for surgical group and control group compared across time

<table>
<thead>
<tr>
<th>Measure</th>
<th>Surgery Baseline</th>
<th>Controls Baseline</th>
<th>Surgery 1-month F/U</th>
<th>Controls 1-month F/U</th>
<th>Surgery 3-month F/U</th>
<th>Controls 3-month F/U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CSHQ Score</td>
<td>42.2 (6.3)</td>
<td>44.5 (8.0)</td>
<td>43.9 (7.1)</td>
<td>44.7 (8.8)</td>
<td>41.1 (7.4)</td>
<td>42.1 (7.7)</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>[39.3 to 45.1]</td>
<td>[40.8 to 48.2]</td>
<td>[40.6 to 47.1]</td>
<td>[40.6 to 48.8]</td>
<td>[37.7 to 44.4]</td>
<td>[38.2 to 46.1]</td>
<td></td>
</tr>
<tr>
<td>CBCL Subscales</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td>45.9 (10.2)</td>
<td>41.8 (12.1)</td>
<td>45.1 (10.7)</td>
<td>41.5 (12.2)</td>
<td>42.5 (8.2)</td>
<td>41.7 (10.8)</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>[41.2 to 50.5]</td>
<td>[36.0 to 47.6]</td>
<td>[40.2 to 49.9]</td>
<td>[35.6 to 47.5]</td>
<td>[38.8 to 46.2]</td>
<td>[36.8 to 46.6]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>46.1b</td>
<td>38.1b</td>
<td>44.2</td>
<td>38.1</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(12.0)</td>
<td>(8.0)</td>
<td>(10.7)</td>
<td>(7.2)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[40.7 to 51.6]</td>
<td>[32.6 to 43.7]</td>
<td>[39.3 to 49.0]</td>
<td>[33.2 to 43.1]</td>
<td></td>
</tr>
<tr>
<td>Total Problems</td>
<td>44.4 (9.1)</td>
<td>39.2 (11.5)</td>
<td>44.2 (11.0)</td>
<td>38.4 (11.4)</td>
<td>41.6 (9.9)</td>
<td>37.3 (9.7)</td>
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</tr>
<tr>
<td></td>
<td>[40.2 to 48.5]</td>
<td>[33.9 to 44.5]</td>
<td>[39.2 to 49.3]</td>
<td>[32.5 to 44.3]</td>
<td>[37.1 to 46.1]</td>
<td>[32.1 to 42.4]</td>
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<tr>
<td>BRIEF</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Global Executive Functioning</td>
<td>48.0 (8.7)</td>
<td>42.3 (8.7)</td>
<td>49.7c</td>
<td>39.9c</td>
<td>49.3 (10.3)</td>
<td>43.5 (12.9)</td>
<td>0.03a</td>
</tr>
<tr>
<td></td>
<td>[43.8 to 52.2]</td>
<td>[37.8 to 46.9]</td>
<td>[43.9 to 55.4]</td>
<td>[34.6 to 45.3]</td>
<td>[44.3 to 54.2]</td>
<td>[37.5 to 49.6]</td>
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</tr>
<tr>
<td>Conners Behaviour Subscales</td>
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<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>52.4 (12.2)</td>
<td>47.7 (8.1)</td>
<td>53.6 (13.8)</td>
<td>44.1 (7.3)</td>
<td>53.3 (14.4)</td>
<td>46.6 (10.6)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>[46.7 to 58.1]</td>
<td>[42.1 to 53.3]</td>
<td>[47.1 to 60.1]</td>
<td>[38.0 to 50.1]</td>
<td>[39.8 to 60.0]</td>
<td>[39.8 to 53.4]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51.2 (9.5)</td>
<td>45.5 (6.5)</td>
<td>52.7 (9.8)</td>
<td>51.1 (12.0)</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[46.7 to 55.7]</td>
<td>[41.1 to 49.8]</td>
<td>[48.0 to 57.3]</td>
<td>[45.4 to 56.7]</td>
<td></td>
</tr>
<tr>
<td>Defiant</td>
<td>49.7 (10.0)</td>
<td>47.3 (4.7)</td>
<td>51.2 (9.5)</td>
<td>45.5 (6.5)</td>
<td>52.7 (9.8)</td>
<td>51.1 (12.0)</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>[45.0 to 54.4]</td>
<td>[42.6 to 52.0]</td>
<td>[46.7 to 55.7]</td>
<td>[41.1 to 49.8]</td>
<td>[48.0 to 57.3]</td>
<td>[45.4 to 56.7]</td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>49.3 (8.2)</td>
<td>46.7 (6.4)</td>
<td>52.1 (10.0)</td>
<td>47.5 (7.7)</td>
<td>52.5 (10.1)</td>
<td>50.3 (11.5)</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>[45.5 to 53.1]</td>
<td>[42.8 to 50.7]</td>
<td>[47.4 to 56.7]</td>
<td>[42.8 to 52.3]</td>
<td>[47.7 to 57.2]</td>
<td>[44.6 to 55.9]</td>
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</tr>
<tr>
<td>Data presented as mean (SD) [95% CI] unless otherwise indicated</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=22 for surgical group, n=18 for control group</td>
<td></td>
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<tr>
<td>a p≤0.05 represents a statistically significant difference between the surgical and control groups across time</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>b Post-hoc testing using Bonferroni revealed statistically significant differences at the 1-month follow-up (p=0.03) between the surgical and control groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Post-hoc testing using Bonferroni revealed statistically significant differences at the 1-month follow-up (p=0.01) between the surgical and control groups.

Table 13 Changes in sleep- and behavioural-related measures from baseline compared between surgical group and control group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean Change from Baseline to 1-month F/U</th>
<th>Mean Change from Baseline to 3-month F/U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Controls</td>
<td>Surgery</td>
</tr>
<tr>
<td>Total CSHQ Score</td>
<td>1.7</td>
<td>0.2</td>
<td>-1.1</td>
</tr>
<tr>
<td>CBCL Subscales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing</td>
<td>-0.8</td>
<td>-0.3</td>
<td>-3.4</td>
</tr>
<tr>
<td>Externalizing</td>
<td>1.3</td>
<td>-0.7</td>
<td>-0.7</td>
</tr>
<tr>
<td>Total Problems</td>
<td>-0.1</td>
<td>-0.8</td>
<td>-2.8</td>
</tr>
<tr>
<td>BRIEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Executive Functioning</td>
<td>1.7</td>
<td>-2.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Conners Behaviour Subscales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>1.2</td>
<td>-3.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Defiant</td>
<td>1.5</td>
<td>-1.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>2.8</td>
<td>0.8</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Postoperative behaviour was also reported to remain unchanged based on the PHBQ. Figure 11 outlines normative scores that indicate unchanged behaviours, where scores lower or higher than the normative score represent positive and negative changes, respectively. Among the 22 surgical subjects that completed behavioural assessments on the 7th postoperative day, and both the 1- and 3-month follow-up, mean scores for various behaviour subscales did not significantly deviate from the normative scores. However, during the first week after surgery, a small proportion of the surgical group exhibited negative behavioural changes, including aggressiveness and sleep anxiety, but the incidence of these behaviours decreased overtime. In contrast, a trend was observed with separation and general anxiety, which increased overtime. Nonetheless, there were no significant differences across time in scores for general anxiety.
(p=0.46), separation anxiety (p=0.72), sleep anxiety (p=0.21), eating disturbances (p=0.52), aggressiveness (p=0.48), and apathy-withdrawal (p=0.15).

Normative scores indicating unchanged behaviour:
- General anxiety = 24
- Separation anxiety = 15
- Sleep anxiety = 9
- Eating disturbances = 9
- Aggression = 6
- Apathy-Withdrawal = 18

**Figure 11** Mean scores for six subscales derived from the post-hospitalization behavioural questionnaire (PHBQ) at post 7 days, and one and three months after surgery

The graph represents mean subscale scores for 22 patients are shown. The blue, red and green bars represent mean scores at post 7 days, 1-month follow-up, and 3-month follow-up, respectively. Scores for each subscale were similar to the corresponding normative score across time, indicating that postoperative behaviour remained similar to that observed prior to surgery.
5.5. Parental Sleep and Anxiety Measures

5.5.1. Comparing Parental Measures between Control and Surgical Groups

Among the surgical group, 18 out of 22 parents completed assessments for parental sleep and anxiety at baseline, and the 1- and 3-month follow-up. Similarly, 18 parents of the control subjects completed similar assessments at all time points. Table 14 compares sleep quality and anxiety between parents of the surgical group and parents of the control group. No statistically significant differences were observed with total sleep time and sleep onset latency (total sleep time: p=0.81; sleep onset latency: p=0.09). A significant difference was found with PSQI global scores between both groups (p=0.01), where parents of the surgical group experienced poorer sleep quality across time. Post-hoc testing was performed using Bonferroni. Corrected p-values revealed statistically significant differences between groups for PSQI at different time points (baseline: p=0.02; 1-month follow-up: p=0.01; 3-month follow-up: p=0.02). Additionally, state and trait anxiety scores did not differ significantly between parents of the surgical group or parents of the control group across time (state anxiety: p=0.98; trait anxiety: p=0.59). In terms of change in parental sleep and anxiety between baseline and follow-up, no significant changes were found for any measure between both groups (Table 15).

5.5.2. Comparing Parental Measures Prior to and Following Surgery

Among the 18 parents of the surgical group that completed caregiver assessments at all time points, the mean parental total sleep time and sleep onset latency prior to their child’s surgery was 421.2±105.6 minutes and 19.0±16.2 minutes, respectively. The mean PSQI global score during baseline was 4.8±3.4. No significant differences were found across time for total sleep time, sleep onset latency or PSQI global scores (total sleep time: p=0.94; sleep onset
Preoperative anxiety for parents is primarily defined by the state anxiety score prior to surgery, where the mean state anxiety score was 32.3±8.6. State anxiety scores did not change significantly between baseline, and one and three months after surgery (p=0.60). Similarly, the baseline score for trait anxiety, which refers to anxiety of a long-term nature, was 32.4±7.3. No significant differences in trait anxiety were observed across time (p=0.71). Additionally, 22 out of 31 parents of the surgical group completed assessments for parental sleep and anxiety at baseline and the 3-month follow-up, where no significant differences were found in any measure between both time points (total sleep time: p=0.65; sleep onset latency: p=0.68; PSQI global score: p=0.18; STAI state anxiety: p=0.60; STAI trait anxiety: p=0.89).

**Table 14 Parental sleep and anxiety measures for the surgical group and control group compared across time**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Surgery Baseline</th>
<th>Controls Baseline</th>
<th>Surgery 1-month F/U</th>
<th>Controls 1-month F/U</th>
<th>Surgery 3-month F/U</th>
<th>Controls 3-month F/U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sleep Time (min)</td>
<td>421.2 (105.6)</td>
<td>421.2 (74.4)</td>
<td>420.0 (89.4)</td>
<td>438.0 (76.8)</td>
<td>424.8 (77.4)</td>
<td>428.4 (78.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>19.0 (16.2)</td>
<td>10.8 (6.0)</td>
<td>20.2 (14.5)</td>
<td>11.8 (7.4)</td>
<td>19.5 (17.7)</td>
<td>11.5 (4.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>PSQI Global Score</td>
<td>4.8b (3.4)</td>
<td>2.1b (2.4)</td>
<td>4.4b (2.7)</td>
<td>2.0b (1.8)</td>
<td>3.9b (1.7)</td>
<td>2.2b (2.1)</td>
<td>0.01a</td>
</tr>
<tr>
<td>STAI State Anxiety Score</td>
<td>32.3 (8.6)</td>
<td>30.8 (9.7)</td>
<td>31.3 (6.8)</td>
<td>30.3 (6.8)</td>
<td>30.7 (6.8)</td>
<td>32.9 (11.1)</td>
<td>0.98</td>
</tr>
<tr>
<td>STAI Trait Anxiety Score</td>
<td>32.4 (7.3)</td>
<td>30.7 (6.4)</td>
<td>33.9 (8.8)</td>
<td>31.0 (8.1)</td>
<td>32.7 (7.8)</td>
<td>33.1 (9.7)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Data presented as mean (SD) unless otherwise indicated
n=18 for surgical group, n=18 for control group

* a p≤0.05 represents a statistically significant difference between the surgical and control groups across time
* b Post-hoc testing using Bonferroni revealed statistically significant differences at baseline (p=0.02), 1-month follow-up (p=0.01) and 3-month follow-up (p=0.02) between the surgical and control groups
### Table 15 Changes in parental sleep and anxiety measures from baseline between the surgical group and control group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean Change from Baseline to 1-month F/U</th>
<th>Mean Change from Baseline to 3-month F/U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Controls</td>
<td>Surgery</td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>-0.02</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Sleep Onset Latency (min)</td>
<td>1.2</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>PSQI Global Score</td>
<td>-0.4</td>
<td>-0.1</td>
<td>-0.9</td>
</tr>
<tr>
<td>STAI State Anxiety Score</td>
<td>-1.1</td>
<td>-0.5</td>
<td>-1.6</td>
</tr>
<tr>
<td>STAI Trait Anxiety Score</td>
<td>1.5</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

### 5.6. Parental Satisfaction Measures

Thirty out of the 34 parents completed questionnaires that assessed their expectations and perceptions of their child’s recovery from anesthesia. From the group, 15/30 (50.0%) parents reported that they were “extremely satisfied” with the information that was given regarding the surgical procedure and recovery. Only 12/30 (40.0%) parents felt that they were “extremely prepared” to care for their child. Out of a maximum score of 105, parents reported an average satisfaction score of 87.1±9.4. During the first 24 hours following anesthetic exposure, 18/30 (60.0%) parents assumed that their child would be awake but tired, and 9/30 (30.0%) parents expected their child to be sleepy but easily awakened. The remaining 3/30 (10.0%) parents expected their child to be very sleepy such that the child could not be easily awakened. The child’s postoperative pain was a great concern for 15/30 (50.0%) parents. Specifically, parents were concerned that their child would be in more pain if he or she quickly emerged from an anesthetic state. Only 8/30 (26.7%) and 5/30 (16.7%) parents were concerned about vomiting.
and sleepiness, respectively. Although 11/30 (36.7%) parents were concerned about the surgical procedure, only 6/30 (20.0%) were worried about the anesthetic. In terms of receiving more information, 18/30 (60.0%) were interested in knowing more about the surgical procedure, while 13/30 (43.3%) parents were interested in knowing more about general anesthesia.

5.7. Summary of Results

In summary, the majority of the children did not experience disturbed sleep following surgery. Sleep parameters including sleep efficiency, total sleep time and wake after sleep onset did not differ significantly between the surgical and control groups; However, sleep onset latency was significantly different between both groups across time, but the degree of change between baseline and follow-up for all sleep parameters was similar between both groups. Subgroup analyses also revealed no statistically significant differences in sleep among children who were exposed to anesthetics either for a duration between 60 and 119 minutes, or for 120 minutes or longer; however, the decrease in postoperative sleep efficiency and increase in sleep onset latency following an anesthetic duration of 120 minutes or longer is generally considered as clinically significant and requires further investigation. In terms of behaviour, the majority of the surgical and control groups did not display clinically abnormal behaviours. Similarly, no significant changes were observed with postoperative behaviour. Furthermore, parents of the surgical children experienced poorer sleep compared to the control group across time, but no significant differences were observed with parental sleep and anxiety prior to and following surgery. Overall, parents were satisfied with the information that was given regarding the child’s surgery and recovery; however, parents expressed an interest to receive more information.
regarding general anesthesia. Such information would be beneficial to establish realistic expectations and provide reassurance about their child’s recovery.
Chapter Six: Conclusions and Discussion

6.1. Main Conclusions

This thesis presented the first analysis of sleep patterns and associated behavioural changes following general anesthetic exposure in children. The primary objective of this thesis was to identify the potential effects of general anesthesia on sleep disturbances in otherwise healthy children undergoing elective surgery. A secondary objective was to identify behavioural changes that may also result from general anesthetic exposure and/or disturbed sleep. The primary hypothesis was that children would experience disturbed sleep following anesthetic exposure, namely more frequent nocturnal awakenings, delayed sleep onset and shorter sleep duration. The secondary hypothesis was that sleep disturbances would be associated with negative behavioural changes including increased aggression, more anxious behaviours and worse attention. However, the main findings from this study were that children did not show significant changes in sleep patterns when measured during the first postoperative week, as well as one and three months following surgery. The children also did not experience significant changes in behaviour following anesthetic exposure. Overall, this study identified that general anesthesia did not result in disturbed sleep in children, and associated negative behavioural changes were not observed following general anesthetic exposure. These findings are important as they challenge beliefs held by clinicians and parents that anesthesia may lead to sleep disturbances postoperatively (Sikich et al., 1997). As such, physicians and families may be reassured regarding the use of general anesthesia in young children. Physicians can also provide anticipatory guidance accordingly, advising parents that a child’s surgery and associated general anesthetic exposure should not result in significant changes in bedtime routine, nighttime awakenings, sleep onset and sleep duration following surgery.
6.2. Specific Findings

6.2.1. Postoperative Sleep Quality in Children

Sleep patterns were compared prior to, and immediately following surgery to assess the probable occurrence of sleep disturbances following general anesthetic exposure. All children received sevoflurane general anesthesia according to standard clinical practice. Compared to baseline, sleep patterns remained relatively consistent during the postoperative 7-day period. The mean sleep efficiency prior to and following surgery was 77.5% and 76.1%, respectively, while the mean total sleep time prior to and following surgery was 473.4 minutes and 472.1 minutes, respectively. Sleep onset latency and wake after sleep onset also did not differ significantly. Similar results were found after removing nights that may have not represented the child’s typical sleep. Sleep patterns also did not change significantly during the 1- or 3-month follow-up. However, among the 34 patients that underwent surgery, 8 out of the 34 (23.5%) experienced a clinically significant decrease in postoperative sleep efficiency (i.e. a decrease of at least 5% during the postoperative 7-day period) (Sadeh et al., 1991). Interestingly, the amount of pain did not significantly differ between those with and without a clinically significant decrease in sleep efficiency. Both groups had a mean pain score that indicated a clinically significant level of pain, and the pain scores gradually decreased across the 7-day period. These findings may suggest that factors, other than pain, can affect a child’s postoperative sleep. For example, 4 out of the 8 patients in the group with a clinically significant decrease in sleep efficiency remained at the hospital overnight after the surgery; thus while staying at the hospital, noises and interruptions may have affected postoperative sleep in these children (Dolan et al., 2016).

Additionally, sleep patterns were compared between the surgical and control groups in this study. Sleep patterns were relatively similar to that of the control group in terms of sleep
efficiency, wake after sleep onset and total sleep time. Furthermore, the degree of change in various sleep parameters between baseline and follow-up was similar for both the surgical and control groups. These findings further support that exposure to general anesthesia did not result in disturbed sleep in the surgical group. However, the surgical group experienced a delayed sleep onset compared to the control group, where the surgical group took approximately twice the amount of time to fall asleep at baseline, and the 1- and 3-month follow-up. Although such a difference in sleep onset latency is considered statistically and clinically significant, sleep onset latency is a limitation for actigraphy (Meltzer, Montgomery-Downs, et al., 2012; Sadeh, 2011). In a sample of children between the ages of 5 and 12, Meltzer and colleagues found a wide individual difference for actigraphy-measured sleep onset latencies compared to polysomnography. The difference between actigraphy and polysomnography ranged between actigraphy underestimating sleep onset latency by 98 minutes to overestimating sleep onset latency by 69 minutes. Additionally, a third of their sample had a sleep onset latency that was overestimated or underestimated by at least 10 minutes. Sleep onset latency is also largely determined by subjective reporting of bedtime; thus sleep onset latency may not be as accurate compared to additional sleep parameters (Meltzer et al., 2016).

Previous studies have compared the incidence of sleep disturbances following exposure to two different types of general anesthetics. For example, Kain and colleagues used actigraphy to assess postoperative sleep, where they found no difference in sleep patterns between children who received halothane anesthesia and those who received sevoflurane anesthesia (Kain et al., 2005). These findings, however, do not assess the occurrence of sleep disturbances within each group following anesthetic exposure. The investigators also did not consider length of anesthetic exposure as a potential factor that can affect postoperative sleep quality. In our study, 26% of the
surgical group was exposed to an anesthetic for less than an hour, and 24% were exposed to an anesthetic for a duration between 60 and 119 minutes. In both groups, sleep patterns were not negatively impacted following anesthetic exposure. Sleep patterns were also compared among 50% of the study population who were exposed to general anesthesia for a duration of 120 minutes or longer. During the postoperative 7-day period, children slept for an average of 10 minutes less, were awake for 4 minutes longer during the night, and took 19 minutes longer to fall asleep. Differences in sleep efficiency, total sleep time, wake after sleep onset and sleep onset latency were not statistically significant, but mean postoperative sleep efficiency decreased by 5%, which may be considered as clinically significant. As there is a lack of studies that assess the risks of prolonged anesthetic exposure, it is difficult to ascertain the clinical significance of our findings. However, a previous study by Steinmetz and colleagues may suggest that prolonged durations of anesthetic exposures can result in disturbed sleep (Steinmetz et al., 2007). The investigators found that infants, aged between 4 and 6 months, experienced shorter sleep durations and frequent nocturnal awakenings following exposure to either TIVA or sevoflurane anesthesia. In that study, all the infants underwent cleft lip-gum-palate surgery that lasted between 166 and 205 minutes. Nevertheless, parent-reported sleep diaries were used as the primary measure. Because of its subjective nature, a sleep diary has limited accuracy and may hinder the reliability of measures including total sleep time and wake after sleep onset (Werner et al., 2008). Moreover, our study population did not consist of infants of a very young age; thus direct comparisons with the current study may not be valid. The PANDA study also compared behavioural outcomes following exposure to various lengths of anesthetic exposure (Sun et al., 2016). The investigators found that a duration of anesthetic exposure of 120 minutes or longer was not associated with poor cognitive performance or poor behavioural outcomes; however, this
subgroup made up a small proportion of their study population (i.e. 17/105 (17%) subjects), and this study did not incorporate sleep measures. Thus, larger-scale clinical studies are needed to evaluate and confirm the effects of prolonged anesthetic exposure, namely a duration of 120 minutes or longer.

6.2.2. Parent- and Actigraphy-Reported Sleep Durations

This study also evaluated parent- and actigraphy-reported sleep durations in surgical subjects. At baseline, parents reported that their child slept for 148 minutes longer compared to actigraphy. Similarly, parent-reported total sleep time and actigraphy-measured total sleep time at the 1- and 3-month follow-up differed by 119 and 136 minutes, respectively. In a previous study, Werner and colleagues monitored healthy children aged 4 to 7 years old and found an average difference of 72 minutes between parent- and actigraphy-reported total sleep time, where parent-reported total sleep time was greater than actigraphy-reported total sleep time (Werner et al., 2008). Another study by Dayyat and colleagues found similar findings in a group of healthy children aged 3 to 10 years. Compared to actigraphy, parents overestimated total sleep time by an average of 113 minutes per night during a one-week period (Dayyat et al., 2011). Reasons for such differences may be related to parents being unaware of their child’s sleep behaviour. For example, parents may be unaware of a child waking up during the night if the child does not alert the parents. Additionally, a child may take longer to fall asleep or wake up earlier during the morning and remain in bed until the parent arrives (Werner et al., 2008). Additionally, parents may be more aware of recommended amounts of sleep for preschoolers and school-aged children. As a result, a social desirability bias may influence parents to report a total sleep time that is higher compared to the observed total sleep time. Parents with poor sleep can also misreport their child’s sleep (Ronnlund et al., 2016). Thus, using parent-reported assessments for
their child’s sleep can be insufficient, and actigraphy is required to provide additional information about a child’s sleep patterns.

6.2.3. Transition Probabilities Analysis

A typical approach to analyzing actigraphy data involves quantifying the amount of time spent in sleep or wakefulness. An additional tool involves a state-transition analysis that quantifies the degree of fragmentation during runs of rest and activity in a 24-hour day. Lim and colleagues constructed an algorithm that computes transition probabilities between periods of rest and activity using raw actigraphy epoch data, but the algorithm has previously only been applied to an elderly population (Lim et al., 2011). This algorithm had not been applied in children. Thus, this thesis introduces a novel means of analyzing actigraphy data in a pediatric population.

Transition probabilities are characterized by weighted average values known as $k_{AR}$ and $k_{RA}$. Higher values of $k_{AR}$ represented fragmented runs of activity occurring during the day, whereas $k_{RA}$ represented fragmented runs of rest occurring during the night; thus $k_{RA}$ was a measure for sleep fragmentation. Although normative values for $k_{AR}$ and $k_{RA}$ are currently not available for children, transition probabilities were compared between a group of healthy children and the surgical group. We found no statistically significant differences in transition probabilities between both groups across time. Statistically significant differences were also not observed in the transition probabilities before and after anesthetic exposure. Similarly, statistically significant differences in transition probabilities were not found before and after surgery for children who were given an anesthetic for a duration between 60 and 119 minutes, as well as a duration of 120 minutes or longer. Similar to findings identified by a conventional
analysis of actigraphy data, our findings involving transition probabilities further support the lack of effect of anesthetic exposure on sleep patterns.

On average, $k_{AR}$ was found to be lower in the control and surgical groups compared to the elderly population studied by Lim and colleagues. As older age tends to be associated with more fragmented runs of activity, children would be expected to show a reduced tendency towards fragmented runs of activity compared to older individuals (Lim et al., 2011). In contrast, mean $k_{RA}$ was higher in the control group and surgical group compared to the elderly, indicating that children have an increased tendency towards fragmented runs of rest. Although sleep patterns become more fragmented as an individual becomes older, individuals over the age of 80 may experience improved sleep quality due to changes in the arousal and sleep neural circuity. Lim and colleagues suggested that a functional or anatomical deterioration within sleep promoting areas such as the VLPO may occur between the ages of 50 and 80 years old, contributing to more fragmented runs of rest. However, beyond the age of 80, such deterioration in the VLPO may be overcome by deterioration within areas necessary for arousal and movement such as the LC, which could be associated with an increase in rest time and a simultaneous decrease in $k_{RA}$ (Lim et al., 2011). As Lim and colleagues primarily assessed sleep in individuals aged between 80 and 100 years old, a lower $k_{RA}$ was found. Implementation of this type of state-transition analysis using larger-scale studies with healthy children would be beneficial in order to develop comparative normative data.

6.2.4. Behavioural Outcomes Following Anesthetic Exposure

After adjusting for age and gender, statistically significant differences were observed for externalizing behaviours and global executive functioning between the surgical and control groups, specifically at the 1-month follow-up, where the surgical group showed more
problematic behaviours compared to the control group. Despite this difference between the control and surgical group, there were no statistically significant differences in behavioural scores before and after surgery. Moreover, the 95% CIs for all behavioural outcomes were within normative range (i.e. below a score of 65) for both groups, indicating that statistically significant differences in behaviour may not be considered a clinical concern. These results concur with findings of the GAS trial and the PANDA study. In the GAS trial, Davidson and colleagues found that sevoflurane general anesthesia during infancy did not increase the risk of adverse neurodevelopmental outcomes at 2 years of age; however, Davidson and colleagues used psychometric testing as a means to assess cognitive performance and behaviour (Davidson et al., 2016). In our study, standardized parent-reported behavioural assessments were used, similar to the PANDA study. In the PANDA study, Sun and colleagues compared cognitive functioning and behaviour during later childhood between siblings with and without a single anesthesia exposure before 3 years of age (Sun et al., 2016). In their study, no statistically significant differences were found between exposed and unexposed siblings in mean scores for internalizing behaviours, externalizing behaviours and total problems after adjusting for gender. Measures of cognitive functioning and global executive functioning also did not significantly differ between both groups. Although our study found statistically significant differences between the surgical and control groups in mean scores for externalizing behaviours and global executive functioning even after adjusting for gender as well as age, both the surgical and control groups showed similar changes in scores across the same time frame for all behavioural outcomes. Additionally, we found no significant differences with behavioural scores in children prior to and following surgery. Thus, children did not display negative behavioural changes following anesthetic exposure. Additionally, in the PANDA study, a greater proportion of exposed siblings had
clinically abnormal internalizing behaviours compared to unexposed siblings, but the investigators were unable to further examine this relationship due to a limited number of females in the study population. Our study population also consisted of fewer females compared to males, but we did not find a significant difference in the number of surgical and healthy children that had clinically abnormal behaviours. Nonetheless, these findings may not be specific to anesthetic exposure prior to the age of 3 years; thus additional studies would be necessary among females to explore and test potential gender-specific effects following anesthetic exposure.

An additional measure included the PHBQ, which is a common instrument used to compare the child’s preoperative and postoperative behaviour. Generally, maladaptive behavioural changes were not observed following surgery. Previous studies, including a study by Kain and colleagues, have also used the PHBQ to measure maladaptive behavioural changes in children following surgery (Kain et al., 2005). Similar to our findings, Kain and colleagues found that children did not experience any behavioural changes by the 7th postoperative day. Stipic and colleagues also used PHBQ to compare short- and long-term changes in behaviour following sevoflurane anesthesia and TIVA (Stipic et al., 2015). In their study, the incidence of negative behavioural changes was significantly higher following sevoflurane anesthesia. Specifically, behaviours pertaining to general anxiety and separation anxiety were more prevalent after sevoflurane anesthesia and remained high following a 6-month period. A similar trend was observed in our study, where the prevalence of general anxiety and separation anxiety did not decrease after one or three months following surgery. The observed trend was not statistically significant, but a larger sample size may replicate the findings of Stipic and colleagues.
6.2.5. Parental Sleep, Anxiety and Perceptions Regarding Postanesthetic Recovery

Based on subjective assessments of parental sleep quality, no statistically significant differences were found in total sleep time and sleep onset latency between parents of the surgical group and control group at baseline, and the 1- and 3-month follow-up. Additionally, no statistically significant differences were found with total sleep time, sleep onset latency and global PSQI scores in parents prior to and following the child’s surgery. Similarly, no significant changes were found for parental sleep and anxiety measures over time between the parents of the surgical and control groups. Although the degree of change was similar for PSQI scores between both groups, parents of the surgical group exhibited poorer sleep quality as evidenced by higher mean PSQI global scores compared to the control group. These results suggest that parents who have children undergoing surgery tend to experience poorer sleep quality as compared to parents of healthy children, but there is an existing gap in the literature that specifically addresses sleep quality in this population. Evaluating the quality of parental sleep is essential as previous studies have shown that parents with poor sleep tend to overestimate their child’s sleeping disturbances compared to an objective measure such as actigraphy (Ronnlund et al., 2016). Parental sleep quality is likely to be important and relevant in the diagnosis, treatment and research exploring sleep disturbance in children. Additional studies using objective sleep analyses in a larger sample of parents are needed to confirm the influence of the child’s surgery on parental sleep, and whether poor sleep quality in parents can affect the child’s sleep quality.

In our study, parents of the surgical cohort of children did not experience a large degree of preoperative anxiety as indicated by similar state anxiety scores at baseline between parents of the surgical and control groups, and a similar trend was found at the 1- and 3-month follow-up. Trait anxiety scores, which provide a degree of long-term anxiety, also did not significantly differ between both groups across time. Overall, these results show that parents did not
demonstrate elevated anxiety scores during the time of their child’s surgery. Although previous studies have found an association between parental anxiety and postoperative sleep problems in children, Caldwell-Andrews and Kain specified that parental neuroticism, which is an indicator of high levels of general anxiety and distress, was associated with a child’s postoperative sleep difficulties. On the other hand, state and trait anxiety were not associated with postoperative sleep difficulties in children (Caldwell-Andrews & Kain, 2006).

In terms of parental expectations regarding postanesthetic recovery, all parents assumed their child would be tired to some extent following anesthetic exposure. Similar to a study by Sikich et al, we found that postoperative pain was the main concern for parents. Secondary postoperative concerns included vomiting and sleepiness (Sikich et al., 1997). Furthermore, parents showed greater concern towards the surgical procedure as compared to the anesthetic; but almost half of the parents were interested in acquiring more knowledge regarding general anesthesia. Providing additional information to parents regarding general anesthesia and surgery will help parents establish realistic expectations and provide reassurance about their child’s recovery.

6.3. Strengths and Limitations

This thesis describes the first longitudinal study to incorporate actigraphy as an objective means to assess sleep disturbances that can occur following general anesthetic exposure in children. This thesis also provides preliminary findings regarding the impact of various durations of anesthetic exposure on sleep. Furthermore, the study entails a comprehensive methodology as an attempt to control for known confounding factors that can contribute to poor postoperative sleep, including pain, and parental-related factors such as parental sleep quality and anxiety.
Additionally, this thesis incorporates a state-transition approach as a novel means to analyse actigraphy data in the pediatric population. This approach is an objective method to quantify fragmentation of runs of rest and activity during a 24-hour day, and does not require subjective recording of sleep and wake times. Lastly, a control group was incorporated into the study to better assess the variability of sleep patterns and behavioural development in children.

However, the study has several limitations that require consideration. Firstly, the sample size of the study population was quite small, resulting in limited subgroup comparisons. Assessing the prevalence of sleep disturbances following exposure to specific anesthetic and sedative agents, including propofol and dexmedetomidine, was difficult as a small proportion of patients were exposed to these agents. Furthermore, the control and surgical groups differed in size, where there were fewer subjects in the control group as compared to the surgical group. Both groups also consisted of a greater number of males as compared to females; as such, gender-specific effects of anesthetic exposure on sleep disturbances could not be evaluated. Large-scale studies are required to confirm these findings and mitigate the potential limitations.

Secondly, the observational nature of this study may introduce a higher potential for bias. During this study, anesthesia was administered according to standard clinical practice and was not influenced in any way. As such, accounting for the influence of additional drugs on sleep and related behavioural outcomes becomes challenging. Moreover, as all children received sevoflurane anesthesia during the surgery, findings of this study cannot be generalized towards all general anesthetics. Additional randomized controlled trials are needed to determine whether other types of anesthetics can cause or reduce potential sleep disturbances.

Thirdly, actigraphy measures including total sleep time referred to nocturnal sleep only. Daytime sleep patterns were not monitored in this study. Given the young age of the study
population, parents were concerned that their child would not feel comfortable wearing the watch during the day. Also, parents raised the possibility that their child may misplace the watch while attending school or taking part in other activities. As such, the actigraph was predominantly worn during the night to assess nocturnal sleep patterns.

Lastly, changes in sleep architecture following anesthetic exposure were not assessed. Actigraphy estimates sleep-wake cycles based on gross motor activity, but cannot differentiate sleep stages or periods of inactive wakefulness due to an inability to record EEG activity. Previous adult studies have documented reduced SWS and REM sleep following exposure to volatile anesthetics; however, these studies incorporated polysomnography as the primary measure for sleep. Although a polysomnogram incorporates various physiological measures to provide a comprehensive evaluation of sleep patterns, a polysomnogram can be burdensome and invasive for children; thus limiting recruitment and potentially influencing recruitment bias. Additionally, a polysomnogram only provides information about the child’s sleep based on one night that may not represent natural sleep patterns. Moreover, polysomnography is resource intensive with limited availability and access for children.

6.4. Future Directions

This study has provided further evidence towards the safety in administering general anesthesia in children. Based on these current findings as well as previous findings, which have shown that anesthetic exposure at an early age is not associated with poor neurodevelopmental outcomes, surgeons and anesthesiologists can feel reassured about having a child undergo a surgery and having minimal sleep disturbances as well as associated behavioral changes.
postoperatively. Physicians can also review these findings with families in order to encourage realistic views about the use of general anesthesia in younger children.

Future research should focus on expanding current knowledge related to anesthetic exposure during early childhood. Specifically, randomized controlled trials can be conducted using actigraphy in order to compare estimated amounts of sleep following exposure to different types of anesthetics such as TIVA. Additional studies can assess the impact of various sedative agents on sleep quality. As previous studies have found improved sleep quality using dexmedetomidine in an adult population, dexmedetomidine can be used as an adjunct to sevoflurane anesthesia in order to explore its impact on sleep quality in a pediatric population. Future studies should also attempt to incorporate specific comparison groups, which can include those with repeated episodes of anesthesia exposure, more prolonged durations of exposures, or specific vulnerable groups such as premature children or children with comorbidities that are not associated with sleep disorders.

Future studies should also focus on assessing the clinical significance of any anesthetic-related physiological changes in sleep. In order to provide a detailed assessment of sleep, ambulatory sleep monitoring could act as an alternative means to measure sleep cycles. In particular, ambulatory, self-application sleep EEG devices could be used to differentiate NREM and REM sleep stages. Although further studies are required to validate the use of these devices in the pediatric population, ambulatory EEG monitoring may be a potential tool for measuring changes in a child’s sleep physiology following exposure to various anesthetics. Overall, these proposed studies will determine whether certain general anesthetics can improve sleep quality in children, as well as extend the applicability of our research findings.
References


doi:10.1542/peds.2015-3425


# Appendices

1. List of surgical procedures

<table>
<thead>
<tr>
<th>Surgical Procedures</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urology</td>
<td></td>
</tr>
<tr>
<td>Hypospadias repair</td>
<td>Corrects defect present at the opening of the penis</td>
</tr>
<tr>
<td>Hydrocele repair</td>
<td>Corrects swelling of the scrotum</td>
</tr>
<tr>
<td>Hernia repair</td>
<td>Corrects a bulge originating from the abdomen</td>
</tr>
<tr>
<td>Orchiopexy</td>
<td>Move an undescended testicle into the scrotum</td>
</tr>
<tr>
<td>Phalloplasty</td>
<td>Reconstruction of penis</td>
</tr>
<tr>
<td>ENT</td>
<td></td>
</tr>
<tr>
<td>Myringotomy</td>
<td>Insertion of tubes into the eardrum to eliminate fluid</td>
</tr>
<tr>
<td>Mastoidectomy</td>
<td>Removal of infected mastoid air cells in the middle ear</td>
</tr>
<tr>
<td>Otoplasty</td>
<td>Reconstruction of outer ear</td>
</tr>
<tr>
<td>Cochlear implant</td>
<td>Insertion of electronic medical device to improve hearing</td>
</tr>
<tr>
<td>Thyroglossal duct cyst</td>
<td>Removal of a lump located on the neck</td>
</tr>
<tr>
<td>Atresia Repair</td>
<td>Reconstruction of the external auditory canal</td>
</tr>
</tbody>
</table>
2. Parent-reported sleep diary

**Actigraphy Diary**

Today is _______________  Today’s Date ____ / ____ / ____

Fill this form out **JUST BEFORE** your child going to bed

What time is it now? __________am/pm

Was your child sick today? ___ Yes  ___ No  
If yes, with what? _____________________

Was there anything else unusual about your child’s day? _____________________

**Did your child take any medications? If so, please list the medication(s), dose and time taken.**

□ Yes  □ No

Medication(s):

Dose(s):

Time(s) taken:

<table>
<thead>
<tr>
<th>Write times when the following occurred (or best estimation) (and circle AM or PM)</th>
<th>START</th>
<th>END</th>
<th>START</th>
<th>END</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shower or Bath</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
</tr>
<tr>
<td>Took off the actigraph</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
</tr>
<tr>
<td>Nap (or accidentally fell asleep)</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
</tr>
<tr>
<td>Very quiet activity (e.g. watching a movie, reading)</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
</tr>
</tbody>
</table>
Actigraphy Diary

Today is _________________  Today’s Date ____ / ____ / ____

Fill this form out FIRST THING in the morning

<table>
<thead>
<tr>
<th>LAST NIGHT</th>
<th>Circle AM or PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>When was the lights turned out for bedtime?</td>
<td>AM</td>
</tr>
<tr>
<td></td>
<td>PM</td>
</tr>
<tr>
<td>After falling asleep, how many times did your child wake up during the</td>
<td></td>
</tr>
<tr>
<td>night?</td>
<td></td>
</tr>
<tr>
<td>In total, how long did these awakenings last?</td>
<td>minutes</td>
</tr>
<tr>
<td></td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Were there any disturbances that woke/kept your child from falling</td>
<td></td>
</tr>
<tr>
<td>asleep last night? If yes, please select from the following options:</td>
<td></td>
</tr>
<tr>
<td>Bedtime Refusal</td>
<td></td>
</tr>
<tr>
<td>Noise</td>
<td></td>
</tr>
<tr>
<td>Anxiety/Worried to be alone</td>
<td></td>
</tr>
<tr>
<td>Nighttime crying</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
</tr>
<tr>
<td>Bed-wetting</td>
<td></td>
</tr>
<tr>
<td>Temper tantrums</td>
<td></td>
</tr>
<tr>
<td>Nighttime hunger</td>
<td></td>
</tr>
<tr>
<td>Nightmares/bad dreams</td>
<td></td>
</tr>
<tr>
<td>Pain/Nausea</td>
<td></td>
</tr>
<tr>
<td>Other, please describe:</td>
<td></td>
</tr>
</tbody>
</table>

| THIS MORNING                                                             |                 |
| What time did your child wake up?                                       | AM              |
|                                                                           | PM              |
|                                                                           | □ Yes □ No      |
| After waking up, what time did your child get out of bed for the day?    | AM              |
|                                                                           | PM              |
3. Proportion of patients undergoing various types of surgeries

<table>
<thead>
<tr>
<th>Types of Surgeries</th>
<th>N (%):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myringotomy</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Mastoidectomy</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Orchiopexy</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Cochlear implant</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>Hypospadias Repair</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Hydrocele Repair</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Thyroglossal Duct Cyst</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Atresia Repair</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Lymphatic Malformation Excision</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Otoplasty</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Phalloplasty</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>
4. Surgical patient data for primary actigraphy outcomes at baseline and post 7 days

Graphs on the right represent related actigraphy data where certain nights were excluded, specifically nights that were not representative of the child’s typical sleep.

\[p=0.51\]  \[p=0.46\]  \[p=0.92\]  \[p=0.59\]
p = 0.41

p = 0.22

p = 0.78

p = 0.48
5. Surgical patient data for primary actigraphy outcomes across time, where nights that were not representative of the child’s typical sleep were excluded.

\[ p=0.28 \quad \text{vs} \quad p=0.18 \]
6. Results from chi-square analysis to compare proportion of clinically abnormal behaviours between surgical patients and control subjects (behavioral score ≥ 65)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Surgery Baseline (n=34) – N above average (%)</th>
<th>Controls Baseline (n=18) – N above average (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internalizing</td>
<td>2 (5.9)</td>
<td>1 (5.6)</td>
<td>0.94</td>
</tr>
<tr>
<td>Externalizing</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Total Problems</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Global Executive Functioning</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
<td>0.30</td>
</tr>
<tr>
<td>ADHD</td>
<td>6 (17.6)</td>
<td>2 (11.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>Defiant</td>
<td>3 (8.8)</td>
<td>1 (5.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>1 (2.9)</td>
<td>0 (0)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measure</th>
<th>Surgery 1-month F/U (n=22) – N above average (%)</th>
<th>Controls 1-month F/U (n=18) – N above average (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internalizing</td>
<td>2 (9.1)</td>
<td>1 (5.6)</td>
<td>0.88</td>
</tr>
<tr>
<td>Externalizing</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Total Problems</td>
<td>0 (0)</td>
<td>1 (5.6)</td>
<td>0.19</td>
</tr>
<tr>
<td>Global Executive Functioning</td>
<td>3 (13.6)</td>
<td>0 (0)</td>
<td>0.15</td>
</tr>
<tr>
<td>ADHD</td>
<td>4 (18.1)</td>
<td>1 (5.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Defiant</td>
<td>2 (9.1)</td>
<td>0 (0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>3 (13.6)</td>
<td>1 (5.6)</td>
<td>0.52</td>
</tr>
<tr>
<td>Measure</td>
<td>Surgery 3-month F/U (n=31) – N above average (%)</td>
<td>Controls 3-month F/U (n=18) – N above average (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Internalizing</td>
<td>1 (6.5)</td>
<td>1 (5.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Externalizing</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Total Problems</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Global Executive Functioning</td>
<td>2 (6.5)</td>
<td>1 (5.6)</td>
<td>0.95</td>
</tr>
<tr>
<td>ADHD</td>
<td>6 (19.4)</td>
<td>1 (5.6)</td>
<td>0.19</td>
</tr>
<tr>
<td>Defiant</td>
<td>3 (9.7)</td>
<td>3 (16.7)</td>
<td>0.40</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>2 (6.5)</td>
<td>2 (11.1)</td>
<td>0.51</td>
</tr>
</tbody>
</table>