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The Efficacy of Oral Dexmedetomidine as an Anesthetic Pre-operative Medication and as a Deterrent to Emergence Delirium

Brian W. Mountain
University of Tennessee, Knoxville

To the Graduate Council:

I am submitting herewith a thesis written by Brian W. Mountain entitled "The Efficacy of Oral Dexmedetomidine as an Anesthetic Pre-operative Medication and as a Deterrent to Emergence Delirium." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Nursing.

John C. Preston, Major Professor

We have read this thesis and recommend its acceptance:

Donald Bell, Sandra McGuire

Accepted for the Council:
Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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Dr. Sandra McGuire, Committee Advisor

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The Efficacy of Oral Dexmedetomidine as an Anesthetic Pre-operative Medication and as a Deterrent to Emergence Delirium

A Thesis
Presented for the
Master of Science
Degree
The University of Tennessee, Knoxville

Brian W. Mountain
August 2008

Dedication

This thesis is dedicated to my dearest and best friend, my wife Deidra. For the last thirty-one months, you have put up with all that it took to get this done. Words cannot express how much your time, patience, understanding, and love have meant to me through all of this. You have been my "rock" and the strength that I needed to persevere and finish. It is because of you that I can now say "THE END"!

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Abstract

Introduction: Emergence delirium (ED) is a mental disturbance sometimes occurring during recovery from general anesthesia. ED presents as hallucinations and confusion, evidenced by moaning, restlessness, involuntary physical activity, and is considered a common post-anesthetic problem in children. This study investigated the role of preoperative dexmedetomidine on parental separation anxiety and anesthesia mask acceptance and its effectiveness in reducing the incidence and severity of ED.

Methods: A double-blind pilot study was conducted with 41 children, 1-6 years of age, undergoing dental restoration and/or extractions under general anesthesia. Subjects were given 4μg/kg dexmedetomidine (Group A) or 0.5 mg/kg midazolam (Group B) orally, prior to anesthesia induction. General anesthesia was initiated using 6% sevoflurane in 50% O_2 with 50% N_2O and was maintained with 0.8-1.5% isoflurane. Subjects were evaluated using the Parental Separation Tool and the Anesthesia Mask Acceptance Tool. Following extubation the subjects were transported to the post-anesthesia recovery room and evaluated using the Pediatric Anesthesia Emergence Delirium Scale.

Results: There was no significant difference between Groups A and B in parental separation anxiety (P=0.138; Pearson Chi-Square) or anesthesia mask acceptance (P=0.438; Pearson Chi-Square). In addition, Group A showed no significant difference in occurrence of ED compared to Group B (P=0.313, independent t-test). Interestingly, males in Group B were 15.75 times more likely to experience parental separation anxiety than males in Group A. This difference was found to be statistically significant with P=0.011 by Pearson Chi-Square and P=0.024 by Fischer's Exact Test.

Conclusions: The clinically significant finding of this investigation is that dexmedetomidine (4µg/kg) is equally as effective as midazolam (0.5mg/kg) in preventing parental separation difficulty and easing acceptance of the anesthetic mask in pediatric patients 1-6 years of age. However, dexmedetomidine is not significantly effective in preventing the occurrence of ED in this pediatric patient population.

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Chapter 1

Introduction

Emergence delirium (ED) has been described as "…a mental disturbance during the recovery from general anesthesia consisting of hallucinations, delusions and confusion manifested by moaning, restlessness, involuntary physical activity, and thrashing about in bed"(Sikich & Lerman, 2004). This phenomenon has been considered a common post-anesthetic problem in children and adults since its description in the literature in 1960. According to Cole, Muray, McAllister & Hirshberg (2002), ED occurs most frequently in the initial ten minutes of recovery, but many children who arrive in a post-anesthesia recovery area asleep experience agitation later during recovery. There are multiple definitions of ED in the literature, with associated prevalence in children ranging from 25-80%, and typically occurring within the first 30 minutes following emergence from anesthesia (Sikich & Lerman, 2004). The most plausible reason for the range in reported prevalence of ED in children is likely attributable to the diversity in definition. Likewise, the reported severity of emergence delirium in the pediatric anesthesia population has varied widely between observers, with the one constant being an almost universally unpredictable presentation.

Dexmedetomidine

Dexmedetomidine is an alpha (α) adrenergic agonist that has a greater specificity for the α-2 receptor versus the α-1 receptor (300:1 for clonidine compared to 1620:1 for dexmedetomidine). (Kamibayashi, Maze, 2000; Smith, Elliott, 2001) "These centrally acting α-2 adrenergic agonists activate receptors in the medullary vasomotor center, reducing norepinephrine turnover and decreasing central sympathetic outflow. These

agents also increase parasympathetic outflow and inhibit sympathetic outflow from the locus ceruleus in the brainstem. The decreased noradrenergic output from the locus ceruleus results in increased firing of inhibitory neurons including the γ-amino butyric acid (GABA) system resulting in sedation, anxiolysis, and analgesia" (Zub, Berkenbosch, & Tobias, 2005).

As stated by Ebert, Hall, and Barney, Uhrich, & Colinco (2000), dexmedetomidine is able to induce a state of "unconsciousness in which subjects could not be aroused by vigorous shaking", while at the same time, subjects where able to maintain adequate respiratory function. According to the manufacturer, the most common side effects of dexmedetomidine include nausea and vomiting, bradycardia, hypotension and fever.

Midazolam

Midazolam is a benzodiazepine that has sedative, amnesic, anxiolytic, and hypnotic qualities. Benzodiazepine's pharmacologic effects appear to result from reversible interactions with the (gamma)-amino butyric acid (GABA) benzodiazepine receptor in the CNS, the major inhibitory neurotransmitter in the central nervous system (Stoelting, & Hillier, 2006). According to the manufacturer, the most common side effects include amnesia, headache, drowsiness, confusion, blood pressure changes, nausea and vomiting, and coughing. However, professional experience with benzodiazepines has consistently demonstrated the potential for profound respiratory depression with the use of benzodiazepines. This effect may be especially unpredictable when midazolam is administered in higher doses or administered in combination with other drugs that also exhibit respiratory depressant effect.

Consequently, investigation into this topical area is both needed and justified in order to seek the safest and most effective interventions for dealing with the phenomenon of emergence delirium. To that end, the focus of this study will seek to investigate the role and effectiveness of preoperative oral dexmedetomidine administration upon the incidence, prevalence, and severity of emergence delirium in children aged one to six years undergoing dental restoration with or without dental extraction.

Research Questions

The questions this research seeks to answer are as follows:

1. Does orally administered dexmedetomidine promote better parental separation and acceptance of an anesthesia face mask as compared to orally administered midazolam in children aged one to six years having dental restoration, with or without dental extractions?
2. Does orally administered dexmedetomidine affect the incidence and severity of emergence delirium in children aged one to six years having dental restoration, with or without dental extractions, as compared to orally administered midazolam for the same population undergoing the same procedures?

Null Hypothesis

In search of the answers to the research questions posed, this author will seek to address the null hypothesis:

> There will be no difference in the incidence or severity of emergence delirium as measured by the Pediatric Anesthesia Emergence Delirium Scale (PAEDS) in subjects aged one to six years who receive oral dexmedetomidine compared to

subjects aged one to six years who receive oral midazolam as an anesthetic pre-medication prior to dental restoration, with or without dental extractions.

Chapter II

Review of the Literature

According to the forth edition of the Diagnostic and Statistical Manual of Mental Disorders, delirium is defined as "a disturbance of consciousness with reduced ability to focus, sustain, or shift attention; a change in cognition (memory deficit, disorientation, language disturbance); or the development of a perceptual disturbance that occurs over a short period of time and tends to fluctuate over the course of a day" (American Psychiatric Association, 2000). Emergence delirium has been considered a common post-anesthetic problem in children and adults. The prevalence of Emergence Delirium (ED) in children ranges from 25-80%, depending on the definition of ED. Sikich & Lerman (2004) determined that ED usually occurs within the first 30 minutes after anesthesia emergence. In a study published in 2001, Veyckemans found documented situations where ED associated agitation was recorded as long as two days post-operatively.

Emergence Delirium Defined

Several terms and definitions for ED have been used interchangeably within the greater body of literature, thereby confounding consistent identification and labeling by health professionals and researchers. Emergence delirium, emergence agitation, and post-anesthetic excitement all are characterized by severe restlessness, nonpurposeful movement, disorientation, incoherence, unresponsiveness, thrashing, and kicking (Manworren, Paulos, & Pop). Some of the distinct but common features of this phenomenon, regardless of nomenclature, include; acute onset of signs and symptoms, variable duration of signs and symptoms, acute onset of new disabilities, acute

incoherency, and spontaneous resolution with treatment (O'Brien, D., 2002). According to Voepel-Lewis, Malviya, and Tait (2003) ED includes nonpurposeful restlessness and agitation, thrashing, crying or moaning, disorientation, and incoherence. This definition of emergence delirium will be utilized by this author in this manuscript as an operational definition.

Research on Clonidine

Malviya et al. performed a double blind study comparing the effectiveness of clonidine to a placebo for the prevention of ED. In their study, the researchers observed 129 subjects, 59 in clonidine group that received 2mcg/kg IV following induction, and 61 in placebo group. Although the clonidine group experienced increased sleepiness, they also experienced less severe agitation. In this investigation, six subjects (10%) in the clonidine group, as compared to 16 subjects (26%) in the placebo group, were identified as moderately to severely agitated upon emergence as evidenced by a score of three or four on a four-point agitation evaluation tool. The possible scores on their tool ranged from zero = quiet, calm; one = mildly agitated but consolable; three = moderately agitated, nonpurposeful and inconsolable; four = severely agitated. Although both groups required analgesia post operatively, clonidine six (10%) and placebo four (7%), the investigators determined the utilization of Clonidine preoperatively significantly reduced the incidence of emergence agitation without altering hemodynamic status. Interestingly, the investigators reported that the parents of the subjects preferred for their children to be asleep and calm rather than awake and alert upon discharge.

Another scientifically sound research study examined the prevention of emergence agitation in association with the use of either tropisetron or clonidine after

sevoflurane anesthesia in subjects undergoing adenoidectomy. In contrast to Malviya et al., which also examined the role of Clonidine in attenuating the effects of ED in children, the Clonidine dosage in this investigation was reduced to 1.5mcg/kg IV as compared to 2mcg/kg IV after induction. (Lankinen, Avela, & Tarkkila, 2006)

The researchers observed 75 subjects aged one to seven assigned to one of three groups: 26 in the placebo group, 25 in the tropisetron group (0.1mg/kg IV after induction), and 24 in the clonidine group (1.5mcg/kg IV after induction). It was observed in this investigation that emergence agitation was less severe in the tropisetron group, eight (32%), compared to the placebo group, sixteen (62%) and the clonidine group was observed to have not prevented emergence agitation with thirteen (54%). These authors utilized the modified Aldrete and pain/ discomfort scales to measure agitation in the subjects under investigation.

Development of Dexmedetomidine

Although not specifically developed for ED, dexmedetomidine was developed to satisfy the need for a drug having the specificity to act upon α-2 receptors without inducing the negative effects associated with the activation of the α-1 receptors. However, the agent's CNS effects, however, would suggest it could be a useful anesthetic adjuvant to attenuate or prevent ED. Dexmedetomidine is an alpha (α) adrenergic agonist that has a greater specificity for the α-2 receptor, primarily found on the presynaptic membrane, versus the α-1 receptor, primarily found on the postsynaptic membrane. Compared to clonidine, with a 300:1 affinity to the α-2 receptor, dexmedetomidine has a 1620:1 affinity to the f α-2 receptor. (Kamibayashi, Maze, 2000; Smith, Elliott, 2001). At this time, dexmedetomidine is routinely being used for short-

term sedation of patients requiring mechanical ventilation in the intensive care unit (ICU) setting. Concurrently, some practitioners are beginning to utilize the agent as a preanesthetic medication in minor and major surgical procedures. This agent is useful in anesthetist's pharmacological armamentarium because it is capable of attenuating the sympathetic response that occurs with intubations and so may decrease the total dosage of opioids necessary for the induction of general anesthesia.

Dexmedetomidine Research

While evaluating the use of dexmedetomidine in the pediatric population undergoing cardiac surgery, Mukhtar, Obayah, and Hassona (2006) found that dexmedetomidine use resulted in decreased HR, MAP, and a reduction in cortisol, catecholamines, and blood glucose levels when measured in these patients as markers of surgical stress response. The conclusion these researchers postulated was that "dexmedetomidine can be a useful adjunct in pediatric cardiac anesthesia because it attenuates the hemodynamic and neuroendocrinal response of surgical trauma and cardiopulmonary bypass".

Mason et al. studied the use of dexmedetomidine for sedation in pediatric patients undergoing computed tomography (CT) imaging studies. They reported that dexmedetomidine was a reliable and effective drug to use for CT imaging, providing adequate sedation without a negative effect on baseline respiration. A similar study compared propofol with dexmedetomidine in the pediatric population undergoing magnetic resonance imaging (MRI). These authors concluded that, while propofol provided quicker onset and emergence in this subject population, dexmedetomidine

preserved mean arterial pressure, respiratory rate without any episodes of arterial desaturations (Koroglu et al., 2006).

Emergence Delirium Research with Children

While studying the incidence of ED in children following general anesthesia, Cole, Murray, McAllister, and Hirshberg (2002) observed 260 subjects between the ages of ten months and six years with a mean age of 2.7 years old. It was reported in their study that 37% (79/260) of the subjects experienced ED. In relation to their investigation;

> *One of the factors believed to contribute to a higher frequency of emergence agitation is a rapid emergence in a foreign environment. We found that children who were asleep for the initial three measurement periods in the recovery room had a similar incidence of emergence agitation (22%) compared with the remainder of the group" (p. 447).*

As a result of their investigation, the influence of rapid emergence and awakening from anesthesia in a foreign environment were taken into consideration during the planning of this author's study.

Of the five hundred twenty-one pediatric subjects aged three through seven who were enrolled in a study by Voepel-Lewis, Malviya, and Tait (2003), 96 (18%) experienced some measure of ED. The observed symptoms ranged in duration from three to forty-five minutes with an average length of occurrence of fourteen minutes. These subjects required pharmacological intervention to control their symptoms, which included thrashing, kicking, restlessness, and incoherency. As a consequence of the interventions necessitated by the exhibited behaviors of the subjects, the subjects as a group were

observed to require longer than estimated lengths of stay in the postanesthisia care unit. Post Anesthesia Care Unit stay for these subjects averaged 117 minutes, resulting in an increased average length of stay by more than 15 minutes when compared to individuals not needing the interventions required by those who exhibited these symptoms. More than half (fifty-six) of the subjects in the ED group required physical restraint, which was defined as being held down by a nurse. A significant percentage of this group (42%) required two or more nurses to physically restrain them until the agitation had subsided and the threats to their safety had passed (Voepel-Lewis, Malviya, & Tait, 2003). According to Voepel et al, in the discussion of their findings, the delirium observed was associated with five adverse advents including increased bleeding from the surgical site, dislodgement of a surgical drain, complaint of increased pain at the operative site and minor injury to the attending nurse.

Shurkey, Mathison, Kalarickal, and Ramadhyani (2006) conducted a study involving two groups of pediatric subjects. One group received intravenous Dexmedetomidine initiated at the time of induction and continued intraoperatively, accompanied by the administration of a sevoflurane-based volatile general anesthesia. The other group received the same volatile general anesthetic, but received an intravenous placebo in place of the dexmedetomidine. According to the authors, upon emergence "the incidence of agitation was significantly different between the two groups, 26% in the dexmedetomidine group versus 60.8% in the placebo group with a p value of 0.036. Additionally, the frequency of observed episodes of agitation was lower in the dexmedetomidine group ($p<0.017$). However, despite the reduction in observed signs and symptoms of ED, the time from extubation until discharge from PACU was the same

for both groups (Shurkey, Mathison, Kalarickal, & Ramadhyani, 2006). Shurkey et al. state that, when compared to benzodiazepines or opioids, dexmedetomidine has a shorter half-life and exhibits less respiratory depression. Based on their conclusions, potential benefits in ED symptom control could be expected with the utilization of dexmedetomidine as compared to the utilization of benzodiazepines while at the same time resulting in a lower potential for the negative side effect of respiratory depression.

Ibacache, Muñoz, Brandes, and Morales, researchers at the Pontificia Universidad Católica de Chile, in Santiago, Chile, studied single dose dexmedetomidine intravenously following the administration of a sevoflurane-based anesthesia in children. They enrolled 90 subjects aged one to ten in their study. Their subjects underwent inguinal hernia repair, orchiopexy, or circumcision. They received sevoflurane in combination with a caudal block. None of the subjects received any premedication. "Group 1 (n=30) received saline 10ml, Group 2 (n=30) received dexmedetomidine 0.15µg/kg, and Group 3 (n=30) received dexmedetomidine 0.30µg/kg" (Ibacache, Muñoz, Brandes, & Morales, 2003, p. 60). Ibacache, Muñoz, Brandes, and Morales (2003) state that their confidence interval was 95% with the incidence of agitation was 37% in Group 1, 17% in Group 2, and only 10% in group 3 with $P < 0.05$. The authors stated that dexmedetomidine significantly decreased the occurrence of emergence agitation when administered to subjects in their study at the 0.30µg/kg dose. Specifically, they stated "The bolus administration of dexmedetomidine in this [0.30ug/kg] dose was safe, and it did not lead to an increased incidence of side effects. However, more studies are needed to determine both the efficacy and safety of dexmedetomidine using either in

different types of surgery or at larger doses" (Ibacache, Muñoz, Brandes, & Morales, 2003, p. 63).

An international research investigation performed at the Erciyes University in Kayseri, Turkey enrolled 60 subjects aged of three to seven who underwent adenotonsillectomy with a sevoflurane based volatile general anesthesia. The subjects were divided into two groups. One group received 0.5µg/kg IV dexmedetomidine diluted in 5ml NaCL 0.9% and the second group received a 5ml sodium chloride (NaCL) 0.9% IV placebo. "Times to emergence and extubation in the dexmedetomidine group were significantly longer than the placebo group. The agitation and pain scores in the dexmedetomidine group were better than placebo group ($p < 0.05$ for each). The incidence of severe agitation, and severe pain were significantly low in the dexmedetomidine group" (Guler et al., 2005, p.764). A particularly interesting and unique finding of this study was a lower frequency of airway problems with subjects in the dexmedetomidine group. It was unknown whether this observation was due to a decreased degree of laryngeal stimulation brought about by the sedative and analgesic effects of dexmedetomidine or whether it was simply observed to have occurred by chance.

Chapter III

Materials and Methods

The objectives of this study were to measure the effects of pre-operative orally administered dexmedetomidine compared to orally administered midazolam for children aged one to six years having dental restoration and possible dental extractions in relationship to: (1) parental separation and acceptance of an anesthesia mask in association with the induction of anesthesia, and (2) the incidence and severity of emergence delirium upon emergence of anesthesia. The Pediatric Anesthesia Emergence Delirium Scale (PAEDS) was utilized to collect data regarding emergence delirium in all of the enrolled subjects. This instrument is a five-question survey that allowed the researcher to distinguish between normal post-anesthesia recovery and post-anesthesia emergence delirium.

Operational Definitions

The following section identifies the operational definitions that were used throughout the remainder of this author's manuscript.

1. Acceptance of Mask tool –A tool used to measure the ease of acceptance of the anesthetic mask.

   Appendix A contains specific definitions

2. American Society of Anesthesiologists (ASA) – The American Society of Anesthesiologists is a professional association involved in educational

research and scientific endeavors for physician members and others with the goal of raising and maintaining the standards of the medical practice of anesthesiology and improves the care of the patient.

3. ASA Physical Status Classification (PSC) – Assessment used to predict the safety of patients receiving anesthesia based on their physical status at the time of surgery.

   Appendix B contains specific definitions.

4. Dental Restoration – The application of caps and or crowns to teeth with dental carries as well as basic dental cleaning.
5. Emergence Delirium (ED) – A mental disturbance during the recovery from general anesthesia consisting of hallucinations, delusions and confusion manifested by moaning, restlessness, involuntary physical activity, and thrashing about in bed.
6. Endotracheal Anesthesia – General anesthesia that is delivered to the lungs through the trachea via an endotracheal tube.
7. Endotracheal tube – A plastic or rubber tube that is inserted through the nose or mouth into the trachea, by which oxygen, anesthetic gases, and/or volatile anesthetics are delivered.
8. General Anesthesia – The loss of consciousness and sensation throughout the entire body following the administration of any combination of medications and agents via an intravenous and/or pulmonary route.

9. Parental Child Separation tool –A tool used to measure the ease of separation of a child from his/her parents and/or legal guardians.

   Appendix C contains specific definitions

10. Pediatric Anesthesia Emergence Delirium Scale (PAEDS) – A valid and reliable instrument designed to measure the presence and severity of emergence delirium in children during the post-anesthesia postoperative period.

    Appendix D contains specific definitions.

Research Design, Sample, and Setting

After approval was obtained from the Investigational Review Board (IRB) committees of the host clinical research site and The University of Tennessee, Knoxville, this randomized, double-blind pilot study was conducted with 41 subjects, consisting of both males and females, aged one to six years having dental restoration and/or dental extractions under general anesthesia at a southeastern united states pediatric specialty hospital. All subjects met the criteria of the ASA physical status classification (PSC) I or ASA PSC II (Appendix B).

Upon scheduling a child for a dental restoration and possible extraction, parent(s) or legal guardian(s) were given an information sheet about the research study and provided a study informed consent form with a request to review prior to the day of

surgery (Appendix E). In addition, the parents or legal guardians were asked to consider allowing their child to participate in the investigation as a study subject. On the day of surgery, the parent(s) or legal guardian(s) were again approached by the staff anesthesiologist about participating as a subject in the research study. If the parent or legal guardian indicated an interest in participation, the purpose of the study was explained in depth by the anesthesiologist who was also a principal investigator. Parent(s) or legal guardian(s) were informed that they were consenting to participation in a double-blinded study comparing the incidence of emergence delirium between the study groups. The anesthesiologist answered any questions the parent(s) or legal guardian(s) had about the study. If the parent(s) or legal guardian(s) subsequently agreed to allow their child to participate in the study, the consent form was presented by a research team member for review and signature. The subject being consented for participate was assigned to one of two the study groups (i.e. oral dexmedetomidine or oral midazolam) based on random assignment as prelisted on the consent form.

Inclusion and Exclusion Criteria

All subjects met the following inclusion criteria in order to be enrolled in the study:

1. Both males and females
2. Between the ages of one to six years
3. Requiring elective dental restoration and possible extractions
4. Requiring general endotracheal anesthesia

5. ASA PSC I or ASA PSC II

The exclusion criterion included the following:

1. Not meeting inclusion criteria
2. Co-existing disease states
3. Known allergies to midazolam, dexmedetomidine, clonidine, benzodiazepines, and/or red dye
4. Evidence or diagnosis of developmental delay and/or mental retardation
5. History of emergence delirium
6. Known previous negative reactions (per history) to a previous anesthesia administration
7. Parents or guardians without access to a telephone
8. No parent or legal guardian present to give informed consent

Informed Consent

In the dental office, upon scheduling a child for a dental restoration with or without possible extraction under general anesthesia, parent(s) or legal guardian(s) were given for review, a copy of the informed consent along with an information sheet describing the research study (Appendix F). The dentist or the office personnel provided these items from a pre-printed supply delivered by the researchers. Parents met with the dental surgeon approximately one month prior to surgery, and so initial solicitation of subjects occurred considerable prior to the request for participation and subject enrolment

procedures. On the day of surgery, the researcher and anesthesiologist discussed the study with the parent(s) or legal guardian(s). The purpose of the study was explained by the anesthesiologist in the presence of the research nurse. Parent(s) or legal guardian(s) were informed that they were consenting to participation by their child in a double-blinded study comparing the incidence of emergence delirium between the two study groups. The anesthesiologist and the research nurse used terms understandable to the subject's parent(s) or legal guardian(s) and answered any questions about the study. They were given sufficient time to consider participation in the study. Parent(s) and legal guardian(s) were notified that, if they chose not to participate in the study, they would not be treated any differently than if they agreed to participate. If the parent agreed to participate in the study, the consent form was presented by the research team member for parent or legal guardian signature. Those parents or legal guardians who agreed to allow their children to participate in the study were notified that at any point in time they could withdraw their child from the study without any detriment to the care or well being of their child. It was at this time that demographic data was obtained for each subject, and entered in the data sheet designed for use in the study (Appendix G).

Study Protocol

The subjects were randomly assigned to the study groups based on the prelisted consent forms, which were prepared in advance of the initiation of the study. The specific group assignments were determined through the use of a computer generated randomization table.

Once randomized, but prior to the administration of any medications, the pharmacy was notified by a member of the research team of the group assignment so medication safety could be evaluated for each subject. The subject's name, study number, and group number were kept in a pharmacy log. Pharmacy provided a supply of pre-operative oral medications labeled *ED Study Drug-A* and *ED Study Drug-B*. The following pre-operative dosing protocol (Appendix H) was utilized on all subjects:

1. Determine the study drug the patient was to receive: Patients whose study consent form had A at the top received the study drug labeled *A*. Those subjects whose consent forms had a B on the top of the form received the study drug labeled *B*.
2. The dose of the study drug, dexmedetomidine, was mixed into a solution at 16 micrograms/milliliter and was dosed at 4 micrograms/kilogram. The resulting milliliter dose was 0.25 milliliters/kilogram with a maximum dose of 10 milliliters.
3. The dose of the study drug, midazolam, will remain at manufacturer's strength of 2 milligrams/milliliter and was dosed at 0.5 milligrams/kilogram. The resulting milliliter dose was 0.25 milliliters/kilogram with a maximum dose of 10 milliliters.
4. The bottles with the medications were labeled ED study Group A or ED study Group B and were kept in the Omnicell.
5. Study patients were prohibited from receiving atropine or any other type of anti-cholinergic medications.

6. The pharmacy staff was to disclose the identity of the study drug when all data had been collected, the study was completed or closed, and if any reaction occurred that was suspected to be an adverse reaction to the study drug. Should adverse reaction have occurred, the study personnel were to be notified immediately, and the subject was to be treated symptomatically as necessary

Regardless of the utilization of study drug A or study drug B, the syringe that contained the drug was opaque, the same size, the same volume, and had no identifiable features. Both study drug A and study drug B were identical in color and texture so as to be unidentifiable between them.

The following protocol was utilized for all subjects:

1. At time of separation of subject from parent(s) and/or legal guardian(s), the researcher evaluates the subject by the Parental Child Separation Tool using a four-point scale (Appendix C).
2. The researcher follows the subject into surgery where the Mask Acceptance Tool is used to score the subject (Appendix A).

The following anesthesia protocol (Appendix I) was utilized on all subjects:

1. Induction is preformed via mask with sevoflurane 6% in oxygen 50%, and nitrous oxide 50%.

2. Volatile anesthesia agents are to be changed to isoflurane at a range of 1.5% to 0.8% for maintenance of acceptable surgical anesthesia as soon as practical following induction.
3. Spontaneous ventilation should be maintained as soon as practical and possible.
4. If positive pressure ventilatory support is required, muscle relaxant is to be avoided, if possible.
5. Avoid medications with anti-cholinergic properties: atropine, glycopyrrolate, meperidine, pancuronium bromide etc. (to avoid confusion between emergence delirium and central anticholinergic syndrome)
6. Maintain acceptable anesthetic depth with isoflurane between a range of 1.5 % and 0.8%, oxygen 50% and nitrous oxide 50%.
7. Administer ondansetron 0.2 mg/kg and decadron 0.25 mg/kg to all subjects as soon as possible after the induction of anesthesia for anti-emesis.
8. Administer fentanyl 1-2 micrograms/kg for narcotic analgesia.
9. Request dental surgeon use local anesthetic blocks for all root canals and extractions when acceptable and record the administration on the anesthesia record.
10. Abandon any of the above guidelines/restrictions if needed for safety of the patient and make study personnel aware of the change in the standard protocol.

11. After completion of the surgical procedure, anesthesia is discontinued, 100% oxygen is to be given to the subject, and subject is to be extubated per criteria (Appendix J).
12. Following extubation, the subject is to be taken to the post-anesthesia recovery room where they will be observed for up to an hour and be evaluated by using the Pediatric Anesthesia Emergence Delirium Scale (PAEDS) tool (Appendix D) measuring for emergence delirium.

The various protocols stated above were created in order to act as a guide for every step of the research process. These protocols protect not only the researcher, but also more importantly the subjects.

Instrumentation

The parental separation measurement tool (Appendix C) is a four-point scale used to measure the subject's willingness to separate from the parent(s) and/or legal guardian(s). Children with scores of one or two on the for-point scale were considered to have had an acceptable separation from the parents immediately prior to the initiation of the surgical procedure; those with scores of three or four were considered to have had difficult pre-procedure parental separations. This tool was used in a previous study (Weldon, 1992) where it demonstrated an acceptable reliability and validity for the purpose it was utilized. However, this tool has not been validated or evaluated for its psychometric soundness. Since no other instruments were available for this purpose, and since instrument construction was beyond the scope of this author's investigation, the use of this instrument was justified and it was utilized with its limitations deemed acceptable.

The mask acceptance tool (Appendix A) is also a four-point scale used to measure the subject's willingness to accept the anesthetic mask from the nurse anesthetist once in the operating room. Children with scores of one or two on the four point scale are designated as having had a "satisfactory" acceptance of the anesthesia mask; scores of three or four were considered "unsatisfactory" (Shukrey 2005, & Weldon, 1992). No psychometric data are available for this tool either, however, since no other instruments were available for this purpose, and since instrument construction was beyond the scope of this author's investigation, this instrument was utilized and its limitations deemed acceptable.

The PAEDS (Appendix D) is a five-question tool that was used to measure the presence of emergence delirium during each possible episode. A score of zero to 20 is possible. When the data are analyzed, a PAEDS score >10 will be considered emergence delirium (ED). As determined by Sikich and Lerman (2004), the coefficient alpha for internal consistency reliability has been reported as .89 with an interobserver reliability of .84 (95% CI, .76-.90). Construct validity was evaluated by six content experts and tested on 100 children to determine correlation between scale scores and factors such as age, time to awakening, and clinical judgment by caretakers. In addition to the scale score, several other items were recorded such as time of pre-operative medication, time operation began and ended, time anesthesia began and ended, time extubated, time entered and left PACU and opioids given in PACU.

Data Analysis

A chi-square was used to determine differences between the control and experimental groups with respect to separation anxiety and acceptance of mask.

Independent t-test statistical procedures were used to determine differences between the occurrence and severity of emergence delirium in the experimental and control groups.

Assumptions

The basic assumptions made regarding this study are as follows:

1. The PAEDS tool is a predictive and accurate instrument for measuring pediatric emergence delirium following general endotracheal anesthesia.
2. The random sample was representative of the population.
3. The Parental Child Separation tool is a predictive and accurate instrument for measuring parental separation anxiety.
4. The Mask Acceptance tool is a predictive and accurate instrument for measuring the willingness to accept the anesthetic mask.

Study Limitations

1. There might possibly have been unanticipated individual varying responses to the prescribed anesthetic plan.
2. Both midazolam and dexmedetomidine were mixed in cherry syrup, which could have potentially changed its makeup in some unknown manner.
3. Neither the Parental Child Separation tool nor the Mask Acceptance tool has undergone statistical testing for external validity or reliability.
4. Neither the Parental Child Separation tool nor the Mask Acceptance tool have been statistically tested and validated to accurately and reliably measure parental separation anxiety or willingness to accept the anesthetic mask.

Specific Risks and Protection Measures for Human Subjects

The most common side effects from dexmedetomidine include nausea, atrial fibrillation, bradycardia, hypertension, hypotension, and supraventricular tachycardia, fever and vomiting. The most common side effects of midazolam include retrograde amnesia, headache, excessive sedation, confusion, hypotension, blurred vision, nausea, vomiting, and coughing

Each research team member was a nurse or graduate student nurse and accompanied the subject through the process. No patient identifiers were used in the publication of this study. All research team members signed a confidentiality form.

The approximate cost of one dose of midazolam is 1/3 the approximate cost of the dexmedetomidine. This increased cost may have been offset because less pain medicine might have been needed after the subject received dexmedetomidine.

Study Benefits

The patients in the study group may have less emergence delirium and may experience less pre-operative anxiety as evidenced by a lower score on the PAEDS tool. The subjects receiving dexmedetomidine may achieve better pain control and therefore receive less opioid, thereby decreasing some of the additional cost. It is hoped that the study will indicate that dexmedetomidine reduces the incidence of emergence delirium without causing any increase in observed negative side effects. If so, it could be utilized in the future as a pre-operative medication to ease the occurrence of ED, and so all of the documented negative effects of emergence delirium. Consequently, everyone who undergoes anesthesia could potentially benefit from the findings of this investigation. Participants of this study received no compensation or incentive to participate in this

study, and the investigators were not paid to conduct this research protocol. Therefore, no monetary gain by either subjects or researchers was a benefit of the work conducted as part of this study.

Chapter IV

Results

There were two objectives of this pilot study. The first objective was to measure the effects of pre-operative orally administered dexmedetomidine as compared to orally administered midazolam in relation to parental separation. The second objective was to evaluate the acceptance of an anesthesia mask and to measure the incidence and severity of emergence delirium in children aged one to six years having dental restoration with or without dental extractions who were administered either oral dexmedetomidine or oral midazolam pre-operatively.

The questions this researcher sought to answer were:

1. Does orally administered dexmedetomidine promote better parental separation and acceptance of an anesthesia face mask as compared to orally administered midazolam in children aged one to six years having dental restoration, with or without dental extractions?
2. Does orally administered dexmedetomidine affect the incidence and severity of emergence delirium in children aged one to six years having dental restoration, with or without dental extractions, as compared to orally administered midazolam for the same population undergoing the same procedures?

In search of the answers to the research questions posed, this author addressed the null hypothesis:

There will be no difference in the incidence or severity of emergence delirium as measured by the Pediatric Anesthesia Emergence Delirium Scale (PAEDS) in subjects aged one to six years who receive oral dexmedetomidine compared to subjects aged one to six years who receive oral midazolam as an anesthetic pre-medication prior to dental restoration, with or without dental extractions.

Descriptive Statistics

The study population consisted of 41 subjects, composed of both males and females age one to six years having dental restoration and/or dental extractions under general anesthesia at a southeastern United States pediatric specialty hospital. All subjects met the criteria of the ASA physical status classification (PSC) I or ASA PSC II (Appendix B). Group A consisted of 19 subjects (46.3%) and Group B consisted of 22 subjects (53.7%). Gender distribution included 21 males (51.2%) and 20 females (48.8%) as seen in Table 1 and Figure 1. Racial distribution of the study subjects, as identified in Table 2 and Figure 2, was as follows: Caucasian 27 (65.9%), African American 9 (22.0%), and Hispanic 5 (12.2%). While obtaining the subject's medical history, the parents or guardians were asked if the subjects were currently taking any medications on a regular basis. It was reported that thirty-one subjects (75.6%) did not take any medication on a regular basis while ten subjects (24.4%) were reported to take medications on a regular basis (Table 3, Figure 3).

Table 1: Gender Analysis

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	21	51.2	51.2	51.2
	Female	20	48.8	48.8	100.0
	Total	41	100.0	100.0	

Figure 1: Gender Description

Table 2: Race Analysis

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Caucasian	27	65.9	65.9	65.9
	African American	9	22.0	22.0	87.8
	Hispanic	5	12.2	12.2	100.0
	Total	41	100.0	100.0	

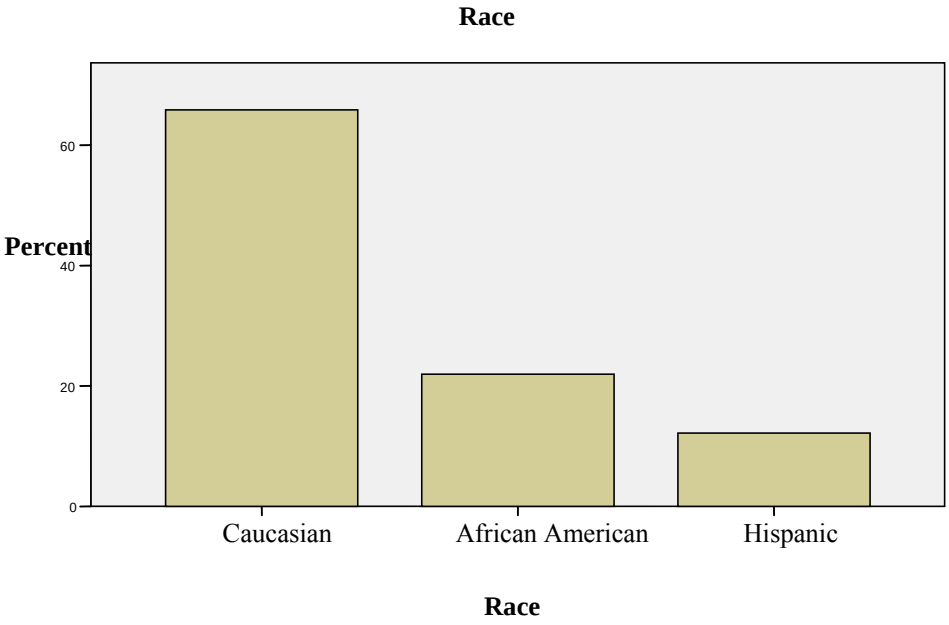

Figure 2: Race Description

Table 3: Medication Frequency

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	31	75.6	75.6	75.6
	Yes	10	24.4	24.4	100.0
	Total	41	100.0	100.0	

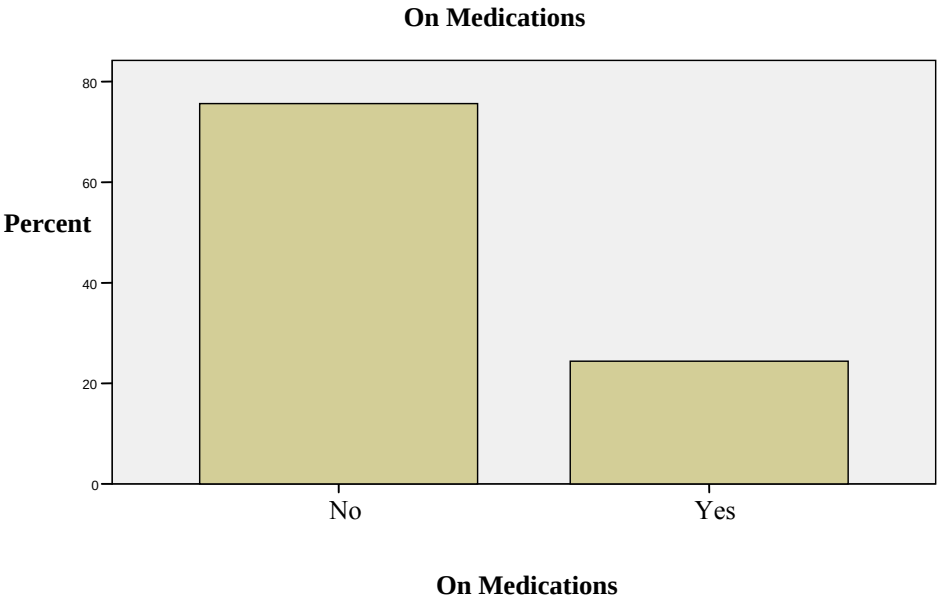

Figure 3: Description of Medication Frequency

All subjects were randomly assigned to the study groups based on the prelisted consent forms (Appendix F), which were prepared in advance of the initiation of the study. The specific group assignments were determined through the use of a computer generated randomization table. Group A, consisting of 46.3% of the study's subjects, received 0.5 mg/kg of orally administered midazolam. Group B, consisting of 53.7% of the study's subjects, received 4mcg/kg of orally administered dexmedetomidine.

Parental Separation

With respect to the first question, which addressed whether subjects receiving orally administered dexmedetomidine exhibited better parental separation and acceptance of an anesthesia face mask as compared to oral midazolam, all 41 subjects were administered the Separation From Parents tool (Appendix C), a four-point scale used to measure the subject's willingness to separate from the parent(s) and/or legal guardian(s). Recalling the study design, subjects with scores of one or two on the four-point scale were considered to have had an acceptable separation from the parents immediately prior to the initiation of the surgical procedure; those subjects who were scored three or four were considered to have had difficult pre-procedure parental separations.

Group A had a total of 19 subjects, 16 (84.2%) of which demonstrated easy separation from parents based on observations and scoring on the Separation From Parents tool. The other three subjects in group A scored in each of the other three categories of the tool, for a total of 5.3% of the group A population in each category. Group B consisted of 22 subjects. Fourteen subjects (63.6%), of the group population experienced easy separation. Four of the subjects in Group B (18.2%), scored a two on

the tool, three subjects, 13.6%, scored a three, and one subject, 4.5%, scored a four, table 4. See appendix C for tool scoring.

After performing a Chi-Square test on the data obtained through the use of the Parental Separation Tool (Table 5), it was determined that the Chi-Square was not the best test for this data as calculation resulted in a Pearson Chi-Square value of only 2.728. Consequently, this would have left only six cells (75%) having an expected count of less than five, with the minimum expected count being 93%. Therefore, in conjunction with a statistical consultant, it was determined that the data needed to be transformed into two groups. Group one was comprised of subjects demonstrating: *Easy Separation*, scoring a one. Group two was comprised of both: *Whimpers + Cries but Not Clinging* and *Crying and Clinging*, scoring two, three or four.

The number of subjects for Group A and Group B remained unchanged, as well as the number of subjects with easy separation score of one. The number of subjects that scored a two, three, or four, in Group A totaled three (15.8%). Group B had a total of eight subjects (36.4%) that scored a two, three, or four (Table 6). This resulted in a total of 30 (73.2%) of the subjects being assigned to the first group as the result of being scored a one, and eleven (26.8%) of the subjects being assigned to the second group as the result of being scored a two, three, or four. This rearrangement allowed a new chi-square evaluation to be performed. The results of this assessment are contained in Table 7. A Pearson Chi-Square p-value of 0.138 and a Fishers Exact Test p-value of 0.173 were also obtained for this data. Based upon these outcomes, it was determined that there was no statistical significant difference in measured amount of distress related to

Table 4: Parental Separation Crosstabulation

			Describe the separation of the child from the parents				Total
			Easy Separation	Whimpers but is easily reassured not clinging to parent	Cries and can not be easily reassured, but not clinging to parent	Crying and clinging to parents	Easy Separation
Group	A	Count	16	1	1	1	19
		% within Group	84.2%	5.3%	5.3%	5.3%	100.0%
	B	Count	14	4	3	1	22
		% within Group	63.6%	18.2%	13.6%	4.5%	100.0%
Total		Count	30	5	4	2	41
		% within Group	73.2%	12.2%	9.8%	4.9%	100.0%

Table 5: Parental Separation Chi-Square Test

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2.728(a)	3	.435
Likelihood Ratio	2.888	3	.409
N of Valid Cases	41		

a) 6 cells (75.0%) have expected count less than 5. The minimum expected count is 0.93.

Table 6: Parental Separation Re-Crosstabulation

			Parent Separation Problems		
			No (parent separation =1)	Yes (parent separation =2,3,4)	Total
Group	A	Count	16	3	19
		% within Group	84.2%	15.8%	100.0%
	B	Count	14	8	22
		% within Group	63.6%	36.4%	100.0%
Total		Count	30	11	41
		% within Group	73.2%	26.8%	100.0%

Table 7: Parental Separation Chi-Square Test after Re-Crosstabulation

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.198(b)	1	.138		
Continuity Correction(a)	1.275	1	.259		
Likelihood Ratio	2.272	1	.132		
Fisher's Exact Test				.173	.129
N of Valid Cases	41				

a) Computed only for a 2x2 table

b) 0 cells (0.0%) have expected count less than 5. The minimum count is 5.10.

separation from parents between subjects in Group A who received orally administered midazolam as compared to the measured distress of subjects in Group B who received orally administered dexmedetomidine. It was not possible to determine if the observed differences between the subjects in each of these two groups was the result of chance rather than the result of the experimental influence introduced by the researchers.

There was one interesting finding in the parental separation data that required further analysis. Upon further review of the data, as seen in table 8, it was noticed that seven out of 11 (63.6 %) of the male subjects in group B (dexmedetomidine group) had parental separation scores two, three or four. This finding was contrasted with only one out of 10 (10%) of the male subjects in group A (midazolam group) experiencing parental separation problems. Although there were only 21 male subjects in the study, eight subjects in group A and group B combined demonstrated parental separation scores of two, three or four. As detailed in Table 9, the Pearson Chi-Square p-value comparing group A (midazolam group) and group B (dexmedetomidine group) was 0.11. The Fishers Exact Test was 0.24, which is less than 0.05, suggesting that there is statistical significance between the two groups. The next step was to assess a risk estimate between group A and group B. Table 10 shows that the male subjects in group B (dexmedetomidine group) were 15.75 times more likely to experience parental separation problems than the males in group A, midazolam group. This finding was not a part of this author's original research investigation, but proved to be interesting and supported the need for further research with a larger study population.

Table 8: Parental Separation Gender Crosstabulation

Gender				Parent Separation Problems		Total
				Yes (parental separation =2,3,4)	No (parental separation=1)	Yes (parental separation =2,3,4)
Male	Group	B	Count	7	4	11
			% within Group	63.6%	36.4%	100.0%
		A	Count	1	9	10
			% within Group	10.0%	90.0%	100.0%
	Total		Count	8	13	21
			% within Group	38.1%	61.9%	100.0%
Female	Group	B	Count	1	10	11
			% within Group	9.1%	90.9%	100.0%
		A	Count	2	7	9
			% within Group	22.2%	77.8%	100.0%
	Total		Count	3	17	20
			% within Group	15.0%	85.0%	100.0%

Table 9: Parental Separation Problems Gender Chi-Square Test

Gender		Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Male	Pearson Chi-Square	6.390(b)	1	.011		
	Continuity Correction(a)	4.318	1	.038		
	Likelihood Ratio	6.988	1	.008		
	Fisher's Exact Test				.024	.017
	Linear-by-Linear Association	6.086	1	.014		
	N of Valid Cases	21				
Female	Pearson Chi-Square	.669(c)	1	.413		
	Continuity Correction(a)	.036	1	.850		
	Likelihood Ratio	.672	1	.412		
	Fisher's Exact Test				.566	.421
	Linear-by-Linear Association	.636	1	.425		
	N of Valid Cases	20				

(a) Computed only for a 2x2 table
(b) 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.81.
(c) 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.35.

Table 10: Parental Separation Problems Gender Risk Estimate

Gender		Value	95% Confidence Interval	
		Lower	Upper	Lower
Male	Odds Ratio for Group (B / A)	15.750	1.424	174.246
	For cohort Parent Separation Problems Yes (parental separation =2,3,4)	6.364	.940	43.073
	For cohort Parent Separation Problems No (parental separation =1)	.404	.180	.907
	N of Valid Cases	21		
Female	Odds Ratio for Group (B / A)	.350	.026	4.654
	For cohort Parent Separation Problems Yes (parental separation =2,3,4)	.409	.044	3.816
	For cohort Parent Separation Problems No (parental separation =1)	1.169	.787	1.737
	N of Valid Cases	20		

Mask Acceptance

The Mask Acceptance Tool (Appendix A) is also a four-point scale used to measure the subject's willingness to accept the anesthetic mask from the nurse anesthetist once in the operating room. Consistent with the study design, the induction of anesthesia with each subject was preformed via face mask utilizing inhaled sevoflurane 6% in combination with 50% oxygen and 50% nitrous oxide. Subjects were observed to determine their resistance to accepting the anesthesia as delivered by face mask. Subjects observed and evaluated to have scored one or two on the four point scale were designated as having had a "satisfactory" acceptance of the anesthesia mask; scores of 3 or 4 were considered "unsatisfactory" (Shukrey 2005, & Weldon 1992).

Mask acceptance scores from each subject group A and B, were divided into two groups: (1) Excellent or Good and (2) Fair or Poor. In group A, 15 of 19(78.9%) of all subjects were evaluated to have displayed either good or excellent relative to anesthesia mask acceptance. In group B, 15 of 22 (68.2%) of all subjects were evaluated to have had scores of good or excellent relative to anesthesia mask acceptance. As identified in Table 11, 73.2% of the study's subjects were scored in the Excellent or Good range and 26.8% of the subjects scored in the Fair or Poor range. A Chi-Square analysis was performed on the Mask Acceptance scores (Table 12). A Pearson Chi-Square score p-value of 0.438 and a Fishers Exact Test p-value of 0.499 were calculated on this data. Results of this analysis evidenced no significant difference in acceptance of mask between subjects in Group A, who received orally administered midazolam, and subjects in Group B, who received orally administered dexmedetomidine. Once again, the evaluated

Table 11: Mask Acceptance Crosstabulation

			Subject's Acceptance of Mask		Total
			Excellent or Good	Fair or Poor	Excellent or Good
Group	A	Count	15	4	19
		% within Group	78.9%	21.1%	100.0%
	B	Count	15	7	22
		% within Group	68.2%	31.8%	100.0%
Total		Count	30	11	41
		% within Group	73.2%	26.8%	100.0%

Table 12: Mask Acceptance Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.602(b)	1	.438		
Continuity Correction(a)	.178	1	.673		
Likelihood Ratio	.609	1	.435		
Fisher's Exact Test				.499	.338
N of Valid Cases	41				

a) Computed only for a 2x2 table

b) 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.10.

results did not support the elimination of chance, rather than scientific manipulation, as the contributing factor resulting in the observed findings.

Emergence Delirium

The second question this researcher sought to answer was: Does orally administered dexmedetomidine affect the incidence and severity of emergence delirium in children aged one to six years having dental restoration, with or without dental extractions, as compared to orally administered midazolam for the same population undergoing the same procedures? To answer this question we administered the Pediatric Anesthesia Emergence Delirium Scale to the subjects. All 41 subjects were administered the test, see table 13. Group A, 19 subjects, had a mean score of 7.42 and group B, 21 subjects, had a mean score of 5.62. See Appendix D for tool and scoring information. There was a standard deviation in group A of 5.210 and in group B of 5.861. As seen in Figure 4, there was a slight skewing of the data, particularly in group B. The standard of error mean for group B was only 1.279 and group A was even lower with a mean of only 1.195. Even though group A had a higher mean PAEDS score, more testing was needed to determine whether or not the data was statistically significant.

A Levene's Test for equality of variances and a T-test for equality of means was performed on the data (see Table 14). Subsequently, equal variances were indicated by these results because Levene's Test for equality p-value was determined to be 0.877. After performing the independent t-test for equality of means between group A and group B, we found the p-value to be 0.313. This result supported the conclusion that there was

Table 13: PAEDS Group Statistics

	Group	N	Mean	Standard Deviation	Standard Error Mean
Total PAEDS Score	A	19	7.42	5.210	1.195
	B	21	5.62	5.861	1.279

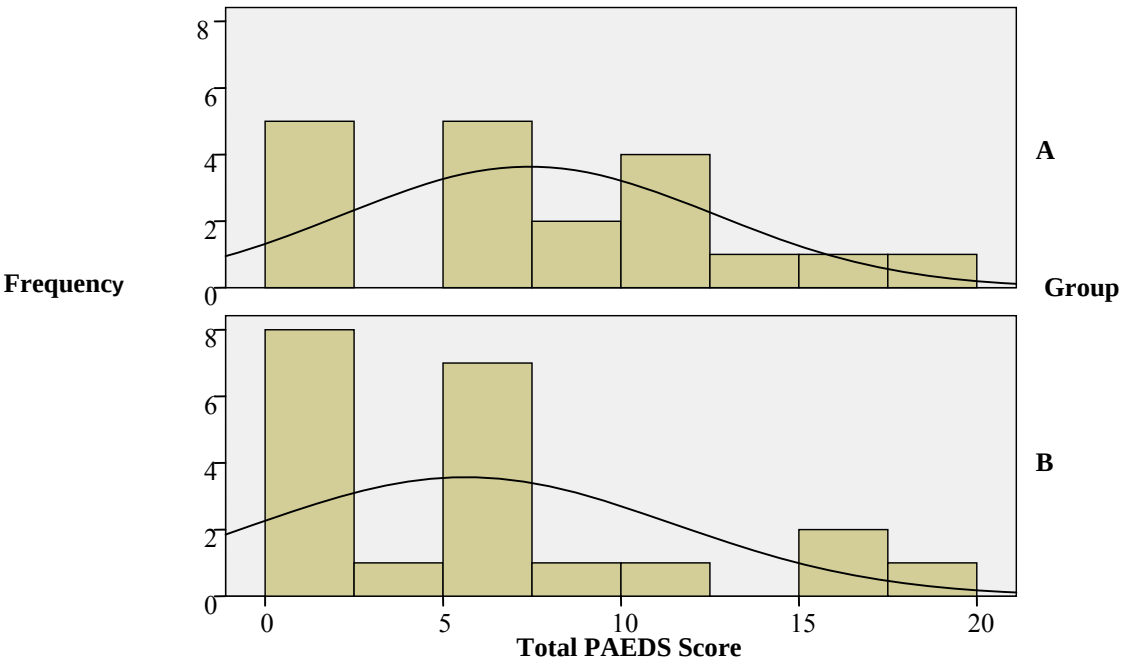

Figure 4: Description of Total PAEDS Score

Table 14: PAEDS Levene's Test and Independent t-test

		Levene's Test for Equality of Variances						
		F	Sig.	T	df	Sig. (2-tailed)	Mean difference	Std. Error Difference
Total PAEDS Score	Equal variance assumed	0.24	0.877	1.023	38	0.313	1.802	1.761
	Equal variance not assumed			1.029	37.992	0.310	1.802	1.751

(Assume equal variances because Levene's Test for Equality p-value = 0.877)

no statistical significant difference in the mean PAEDS scores between group A and group B, which could not be attributed to chance.

Chapter V

Discussion

According to Voepel-Lewis, Malviya, and Tait (2003), patients experiencing emergence delirium may exhibit one or more of the following signs and symptoms; nonpurposeful restlessness and agitation, thrashing, crying or moaning, disorientation, and incoherence. This phenomenon has been considered a common post-anesthetic problem in children and adults since its description in the literature in 1960. Although the exact cause of emergence delirium is not known, the observations made of pediatric patients emerging from anesthetics in this study were consistent with the literature, which has described some association between rapid emergence and awakening from anesthesia in a foreign environment and a higher frequency of emergence delirium (Cole, Murray, McAllister, & Hirshberg, 2002).

In this pilot study of 41 subjects, the investigator sought out to answer two unique questions:

1. Does orally administered dexmedetomidine promote better parental separation and acceptance of an anesthesia face mask as compared to orally administered midazolam?
2. Does orally administered dexmedetomidine lessen the incidence and severity of emergence delirium in children 1-6 years having dental restoration, with or without dental extractions, as compared to orally administered midazolam?

In search of the answers to the research questions posed, this author addressed the null hypothesis:

There will be no difference in the incidence or severity of emergence delirium as measured by the Pediatric Anesthesia Emergence Delirium Scale (PAEDS) in subjects aged one to six years who receive oral dexmedetomidine compared to subjects aged one to six years who receive oral midazolam as an anesthetic pre-medication prior to dental restoration, with or without dental extractions.

Although the size of this pilot study did not provide definitive answers to the research questions under investigation, the data collected did provide the groundwork for a larger future study. While the observations recorded as a result of this investigation were not generalizable to larger populations because of the small number of subjects in the pilot, the results observed were clinically significant and support the need for further investigation into the factors surrounding emergence delirium prevention in the pediatric population.

Confounding Variables

Several confounding variables were identified as the research study was conducted. These variables added to the difficulty in obtaining subject participation, data collection, and contributed to the overall consumption of time that this study required. The first variable was that the youngest patients were usually scheduled for surgery first on any particular day. This made patient acquisition only possible in the mornings. Having more surgeons involved with the study increased potential subject pool and required increasing the number of research assistants to alleviate this problem. This increased the potential for variation in subject scoreing and added threat to the validity of observed results, although this was considered a negligible threat.

Second, there was only one Anesthesiologist available to screen all patients preoperatively and to provide witness to informed consent required for subject enrollment and participation. This made it impossible to obtain consent on the first patient scheduled each day, as well as difficult at times to obtain consent at other periods through the day when the anesthesiologist was needed elsewhere for patient care. Having one anesthesiologist specifically dedicated to screening and witnessing of informed consent for the study would have greatly reduced or alleviated this variable.

Another variable that was identified in retrospect was related to the role of the research site pharmacy. Once a subject was consented and enrolled in the study, their information was faxed to pharmacy. It was only then that the research protocol specific medication was customized for each subject by weight and for their specific randomized study group. This process took upward of thirty minutes for each subject. The subject's preoperative medication was to be given upon the operating rooms call, thirty minutes before transport. Consequently, numerous would not show up on time and they would need to receive their preoperative medication immediately. These occurrences made the enrollment of many subjects impossible. Having a research dedicated pharmacist would have significantly decreased the waiting period encountered by researchers to receive the study drug preparations. Unfortunately, nothing could be done about the patient's tardiness and this factor was not anticipated by any of the members of the researcher's team.

Lastly, there were times when the data collector was with one subject while another subject needed to be screened and consented. Due to the lack of data collectors,

there were multiple subjects that the researchers were not able to provide an opportunity to participate in the study. Once again, while additional research assistants might have created additional confounding issues, having more research assistants would have helped to alleviate this fairly significant obstacle encountered by the research team.

Limitations

This study was specifically designed to eliminate several outside variables such as age, ASA classification, co-morbidities, type of operation, type of induction and maintenance of general anesthesia, intraoperative and postoperative pain control, the avoidance of anti-cholinergic medications, dental surgeon use of local anesthetic blocks for all root canals and extractions when acceptable, and the application of all tools by a trained research team member. Despite best efforts, there were some limitations that were identified for this study. First, there might possibly have been unanticipated individual varying responses to the prescribed anesthetic plan. However, this is always a possibility whenever human subjects are utilized in any research protocol. Next, both midazolam and dexmedetomidine were mixed in cherry syrup, which could have potentially changed the pharmacodynamics in some unknown manner; however this is only postulated and not supported by any of the scientific literature currently available to this author. Third, neither the Parental Child Separation tool nor the Mask Acceptance tool has undergone statistical testing for external validity or reliability, nor have they been statistically tested and validated to accurately and reliably measure parental separation anxiety or willingness of subjects to accept the anesthetic mask. Lastly, the greatest limitation to this study was its subject pool size. With only 41 subjects,

generalizations are unable to be made to the general population. This study was, however, able to bring to light certain data that justifies further future research investigation with a larger study population to better allow greater generalizability beyond the confines of the pilot study subjects.

Strengths

The strengths of this study included the fact that it was a double blinded and randomized study. The code, which protected the pharmacologic intervention, was only known to the pharmacy staff and none of the other staff, including anesthesia providers, surgeons, nurses, and researchers, had access to the code key unless specific safety breaches were declared which would have mandated aborting the investigation for the subject involved and supplying any necessary intervention for rescue and stabilization. Fortunately, no such aborting or rescue was required of any subjects involved in this investigation. Randomization of the subjects was obtained by a computer generated randomization table, thus inhibiting any bias for drug selection by any of the staff or research team. As stated above, multiple outside variables were identified and negated prior to the start of the study. Each research team member was trained in data collection and the use of each tool. The training, as stated in Appendix K, was carried out consistently for each participant and accomplished with video simulation of tool application as well as the use of seven case studies (Appendix L) that were unique to the application of each one of the three tools used in this investigation. At the time of enrollment of the twentieth study subject, two team members scored the subject with all three tools simultaneously. Only the designated team member's scores were recorded,

but it allowed the team to validate the application of the tool in the correct manner through a modified inter-rater reliability exercise. Although, at times it proved to be a weakness of the study, utilizing a small research team allowed there to be a greater amount of consistency in the application of the three tools across the spectrum of all 41 subjects that participated in the study and from whom data was collected.

Conclusion

Although Emergence Delirium is often a neglected topic in the field of anesthesia, the occurrence of this phenomenon can have detrimental effects for individuals undergoing anesthesia intervention, as well as their care givers and the families. The findings in this pilot study were not statistically significant, however, the data obtained through the implementation of this study identified areas that need to be further expanded upon and studied in much greater numbers. Currently it is unknown exactly what causes emergence delirium. The goal of this research investigation was aimed not only at examining measures to aid in the prevention of ED, but ultimately to also bring awareness to an often dismissed occurrence in the anesthesia community.

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APPENDICES

Appendix A

Acceptance of Mask Tool

1. excellent (unafraid, cooperative, accepts mask readily)
2. good (slight fear of mask, easily reassured)
3. fair (moderate fear of mask, not calmed with reassurance)
4. poor (terrified, crying combative)

Time of Mask_____

Appendix B

ASA Physical Status Classification

http://www.asahq.org/clinical/physicalstatus.htm

ASA Physical Status Classification

PSC I	A normal healthy patient
PSC II	A patient with mild systemic disease
PSC III	A patient with severe systemic disease
PSC IV	A patient with severe systemic disease that is a constant threat to life
PSC V	A moribund patient who is not expected to survive without the operation
PSC VI	A declared brain-dead patient whose organs are being removed for donor purposes

Appendix C

Parental Child Separation Tool

1. easy separation
2. whimpers but is easily reassured, but not clinging
3. cries and cannot be easily reassured, but not clinging to parents
4. crying and clinging to parents

Time of Separation_____

Appendix D

Pediatric Anesthesia Emergence Delirium Scale

1. The child makes eye contact with the caregiver

   (4) not at all (3) just a little (2) quite a bit (1) very much (0) extremely

2. The child's actions are purposeful

   (4) not at all (3) just a little (2)quite a bit (1) very much (0) extremely

3. The child is aware of his/her surroundings

   (4) not at all (3) just a little (2)quite a bit (1) very much (0) extremely

4. The child is restless

   (0) not at all (1) just a little (2)quite a bit (3) very much (4) extremely

5. The child is inconsolable

   (0) not at all (1) just a little (2)quite a bit (3) very much (4) extremely

Time of ED_____ End of ED_____

Appendix E

Informational Letter

Children's Hospital Research Study

Children's Hospital wants to make waking up from anesthesia more comfortable for children. We are doing a research study on a medication, dexmedetomidine. This medicine is very safe because it does not slow down breathing. Dexmedetomidine provides pain relief and sedation, which we believe will help children wake up more comfortably. The information provided here will help you decide if you would like your child to be a part of this study.

About 20% of children having surgery wake up crying, thrashing about, and are out-of-control. This is called emergence delirium and may be harmful. It may cause them to pull out their IV tubing, to have more pain or to get an injury. If this happens we treat this condition with medicine and comfort measures like swaddling, holding gently, pacifier and going to parent early if able. Emergence delirium is caused from the anesthesia medicine used to put children to sleep, not from children being bad.

The medicine we use now, midazolam, works very well to relax children before surgery but does not help when they are waking up. Based on studies, we believe dexmedetomidine will help children relax before surgery and wake up with less chance of emergence delirium. Once your child is admitted to the hospital floor we will ask if your child can be in this study. If you agree, your child will either receive midazolam or dexmedetomidine to drink before surgery. The research nurse will follow your child to surgery and to the recovery room.

The research nurse will record how your child is when:

- leaving you.
- breathing the gas in the operating room.
- waking up.

Your child will be watched at all times to be sure he or she is safe.

Dexmedetomidine has been used safely in children when given in the vein. But it has not been studied when given by mouth. This is why Children's Hospital is doing research about it.

MOST COMMON SIDE EFFECTS

Dexmedetomidine (study medicine)	Midazolam (medicine we use now)
Blood Pressure Changes	Headache
Nausea & Vomiting	Drowsiness
Fever	Blood Pressure Changes
Heart rate Changes	Nausea &Vomiting
	Confusion
	Not Remembering
	Coughing

Thank you for thinking about helping out with this research. Your child will not be included unless you sign the research consent form before surgery. No personal information will be published with this research. If you have questions after you read the consent, please ask the research nurse or the anesthesiologist (doctor who puts people to sleep for surgery).

Linda Smithson (phone-541-8510)

Appendix F

Informed Consent

STUDY NUMBER_____
GROUP_____

East Tennessee Children's Hospital
University of Tennessee College of Nursing
Parental Permission for My Child to Act as a Subject in an Experimental Study

THE EFFICACY OF ORAL DEXMEDETOMIDINE AS AN ANESTHETIC PRE-OPERATIVE MEDICATION AND AS A DETERRENT TO EMERGENCE DELIRIUM

I. Purpose of the Study:
Your child is being asked to participate in a clinical research study being conducted by Children's Hospital and The University of Tennessee College of Nursing. The purpose of the study is to determine if giving dexmedetomidine orally reduces the rate and severity of emergence delirium (ED). Emergence delirium causes children to wake up from anesthesia crying, screaming and uncontrollable. It can cause harm to the children, like causing them to pull out their IV tubing, causing more pain, or causing an injury. This condition happens in about 20% of young children having anesthesia and is treated with medicine in the recovery room. Even if it does reduce the rate of ED, oral dexmedetomidine would not be beneficial if it is not a good pre-operative medicine like the one we use now, which is midazolam. Therefore the study will also measure if dexmedetomidine works as well as midazolam to relax your child before surgery. Anxiety will be measured by how your child separates from you at the operating room door and how your child accepts the anesthesia mask.

Procedures to be Followed:
Study subjects will be randomly assigned to receive either dexmedetomidine or midazolam in outpatient surgery for their pre-operative medicine before going to surgery. This will be done using a computer chart of numbers. A research nurse (RN) will follow your child to the operating room and recovery room.
The research nurse will record how your child is when:
leaving you.
breathing the gas in the operating room.
waking up.

Your child will be watched at all times to be sure he or she is safe.

A limited amount of general information that is important to the study, like age, previous surgery, medications etc. will be recorded. The dental surgeons are only indirectly involved in the study by allowing their patients to participate.

The information gathered will be assigned a study number. The key that identifies the subjects name will be locked in the anesthesia office. The data will be kept in the research files and not your child's medical chart. Upon publication there will be no patient identifiers used.

Potential Risks of Participation in the Study:
The most common side effects of dexmedetomidine are nausea and vomiting, blood pressure changes, heart rate changes, and fever. The most common side effects of midazolam are not remembering, headache, drowsiness, confusion, coughing, blood pressure changes, nausea and vomiting. Midazolam is used on most patients now and provides good relaxation. The study will determine if dexmedetomidine provides as much relaxation. A risk may be that the patients getting dexmedetomidine will not be as relaxed before surgery. The approximate cost of one dose of midazolam is 1/3 the approximate cost of the dexmedetomidine. This increased cost billed to the patient may be offset because less pain medicine may be needed after the subject receives dexmedetomidine.

Potential Benefits:
Your child may have less risk for emergence delirium if he/she receives dexmedetomidine. If your child experiences emergence delirium, it may be less severe after getting dexmedetomidine. The information obtained from this study will be used to benefit future patients. No financial reward will accompany acceptance to participate.

Alternative Therapy:
If for any reason you decide not to have your child participate in this research study, your child will receive the same care that other children having dental surgery with general anesthesia receive. Participation is voluntary. This study does not affect any other health care your child is receiving, and there are no penalties to you or your child if you decline to participate.

Confidentiality of Study:
The information obtained by this study will be held strictly confidential and disclosure to third parties other than those noted below is prohibited. Under federal privacy regulations, you have the right to determine who has access to your child's personal health information (called "protected health information" or PHI). PHI collected in this study may include your child's medical history, the results of physical exams, lab tests, x-ray exams, and other diagnostic and treatment procedures, as well as basic demographic information. By signing this permission form, you are authorizing the researchers at East Tennessee Children's Hospital and the University of Tennessee to have access to your child's PHI collected in this study and to receive your child's PHI from facilities where your child has received health care. In addition, your child's PHI may be shared with other persons involved in the conduct or oversight of this research, including the

Department of Health and Human Services (DHHS). The Institutional Review Board (IRB) at East Tennessee Children's Hospital and the University of Tennessee may review your child's PHI as part of its responsibility to protect the rights and welfare of research subjects. Your child's PHI will not be used or disclosed to any other person or entity, except as required by law, or for authorized oversight of this research study by other regulatory agencies, or for other research for which the use and disclosure of your PHI has been approved by the IRB. Your child's PHI will be used only for the research purposes described previously in this form. Your child's PHI will be used until the study is completed.

You may cancel this authorization in writing at any time by contacting the principal investigator listed in this form. If you cancel the authorization, continued use of your child's PHI is permitted if it was obtained before the cancellation and its use is necessary in completing the research. However, PHI collected after your cancellation may not be used in the study. If you refuse to provide this authorization, your child will not be able to participate in the research study. If you cancel the authorization, then your child will be withdrawn from the study. Finally, the federal regulations allow you to obtain access to your child's PHI collected or used in this study. However, in order to complete the research, your access to this PHI may be temporarily suspended while the research is in progress. When the study is completed, your right of access to this information will be reinstated.

Liability:
There will be no payment to you or your child for their participation in this study, and no payment for treatments or injury resulting from participation in this study.

Research Related Inquiries:
You may contact Mark Cramolini, MD at 865-541-8485 or Linda Smithson, MSN, RN at 865-541-8510 with any questions related to this research study.

Patient Rights Information:
General questions concerning your child's rights as a participant in research protocols or questions about research related issues may be addressed to the Institutional Review Board Chairman, East Tennessee Children's Hospital through his secretary at (865) 541-8477 or through the University of Tennessee Office of Research at (865) 974-3466.

Voluntary Participation Statement:
Participation in this study is voluntary. There will be no penalty or loss of benefits for declining to participate, and you may withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled.

Parental Permission:
I have received a copy of this permission form. I certify that I have read the above permission form and that I have received satisfactory explanations of the potential risks

and benefits. I willingly volunteer and give my permission to allow my child to participate in this study.

_____
Patient Name

_____ _____
Signature of Parent Date

_____ _____
Signature of Parent Date

_____ _____
Signature of Person Obtaining Consent Date

Appendix G

Demographic Information Form

Oral Dexmedetomidine Pre-Op Study Demographic Information

Study Number:_____

Name:

E Number:

M Number:

Date:

Age:

Gender:

Race:

Allergies:

Medical Problems:

Previous surgery:

Anesthesia Problems:

Medications:

Appendix H

Pre-operative Dosing Protocol

Emergence Delirium with Dexmedetomidine vs. Midazolam

Pre-operative Dosing Protocol

1. Verify consent for participation in study
2. Verify no allergies to dexmedetomidine, clonidine, midazolam, other benzodiazepines or red dye.
3. Pharmacy will provide a supply of pre-operative oral medication labeled “ED Study Drug-A” and “ED Study Drug-B”.
4. Check which study drug patient is to receive: Patients whose study consent has an “A” at the top get the study drug labeled “A” and those with a “B” on the consent get the study drug labeled “B”
5. The dose of the study drug is 0.25 milliliters/kg with a maximum dose of 10 milliliters
6. Study patients should never receive atropine or any anti-cholinergic medication.
7. Should any reaction occur that you suspect may be an adverse reaction to the study drug, notify the study personnel. If the anesthesiologist decides it is needed, the identity of the study drug can be revealed by the pharmacy.

Appendix I

Anesthesia Protocol

Emergence Delirium with Dexmedetomidine vs. Midazolam

Anesthesia Protocol

1. Mask induction with Sevoflurane, oxygen, and nitrous oxide
2. Change to maintenance Isoflurane as soon as possible
3. Maintain spontaneous ventilation as possible
4. If ventilatory support is required, avoid muscle relaxant, if possible
5. Avoid drugs with anti-cholinergic properties: atropine, glycopyrrolate, meperidine, pancuronium bromide, etc. (to avoid confusion between emergence delirium and anticholinergic toxicity)
6. Maintain anesthetic with isoflurane, oxygen and nitrous oxide.
7. Give every patient ondansetron 0.2 mg/kg and decadron 0.25 mg/kg as soon as convenient at the beginning of the case (for anti-emesis)
8. Use fentanyl 1-2 micrograms/kg for narcotic analgesia
9. Ask dentists to use local anesthetic blocks for all root canals and extractions (and as usual, record that they have done so on the anesthesia record).
10. Finally (and obviously), abandon any of the above guidelines/restrictions if needed for safety of the patient, and let study personnel know.

Appendix J

Extubation Criteria

(Sahn, & Lakshminarayan, 1973)

1. Resting minute ventilation of greater than ten liters
2. The ability to voluntarily double the resting minute ventilation
3. Peak negative pressure on maximal inspiration of greater than 30cm of water
4. Forced vital capacity greater than ten to fifteen ml/kg

Appendix K

Teaching Plan

TEACHING PLAN

1. The Co-PI's (Brian Mountain and Linda Smithson) will show the RA's the tools and explain how to use them. The symptoms of emergence delirium, anxiety on separation from parents, and anxiety when receiving anesthesia from the mask will be explained.
2. The RA's will practice scoring a scenario that has been video-taped for that purpose and discuss it with the Co-PI.
3. The Co-PI's will develop case studies to be used with video-taped scenarios.
4. The case studies will be videotaped.
5. Each member of the research team will view the videos and read the scenarios related to the parent/child separation scale, mask acceptance scale and emergence delirium.
6. The member will then score each case study with the scale.
7. The Co-PI's will grade the scores and discuss the results with the team member. 100% reliability is the goal.
8. A Co-PI and RA or two RA's will score a subject together so that all RA's are re-graded during the study. If there is a variance the variance will be rectified in the subject data and the RA will be re-trained**.**

Appendix L

Case Studies

Case Study 1

As a 6-year-old child separates from his parents he starts to cry. The mother gives him kiss and says she will see him soon. The transporter tells him they are going on a little trip, he will need to lie on back, and will see his parents really soon. The child stops crying and lies back in bed. As they go through the doors to the surgery hallway, he waves to his parents.

Case Study 2

As a 3-year old child is about to go into surgery, his mom is holding him at the surgery doors while he stands in the bed. The mom says that she will see him really soon and he needed to lay down now. The transporter says that they are going on a special trip and will take him on a ride. The child starts crying and clinging onto him mom. She tries to make him lie down but he starts screaming and grabbing tightly to his mom.

Case Study 3

As the CRNA applies the mask to a 6-year old oral surgery patient, he tells him it smells a lot like bubble gum. He tells the child to just breathe normal. The child lies there quietly and is induced without incidence.

Case Study 4

In the OR, the CRNA tells a 4-year old oral surgery patient that he will smell bubble gum in the funny looking mask. The child starts to cry a little and pushes the mask away. The CRNA asks him if he would like to hold it. The child gingerly takes the

mask and smells it. He says it smells funny. With minimal time passing, the child is induced easily.

Case Study 5

In the PACU, you are watching a 2-year old child recover from oral surgery. As the child first awakens, she starts crying and asking for her mommy. She starts crying louder and is pulling at an IV placed in her forearm. She is trying to sit up in bed and the RN tries to console her and tell her she can see her mommy really soon. She sits the bed up a little and the child opens her eyes and looks at the RN. She continues to cry. The RN asks if she is hurting and she says yes. Medication is given per orders. The child settles down and stops crying.

Case Study 6

As a 6-year old begins to awaken from surgery in the PACU, he tries to sit up and slide out the side of the bed. The RN slides him back into bed. He immediately starts to cry and swing his arms. As he does this he also wipes his arm against his surgically repaired nose and mouth causing bleeding. Another RN comes over to help control the child and protect his safety. The RN asks him to open his eyes, and he fails to respond. He continues to scream and kick in bed. He eventually tries to stand up in bed and another RN and the surgeon have to come over to try to stabilize him. The administer pain medicine 2 times and reach the maximum dose. Each time he calms down for 30-45 seconds and repeats his same actions.

Case Study 7

As a 5-year old begins to awaken from surgery in the PACU, he tries to sit up and slide out the side of the bed. The RN slides him back into bed. He immediately starts to

cry and swing his arms. As he does this he also wipes his arm against his surgically repaired nose and mouth causing bleeding. Another RN comes over to help control the child and protect his safety. The nurse administers pain medicine and he calms down and lies back in bed. After approximately 5 minutes he opens his eyes and asks for his mommy. The nurse assures him that he will see her really soon.

Vita

Brian Wesley Mountain was born in Jacksonville, North Carolina on June 15, 1979. He graduated from Columbia Central High School in 1997. He attended Carson-Newman College, located in Jefferson City, Tennessee, where he received his Bachelor in Science in Nursing in 2002. Upon graduation and passing nursing boards, he worked in the cardiovascular intensive care unit as a registered nurse. He was an active member in the AACCN and on multiple committees within the hospital.

After working as a cardiovascular critical care nurse for four years, Brian is currently pursuing his Master's in Nursing, with a concentration in Nurse Anesthesia, at the University of Tennessee in Knoxville, Tennessee. While in the Nurse Anesthesia Concentration, Brian has been an associate/active member of the American Association of Nurse Anesthetist (AANA), Tennessee Association of Nurse Anesthetist (TANA), Sigma Theta Tau, and the National Association of Scholars Honor Society. He has been named to the Chancellor's List and the National Dean's List. He has attended multiple AANA meetings as the Student Representative for the University of Tennessee Nurse Anesthesia Concentration while participating in the AANA Student Mentoring Program. In 2008, he was named the AANA Program Director's Student Researcher of the Year for his research entitled, "The Efficacy of Oral Dexmedetomidine as an Anesthetic Pre-operative Medication and as a Deterrent to Emergence Delirium".

His presentations include the following**:** "Emergence Delirium-A Review of the Phenomenon and Current Interventional Thought" at the Tennessee Association of Nurse Anesthetist 2006 Annual Meeting, "Hypothermic Circulatory Arrest" at the University of Tennessee College of Nursing, Nurse Anesthesia Concentration Basics of Anesthesia

Class, Defense of thesis for Master of Nursing entitled "The Efficacy of Oral Dexmedetomidine as an Anesthetic Pre-operative Medication and as a Deterrent to Emergence Delirium", "The Efficacy of Oral Dexmedetomidine as an Anesthetic Pre-operative Medication and as a Deterrent to Emergence Delirium" at the American Association of Nurse Anesthetist 2008 Annual Meeting. Future plans include a job in Knoxville, Tennessee as a nurse anesthetist after graduation on August 18, 2008.