

Study Protocol with SAP

Study Title: Effectiveness of Healing Touch on Sleep, Pain, Anxiety, Anesthesia Emergence, Satisfaction and Cost of Care in Surgical Patients

Brief Title: The Effect of Healing Touch on Sleep (Sleep 7)

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TITLE: Effectiveness of Healing Touch on Sleep, Pain, Anxiety, Anesthesia Emergence, Satisfaction and Cost of Care in Surgical Patients

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PROTOCOL SIGNATURE PAGE

The signature below provides the necessary assurances that this trial will be conducted according to the stipulations of the protocol, including all statements regarding confidentiality. This is in compliance with the principles outlined in applicable US Federal regulations and Good Clinical Practice Guidelines (ICH E6 Section 4.5.1, 6.2.5, and 8.2.2)

Michele M. Gottschlich, PhD

Site Investigator's Name (please print)

Michele Gottschlich

Site Investigator Signature

April 1, 2015

Date Signed

List of Abbreviations

Adverse Event	AE
American Academy Sleep Medicine	AASM
Analysis of Variance	ANOVA
Area under the Curve	AUC
Case Report Form	CRF
Center for Clinical and Translational Science and Training	CCTST
Cincinnati Children's Hospital Medical Center	CCHMC
Complementary and Alternative Medicine	CAM
Common Terminology Criteria for Adverse Events	CTCAE
Cost-to-Charge Ratio	CCR
C - reactive protein	CRP
Dehydroepiandrosterone	DHEA
Electroencephalography	EEG
Electromyogram	EMG
Electronic Medical Record	EMR
Electrooculogram	EOG
Food and Drug Administration	FDA
Fast Fourier Transform	FFT
Generalizing Estimating Equations	GEE
Healing Touch	HT
Health Insurance Portability and Accountability Act	HIPAA
Institutional Review Board	IRB

Intensive Care Unit	ICU
Intravenous	IV
Multiple Imputation	MI
National Cancer Institute	NCI
National Center for Complementary and Alternative Medicine	NCCAM
Observational Pain Assessment Scale	OPAS
Pharmacodynamics	PD
Pharmacokinetics	PK
Polysomnography	PSG
Post Anesthesia Recovery Unit	PACU
Principal Investigator	PI
Private Health Information	PHI
Rapid Eye Movement	REM
Same Day Surgery	SDS
Shriners Hospitals for Children	SHC
Standard Operating Procedure	SOP
Statistical Analysis Software	SAS
Total Sleep Time	TST
Wake After Sleep Onset	WASO

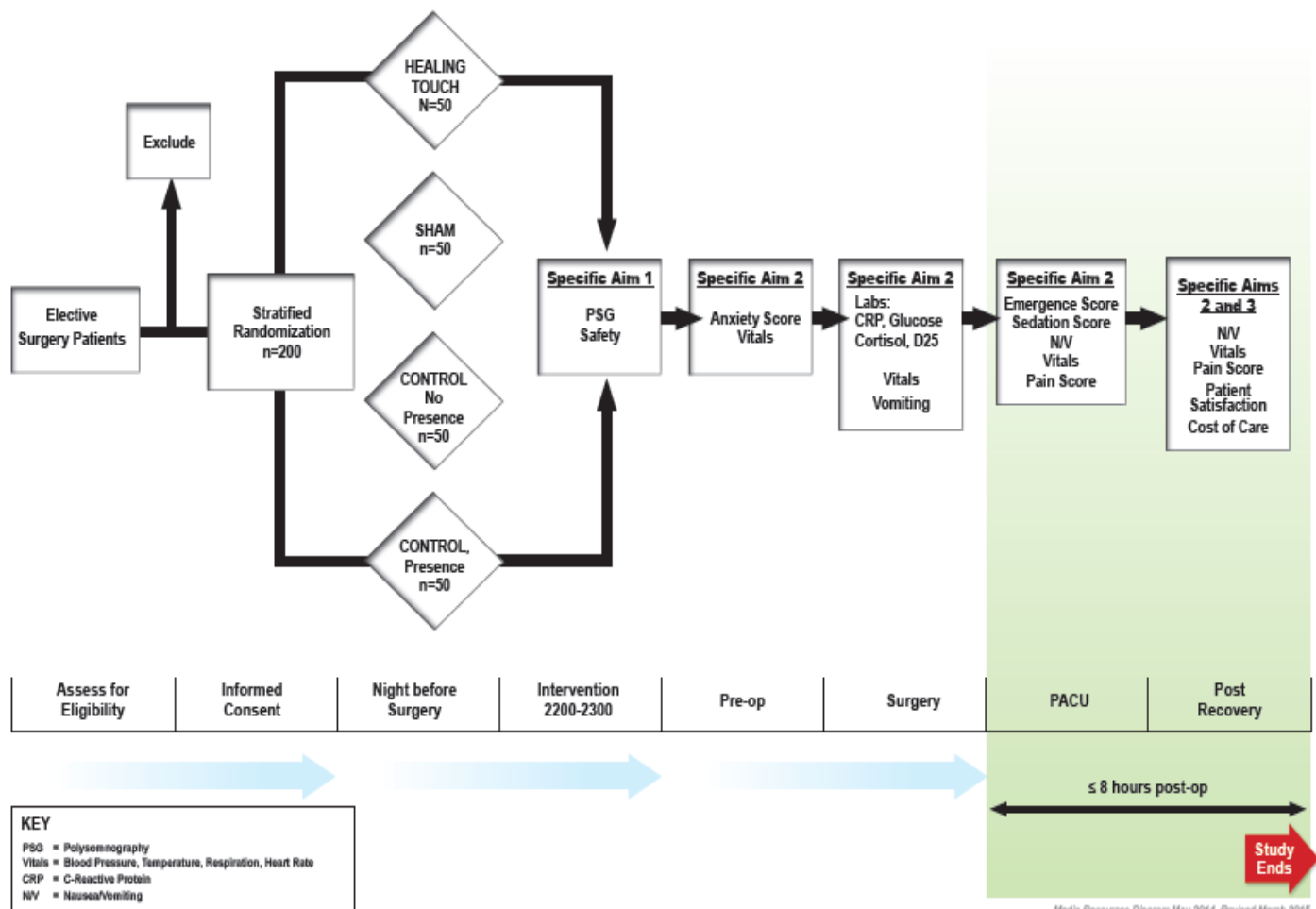
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STUDY SUMMARY

Title	The Effectiveness of Healing Touch on Sleep, Pain, Anxiety, Anesthesia Emergence, Satisfaction and Cost of Care
Population:	5-25 years; admitted for an elective surgery procedure
Number of Subjects	200
Study Duration	Study duration is from approximately 9 pm (when the electrodes are applied for the sleep test) the evening prior to surgery through no more than 8 hours after surgery the following day.
Study site(s)	Shriners Hospital for Children, Cincinnati
Objectives	<p>We hope to learn the following:</p> <ul style="list-style-type: none"> • Determine if Healing Touch improves the quality and quantity of patient sleep the night before surgery • Define any side effects associated with Healing Touch • Establish the value of Healing Touch on the patient's pain, stress, anxiety and recovery from anesthesia. • Determine if Healing Touch is associated with measures of patient satisfaction and cost of care.
Statistical Methodology	Bivariate comparisons will be used to evaluate differences in baseline variables between Healing Touch and control groups (ex. age, gender and race, also type of surgical procedure e.g. burn versus other reconstructive procedure). These latter variables are potential covariates for secondary analysis. Analysis of variance (ANOVA) or Kruskal-Wallis test and Chi-square analysis will be used for these comparisons. Similarly, the association between outcome variables and baseline variables will be examined; correlation and ANOVA or Kruskal-Wallis will be used as appropriate.

Sleep 7 – Study Design Schematic



Media Resources Diagram May 2014, Revised March 2015

1.0

Introduction

1.1 Background

Tension between art and science is fueling insurgency against mainstream medicine as the general public, patients, caregivers and health care professionals alike are integrating complementary and alternative medicine (CAM) into wellness routines and treatment practices with increased frequency.¹ From acupuncture to zinc, the portfolio of CAM options is blossoming as evidenced by the formation of the National Center for Complementary and Integrative Health (NCCIH) within the National Institutes of Health (NIH).² Energy medicine is one of five domains of CAM recognized by NCCAM.³ It is based on the concept that there is universal energy, the human energy field is subject to imbalances, and a therapist can re-pattern the disrupted field by using compassionate intent to channel healing energy into a person to improve health.

Energy-derived healing such as healing touch (HT) is based on principles of quantum physics that humans are energetic organisms that occupy a physical space.⁴ We create heat, generate electricity and even have a measurable magnetic field. Many integrative medicine practitioners believe that we have specific energy vortices that control the flow of subtle energy in the body (referred to as chakras) and that energy travels through the body along vertical pathways called meridians. Layers of energy within and surrounding the body are important for health and well-being. Disease and injury are believed to be related to disturbances in the chakras, meridians and energy fields.⁵⁻¹⁰ In theory, HT uses noninvasive hand techniques to balance human and environmental energy disturbances, remove biofield blockages, restore innate healing forces and reactivate the mind-body-spirit connection.^{6,7,9,10}

Bioenergy healing is controversial. Whereas the art of HT has long been established, only recently has science begun to explore the bioenergy healing realm; hence definitive proof of its clinical value is sparse. There is however, good scientific evidence to indicate that bioenergy fields exist.^{4,5,11} Yet neither the ability to manipulate these energies by thought or intention, nor the existence of chakras and meridians have been conclusively proven. This lack of knowledge makes it difficult for professionals to respond to the voluminous testimonials of success. Without evidence that either supports or refutes the benefit(s) of energy medicine, health fraud and quackery will prevail. The problem is serious. Unproven remedies may be harmful and waste money, and using ineffective practices may prevent people from getting necessary medical treatment.

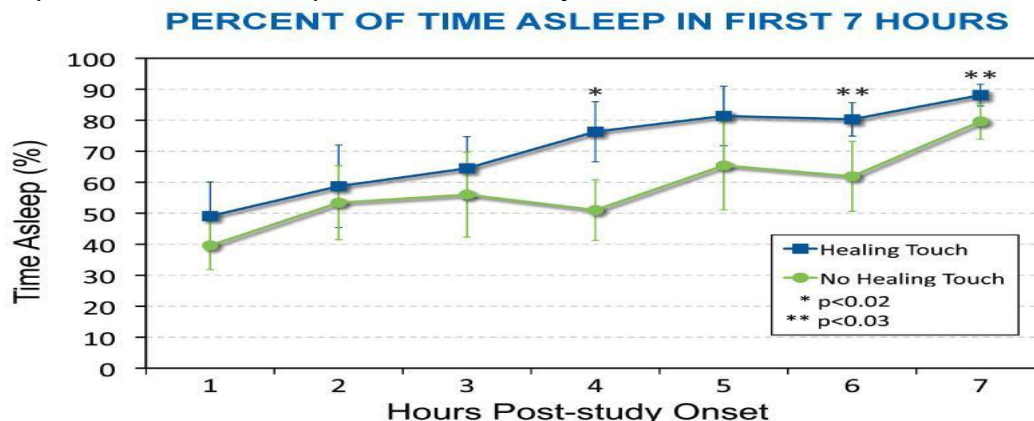
The clinical efficacy of HT within conventional medical science appears to be in 5 main areas: reduction of anxiety/improvement in mood/well-being,¹²⁻²⁰ relief of pain,^{15,16,19-24} hastening of wound healing,²⁵⁻²⁷ immune modulation^{28,29} and improvement of sleep.^{20,22,30,31} Much of the research demonstrating benefit has employed observational approaches (qualitative studies, case studies or patient satisfaction measures) rather than experimental design. However a few rigorous studies exist, such as the randomized trial²⁰ that demonstrated burn patients receiving HT compared to sham treatment had reduced pain scores after 5 days of treatment.

Whereas estimated incidence of insomnia in the general population is 10 to 20%,³⁹ sleep deprivation is present in nearly every critically ill burn patient⁴⁰

and ranges between 20 – 40% in children multiple years following injury.^{31,41-43} The cause of pervasive degradation of sleep quantity and quality in acutely injured patients is multifactorial, including nocturnal treatment interruptions and medication side effects.^{33-35,41,43-50} Physiologic deterrents to sleep include the wound itself and the metabolic response to injury and infection.⁴⁴⁻⁵³ Psychological stress such as pain and anxiety disturb sleep.⁵⁴⁻⁵⁷ Sounds associated with patient care, monitoring equipment, infusion pumps, phones, pagers, television and conversation as well as room light interfere with sleep and body rhythms normally entrained by daylight and darkness.^{44,46,47,49-74} More difficult to explain is the finding that sleep disruption continues post discharge, long after the wound has healed.^{31,41-43,75-79} The chronic nature of postburn and/or postsurgical dyssomnia is unsettling in view of its insidious effects on quality of life, wound healing and health. Experts in sleep medicine have also demonstrated significant psychological consequences of sustained sleep inadequacy and sleep fragmentation. Sleep disturbances predispose individuals, especially children, to heightened anxiety, attention-deficit hyperactivity disorder, impaired memory, reduced cognition and poor social integration.⁸⁰⁻⁸⁵

Sleep deficiency is of concern because insufficient restorative sleep is an added stressor to the patient and may be a potential impediment to recovery.^{46,86} Achieving adequate sleep represents an unmet need during hospitalization. We speculate that re-establishing normal sleep patterns will help to accelerate patient recovery from the metabolic and psychological abnormalities commonly associated with surgery and ultimately improve well-being. The significance of this study is that it will establish the efficacy of HT as a therapeutic intervention for improving sleep in hospitalized children during the perioperative period as well as characterize electroencephalographic energetics associated with HT using a prospective, randomized blinded design.

Because clinical and pharmacological modulation of postburn sleep disturbance has been largely ineffective,^{32-38,87,88} we explored the utility of HT as a potential sleep intervention. The investigation involved 10 children undergoing burn reconstructive care.³¹ Patients were studied an average of 7.2 ± 2 years postburn. Subjects were randomized to HT versus no HT treatment using a 2 period crossover design. Data revealed that HT had a significant effect on both the quantity and quality of sleep. Total sleep time (TST), sleep efficiency, stage 2 sleep (N2) and number of REM periods were significantly enhanced with HT. The percent of time asleep increased during the first 7 hours, which suggests that HT had an extended effect on the parameters being examined beyond that incurred during the HT procedure. Findings of remarkable HT benefit³¹ provide the impetus for this follow-up confirmation study.



EFFECT OF HEALING TOUCH ON SLEEP

VARIABLE	HEALING TOUCH NIGHT N=10	NON-HEALING TOUCH NIGHT N=10	p-value
Total sleep time	391 (251, 476)	331 (268, 373)	.02
Sleep efficiency	76 (53, 90)	66 (55, 78)	.04
Sleep latency	8.4 (2.8, 34.9)	17.2 (13.5, 48.0)	.20
Awakenings	32 (25, 38)	30 (23, 32)	.42
Wake after sleep onset	99 (46, 210)	107 (53, 194)	.77
REM periods	4.5 (2.0, 5.0)	3.5 (2.0, 4.0)	.03
N1 minutes	26 (21, 32)	28 (18, 30)	.83
N2 minutes	213 (136, 236)	160 (107, 204)	.03
N3 minutes	63 (29, 93)	34 (8, 120)	1.0
REM minutes	83 (62, 91)	60 (40, 86)	.20
N1 % norm	212 (174, 241)	304 (197, 531)	.11
N2 % norm	110 (103, 136)	123 (85, 132)	.23
N3 % norm	67 (44, 110)	49 (31, 125)	.43
REM % norm	95 (82, 101)	86 (47, 116)	.73
Efficiency % norm	80 (56, 94)	69 (58, 83)	.04

Data shown as median (25th, 75th percentile)

Taken together, our extensive prior work characterizes significant dyssomnia following injury. Sleep disturbances are long term in nature with widespread health implications for children recovering from burns. Compared with a normal population, seriously burned patients (both acute and rehab/outpatients) demonstrate significant sleep disturbance manifested by decreased total sleep time, frequent arousals, impaired sleep efficiency, nightmares and deficient stages of 3+4 and REM sleep. The pathophysiology underlying postburn sleep deprivation is clearly multifaceted and has not been fully elucidated. Our investigations have led to breakthrough preliminary findings demonstrating the possible clinical efficacy of HT as a sleep intervention.³¹

1.2 Rationale and Risks/Benefit

1.2.1 Rationale: Our work is unique because no one has ever related electroencephalography (EEG) recordings of energy to HT. Healing touch may prove useful in the treatment of refractory sleep disorders common during recovery and could lead to widespread application worldwide in terms of its development as a safe, economical and non-invasive procedure that promotes sleep, physiological restoration and psychological well-being. Such findings would dovetail nicely with the Affordable Care Act as America transitions to value based care, requiring the adoption of therapies that emphasize lower costs and improved quality of life.

1.2.2 Risks/Benefit: This study involves no more than minimal risk. There may not be direct benefit noted for study subjects; information from this study may influence the care of surgical populations in the future. This information is communicated to participants/consenting parents/legal guardians upon study introduction and is noted upon consent. The risks of this study are minimal; however, the potential for HT therapy to promote sleep and improve postoperative morbidity in elective surgery populations is novel and significant.

2.0 Objectives:

There is a fundamental gap in understanding how the energy-based, CAM approach of HT can be used to maximize health and improve recovery following disease or injury. Whereas the art of HT has long been established, there has been a recent explosion in its integration as a therapeutic intervention. However, proof of its mechanistic action and clinical value is lacking. Our long-term goal is to expand the capacity for improved

medical care and enhanced quality of life of children and young adults in alignment with the Affordable Care Act which emphasizes value and reduced health care spending. The objective of this study is to develop foundational scientific evidence that validates efficacy of a standardized HT intervention designed to promote sleep, a proven integral component of repair and recovery. These data are critical to advance the science and practice of HT, ultimately providing understanding of how this type of CAM can make a positive contribution to patient care. Our central hypothesis for this investigation is that HT generates improvement in a recipient's sleep in association with electroencephalographic changes. We formulated this hypothesis on the basis of strong preliminary data demonstrating that HT has a positive impact on PSG outcomes. We further postulate that HT and its associated increase in restorative sleep will benefit common sources of preoperative stress and/or postoperative anguish (e.g. anesthesia emergence, pain, anxiety, nausea). With recognition that well-designed clinical trials of HT are sparse; secondary objectives of this application are to produce cost to benefit information and to determine if patient satisfaction is enhanced by the addition of HT.

- 2.1 The *primary objective* of this study is (Aim 1) to determine the safety and efficacy of healing touch intervention on improving measures of sleep.

With recognition that our original work demonstrating deficits in sleep and quality of life outcomes in hospitalized children, this prospective randomized trial will examine a new method for improving sleep. We postulate that HT will safely modulate changes that favor enhanced restorative sleep outcomes measured by PSG variables such as total sleep time (TST), sleep efficiency, sleep stages and time awake after sleep onset (WASO).

- 2.2 A *secondary objective* of this study is to establish the value of HT on perioperative management of surgery-related outcomes (Aim 2).

The intent of this aim is to evaluate the impact of HT on distress preceding surgery as measured by anxiety, pain, and laboratory indices of stress. This investigative aim will also assess the effectiveness of HT postoperatively in management of anesthesia emergence, sedation, anxiety, and pain reflected by clinical, psychometric and medication measures of well-being as well as track the incidence of postoperative nausea/vomiting. Upon completion of this study objective, it is expected that important information will be provided that determines whether HT intervention can mediate clinical improvement and comfort measures.

- 2.3 An additional secondary objective is to examine measures of patient satisfaction and cost of care associated with HT (Aim 3). There is a need to ensure the value of healthcare services. Therefore, in addition to safety/efficacy considerations, additional key determinants of quality-based surgical care include patient satisfaction and financial outcomes. We will connect satisfaction and cost findings to clinical outcomes, with the goal of providing an objective interpretation of benefits and costs. These essential steps will justify (or contest) the value of HT services within the framework of perioperative clinical practices.

- 2.4 The rationale of selection of outcome measures (sleep, surgery- related outcomes, patient satisfaction and cost of care) is that Healing Touch is expected to provide an inexpensive, non-invasive method that will prosper as a safe and efficacious adjunctive preoperative treatment.

3.0 Subject Selection:

- 3.1 Inclusion Criteria
 - 3.1.1 5 years to 25 years of age
 - 3.1.2 Scheduled for an elective operative procedure
 - 3.1.3 Written informed consent and HIPAA release signed by parent or legal guardian; assent as appropriate
- 3.2 Exclusion Criteria
 - 3.2.1 History of anoxic or suspected brain injury
 - 3.2.2 History of head injury within the last year
 - 3.2.3 Face/head phenomena that prevents proper placement of PSG leads
 - 3.2.4 No informed consent or HIPAA release
- 3.3 Inclusion of Gender and Minorities
 - 3.3.1 Entry into this study is open to patients of both genders and all ethnic backgrounds.
- 3.4 Subject Recruitment, Enrollment and Consent Process
 - 3.4.1 Study specific recruitment cards, a 1 page flyer and also a patient education brochure describing healing touch will be used for marketing. Patients requiring surgery will be invited to participate by receiving recruitment information in person and/or via a mailing of related study materials to their home. Before surgery, a staff member from Patient Access may encourage patient or caregiver to look for study information when they receive their study packet mailing (per script). This will occur during the normal preoperative phone call. In addition, a study co-investigator may contact patients or caregivers) per script who are identified as potential candidates. Once study information has been reviewed by the patient/family, and the patient/family is agreeable to participate in the study, a study co-investigator will work with scheduling personnel to plan research admission the evening before elective surgery.
 - 3.4.2 Informed consent will be obtained from the participants and/or their legal guardians by trained staff authorized to consent for this study.
 - 3.4.2.1 The conversation is expected to include a thorough discussion of what is expected to happen during the study, risks and benefits of the planned therapy, and any possible alternatives.
 - 3.4.2.2 The family will be given a copy of the signed consent form.
 - 3.4.2.3 For participants who are less than 18 years of age, some of these participants are able to give assent and others are too young. If it is determined that a participant is able to give assent (generally children 11 years or older), the consenting staff will attempt to explain the study at both the participant's and the legal guardian's comprehension level.

4.0 Study Design/Procedures:

- 4.1 General Design
 - 4.1.1 Elective surgery patients will be prospectively assigned to treatment group using single blinded stratified randomization. A cross-over trial was considered but because our prior work suggests that HT has an extended carryover and thus an effect on outcome,³¹ we felt this would not be an appropriate approach. If HT is performed before the non-HT period, there could be residual HT effects manifested during the non-intervention period.

A single blinded stratified random block randomization scheme⁸⁹ will be generated by the study statistician (LJ) who will conceal group assignment from the blinded polysomnography technician and blinded board certified sleep physician as well as the blinded biostatistician (JK) who will analyze the data. Intervention assignment will also not be conveyed to the study subject/caregiver(s). The stratification is based on possible influential variables grouping for age (5 to 11, >11 years) and also acuity (levels 1 and 2) whereby level 1 is defined as same day surgery and observation (e.g. patients are technically never admitted as inpatient). Level 2 represents patients admitted for ≥ 24 hours and therefore assigned an inpatient encounter of surgical procedure. Also carefully considered was the study design; the blinding and suitable control groups.⁹⁰⁻⁹⁶ Following screening per inclusion/exclusion criteria and upon verbal agreement to participate, 200 subjects will be randomly assigned to receive one of four interventions: healing touch, sham, control no presence, or control presence. The subjects will not be informed of group assignment. No study procedures will be performed until written informed consent (and assent as appropriate) is obtained. The consenting process will take place in a private area. The investigator will ask open-ended questions of the consenting parent(s)/assenting subjects regarding study methods to determine level of comprehension. The consent process including consenting parents/assenting subjects verbalization of understanding of the study will be documented in the medical record.

This is a prospective, randomized trial with 4 treatment groups: Healing touch (active intervention, focused intention) will be performed by certified HT practitioner. Our pilot work revealed a HT effectiveness covariate to be therapist stress e.g. divorce (unpublished findings) therefore prior to each HT procedure, the practitioner will complete a stress survey. No interpretation of survey results will be made relative to the assigned therapist performing HT. The HT practitioner will be entered into the model as a fixed effect. Rather, the survey score will be examined during data analysis to determine if stress is an effector of HT effectiveness. HT will begin per standardized HT methodology⁹⁷ at approximately 2200 on the night prior to surgery. The HT practitioner will have the appearance of listening to music using a headset that is not connected to a media player. Before onset of HT, the subject will be encouraged to relax while lying down. The HT practitioner will perform self-centering exercises at the patient's bedside in order to center or quiet the practitioner's own mind, creating an atmosphere devoid of anxiety so the practitioner can focus compassionately and with full presence. Once centered, the practitioner uses three techniques in conjunction with approximately 60 minutes of soft background music during the study intervention: 1) *Magnetic clearing* (approximately 10 minutes) which cleanses the subject's energy field to assist in releasing emotional debris and feelings of fear, anger, worry and tension. The practitioner does the energy clearing by making 15-30 full length smooth, gentle, continuous passes (usually downward and outward direction) with both hands one to six inches from the patient's body. 2) *Mind Clearing* (approximately 10 minutes) used for relaxation and to focus or quiet the patient's mind. It consists of the practitioner's hands placed lightly on or above specific sites around the head, neck, forehead and face with the intention of balancing the right and left sides of the brain. 3) *Full Body* (Chakra) Connection (approximately 20 minutes) connects, opens and balances the energy centers to enhance the flow of energy in the body. The hands are placed on the ankle and knee, then knee

and hip, then the same sequence is repeated on the other leg, then both hips, then at the root chakra (between the legs, off the body about 12 inches away) and lower abdomen, then at the lower abdomen and solar plexus, then the solar plexus and spleen area, then the heart (mid chest) and solar plexus, then the heart and thymus, then at the wrist and elbow, then the elbow and shoulder, then the other arm, then both shoulders, then the neck and brow, then the brow and top of the head, and then the top of the head and about 12 inches above the head. The next morning, the HT practitioner will extend healing and compassionate thoughts to the subject from a remote location as the subject prepares for surgery.

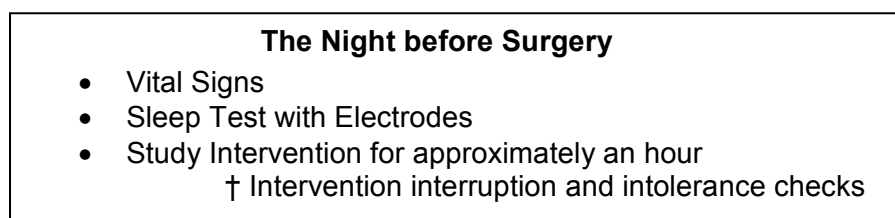
Sham (placebo treatment) session will also be conducted at comparable time and duration as the active intervention and with analogous environmental conditions including presence of identical soft background music. The sham HT aide will be engaged with the subject yet has no experience with or knowledge about healing touch. The standardized clinical encounter will appear to be similar to the active treatment and the well-trained sham aide will interact with the patient in accordance with a standardized, choreographed mock routine involving body motions that mimic HT. There will be no positive intent or patient contact; instead the sham aide will silently count backward from 100 to 1, continuously repeating this sequence during the entire sham procedure while listening to music from portable compact media player with ear phone headset with the purpose of distracting the sham aide's mind so that compassionate thoughts are circumvented.

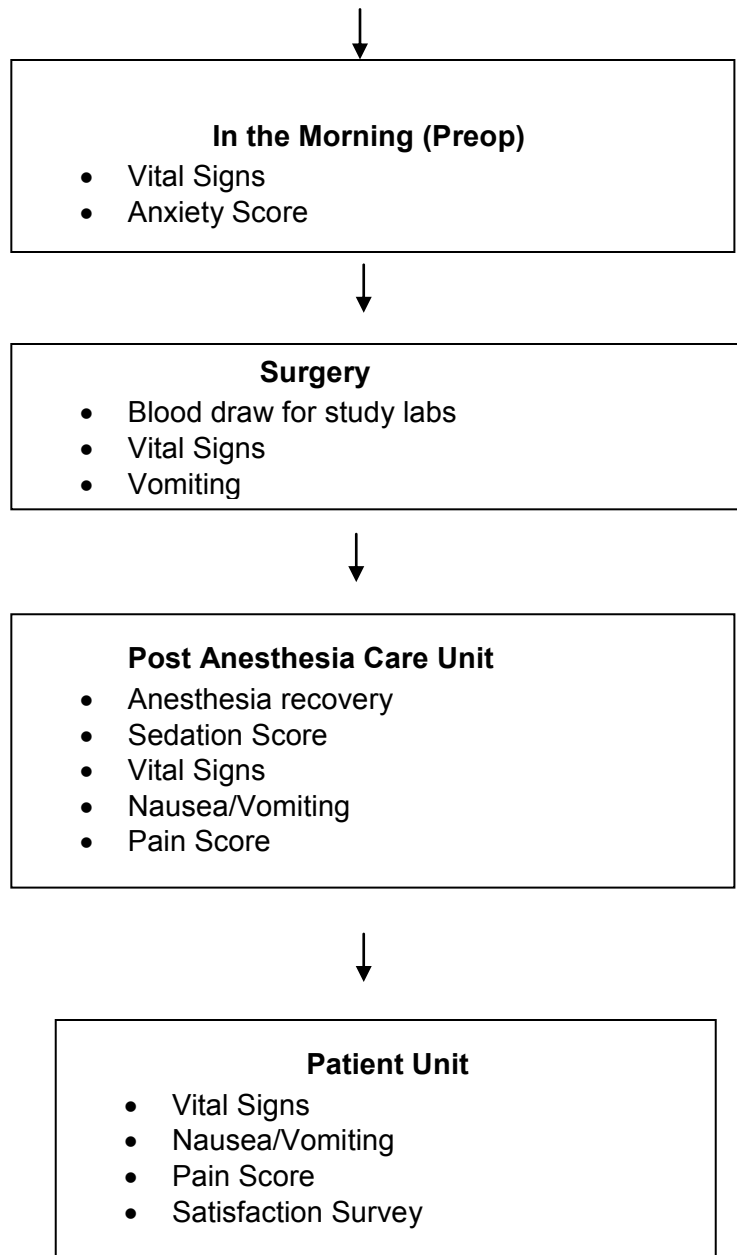
Control presence whereby a research aide who is not familiar with HT will be present in the patient's room from approximately 2200 – 2300. The research aide will not engage/interact with the research subject. A staff nurse will inform the patient that the aide is not permitted to converse with the subject. The aide will quietly sit in a corner of the patient's room, listening to media player using earphones similar to that described during active intervention. Identical soft background music to that used during active intervention will be audible to the patient during the approximate 1-hr study period.

Control no presence involves no study aide presence in the room. A course of soft background music identical to intervention groups will begin at approximately 2200.

The sleep technician will document that an experimental procedure was performed and note any unexpected occurrences (interruptions, HT side effects) at the end of the 1 hour intervention/control period using the demos/safety CRF.

- 4.1.2 Study duration is from approximately 9 pm (when the electrodes are attached for the sleep test) the evening prior to surgery until 8 hours after surgery the following day (unless patient is discharged earlier than 8 hours postop).
- 4.1.3 A description of the sequence and duration of the study procedures are summarized in the below diagram:





4.2 Study Procedures

PSG will be performed the night before surgery. PSG (Sandman ELITE Sleep System, Natus Medical Inc, Buffalo NY) will include simultaneous nocturnal recording of EEG, electromyogram (EMG), electrooculogram (EOG), respiration, heart rate, oxygen saturation, video and audio recordings and body movement in 30-second epochs. Subjects will be connected to PSG at approximately 2100 with recordings from approximately 2200 until 0600 the following morning (unless patient has an early surgery time). Soft music will play for approximately 60 minutes in all groups after the sleep machine is turned on.

In an effort to assure concealment of group allocation during scoring of the sleep data, scoring will be delayed for approximately one month following study intervention. In addition, the video will be turned off during the first hour of

scoring performed by the registered sleep technologist. The American Academy of Sleep Medicine's (AASM) newly released guidelines, The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications⁹⁸ will be used for scoring and interpretation of sleep stages. PSG provides comprehensive summary reports of sleep stages and also generates sleep latency, TST, WASO, arousals and sleep efficiency measures. Narong Simakajornboon MD, Director of the CCHMC's Hospital Sleep Disorders Center and board-certified sleep specialist, blinded to experimental conditions, will perform the specialized data interpretation. A copy of the sleep test report will be provided to study participants.

Patients will have vital signs (temperature, respiration, heart rate, blood pressure) assessed prior to the sleep study and repeated preoperatively (the morning of surgery). Vital signs and vomiting will be assessed in the operating room. Vital signs, and pain score (using an observational scale⁹⁹ [OPAS] and/or numeric rating [1-10 scale] as appropriate) will be assessed post-operatively both upon arrival to the post-anesthesia care unit (PACU) and before PACU discharge. Vital signs, and pain score will also be recorded upon arrival to post-recovery patient room and at discharge. Nausea and vomiting will be assessed in the PACU and in the post-recovery patient room. Minutes in the OR, PACU and patient room (time from arrival until discharge) will be recorded.

Laboratory parameters (C-reactive protein, glucose, cortisol and D25) will be obtained (from approximately 5 mL of blood) in the operating room. Since there is a strong argument that HT reduces stress and anxiety, the results of this study could provide data demonstrating improved hormonal balance following HT intervention. There also exist reports linking sleep with metabolism of glucose and vitamin D.

An anxiety test (Yale Preoperative Anxiety Scale) will be obtained preoperatively (in patient unit prior to preoperative meds and repeated in the preoperative surgery area).¹⁰⁰ Anesthesia emergence score, sedation score and nausea and vomiting will be assessed in the PACU.¹⁰¹⁻¹⁰³ Incidence of nausea and vomiting in the post recovery patient room (on the floor) will also be recorded.

A patient satisfaction survey will be administered post recovery that includes questions specific to the HT procedure, sleep and also includes four questions identical to that contained in Press Ganey Pediatric Inpatient survey (questions B5, D4, K3 and I9; <http://www.pressganey.com/>) to assess contentment with overall inpatient care.

Implicit in the definition of economic consequences of healing touch, we will also collect select utilization and cost outcome measures including total charges from admission to study discharge as well as charges specific to the Post Anesthesia Recovery Room. Labor cost of HT, length of stay in recovery room (number of minutes), length of hospital stay (number of hours) and medications administered for sleep, anxiety, pain, itch, nausea, vomiting and anesthetics during the defined study period all have high cost implications and thus will be examined as well.

5.0 Subject Safety

- 5.1 Patients will be closely monitored by clinical investigators via the Sleep 7 Data Safety Monitoring Plan as well as comply with the SHC-Cincinnati Safety Monitoring Process for Clinical Research CR 6.10 standard operating procedure whereby Adverse Events, Serious Adverse Events, Unexpected Adverse Events and Expected Adverse Events are defined therein.
- 5.2 Subject Risk
- 5.2.1 No extraordinary risks are expected with this investigation. The risks explained below are reasonable given the expected benefits described herein.
- 5.2.2 Healing Touch Procedure - There are no known safety concerns. Rare side effects include emotional outbursts, muscle spasm, restlessness, dizziness and headache. Empirical explanation for such responses: recipient release of stagnant blocked energy resulting in outburst or physical jerks; hours later the subject may express a cathartic outcome (unpublished data, Lois Cone 3-5-15).
- 5.2.3 Polysomnography - Risks associated with PSG include possible difficulty sleeping and local skin irritation from electrode placements.
- 5.2.4 Venipuncture - The risks from blood draw of study labs include: commonly, the possibility of discomfort and/or bruise at the site of needle stick and, less commonly, the formation of a small blood clot or swelling of the vein and surrounding tissue, and bleeding from the needle stick site.
- 5.3 Safety Assessment
- 5.3.1 Healing Touch Procedure - We seek to document the safety of HT bioenergy therapy as a modality contributing significant benefit with minimal to no risk to the patient. As such, each subject's tolerance to the healing touch procedure will be monitored. Safety assessment includes observing the patient for emotional outburst(s), muscle spasms, restlessness, dizziness, or headaches during the bioenergy, sham and control/presence nights. The safeguards and/or precautions that will be taken to avoid risks and discomforts are that study staff will monitor tolerance during the HT intervention and document any noted symptoms or complaints before, during, and immediately after the intervention. The HT session will be stopped as needed. Results from the satisfaction survey will also be examined for tolerance.
- 5.3.2 Polysomnography - The known minimal risk of participation in this study (ie - risk reaction to PSG leads) and other postulated tolerance risks will be monitored. The safeguards and/or precautions that will be taken to avoid risks and discomforts from the sleep study include that study staff will monitor tolerance during the sleep study; testing will be stopped as needed; an experienced, licensed sleep study specialist will attach the electrodes to the face/head areas.
- 5.3.3 Venipuncture - Experienced medical personnel will be responsible for obtaining the blood sample, prior to surgery.
- 5.3.4 To the extent that Shriners Hospitals for Children® (SHC) provides medical services at its facility, care for these rare (and speculated) side effects will be at no cost to the family. Although not anticipated, any intolerance noted to the HT, PSG and/or venipuncture procedure(s) will be documented; and depending on severity, may precipitate study withdrawal.
- 5.3.5 This study involves no more than minimal risk. There is no direct benefit noted for study subjects; however, information from this study may influence the care of surgical populations in the future. This information is communicated to

participants/consenting parents/legal guardians upon study introduction and is noted upon consent.

5.4 Serious Adverse Event (AE) Reporting

5.4.1 In accordance with our study specific safety monitoring plan as well as the SHC-Cincinnati Safety Monitoring Process for Clinical Research CR 6.10 SOP, patients will be closely scrutinized by clinical investigators for AEs. Even though there are no known serious side effects reported with HT therapy, subjects will be screened for dizziness, headache, and restlessness prior to the intervention/control session. In addition, subjects will be evaluated during the HT, sham and control/presence groups for emotional outburst, muscle spasm and restlessness during the study intervention time as well as any changes in the status of dizziness or headache following the study intervention period. Continued monitoring will occur until end of study (up to 8 hours postoperatively) to assess for persistent treatment effect.

5.4.2 Any Serious **and** Unexpected AE and Grade 3 or above, with a reported causality of “possible,” “probably,” or “likely” must be reported to the Study PI and Medical Staff Co-Investigator in an expedited method.

5.4.3 All reported AEs will be classified using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.

5.4.4 Each AE is associated with a grade. Grade refers to the severity of the AE. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity based on this general guideline: Grade 1 = mild, Grade 2 = moderate, Grade 3 = Severe, Grade 4 = Life-threatening or disabling, Grade 5 = Death.

5.4.5 Grade 4 or 5 events must be reported to Study PI within 24 hours with written documentation of the event filed within 7 days of the event.

5.4.6 CCHMC’s IRB must be notified of any Serious **and** Unexpected adverse event within 7 days.

5.4.7 Study PI will ensure that SHC home office and all applicable regulatory organizations are notified per regulatory guidelines.

5.4.8 Study PI will notify all participating investigators of any reported SAE associated with the trial.

5.5 Annual Reporting

The principal investigator will report all other safety events to the CCHMC IRB consistent with current institutional policy/SOP. Serious AEs that do not meet the criteria for expedited reporting as well as non-serious adverse events will be reported at the time of submission of annual IRB Progress Reports. Likewise, minor deviations will be reported in annual reporting to the CCHMC IRB. All other reportable events will be conveyed to the CCHMC IRB office, in summation form, at the completion of the study.

6.0 Data Handling and Record Keeping

6.1 The specific variables involved in data collection are detailed under study procedures and reflected in CRFs as well as within the listing of Sleep 7 source documents.

6.2 Data collection for this study will primarily be through an online data management system housed on SHC servers. Members of the SHC research team will enter data into SHC system with unique user IDs and passwords. All secure web-based information transmission is encrypted and complies with HIPAA security guidelines and 21 CFR 11.

6.3 Confidentiality and Security

- 6.3.1 Information about study subjects will be kept confidential and managed according to the requirements of HIPAA.
- 6.3.2 Access to data collected for this study is limited to study investigators.
- 6.3.3 In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use Private Health Information (PHI), attempts should be made to obtain permission to collect at least vital statistics (i.e. that the subject is alive) at the end of their scheduled study period.
- 6.4 Source Documentation
 - 6.4.1 Source data are contained in source documents. Examples of original documents and data records specific to this study include: hospital records and PSG reports.
 - 6.4.2 When observations are entered directly into a computerized system, the electronic medical record (EMR) or other electronic record (ex. PSG) is the source document. Examples of EMR source documentation specific to this study include: patient demographics, medication records, time in PACU, vital signs, pain scores, and laboratory parameters.
 - 6.4.3 Select data will be recorded directly on case report forms. These forms will be used as “source documentation” and include the intervention safety assessment, HT practitioner stress survey, the preoperative data collection form and HT satisfaction survey.
 - 6.4.3.1 All data requested on the CRF must be recorded.
 - 6.4.3.2 All missing data must be explained.
 - 6.4.3.3 If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”.
 - 6.4.3.4 If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black or blue ink.
 - 6.4.3.5 If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.
- 6.5 Record Retention
 - 6.5.1 Clinical research records will be retained per SHC standard operating procedure on *Clinical Research Records Retention (MR-002)*.
- 6.6 Laboratory Specimens
 - Lab tests (CRP, glucose, cortisol and vitamin D25) will be processed and managed by SHC Laboratory Medicine.

7.0 Quality Control and Quality Assurance

- 7.1 Internal auditing will be performed quarterly to ensure that the data are accurate, consistent, complete and reliable and in accordance with ICH GCP guidelines and 21 CFR 11.
- 7.2 The study PI will assess the audit worksheet, classify type of discrepancy and develop appropriate action plan.

8.0 Statistical Considerations

- 8.1 All data will be managed and analyzed using SAS® Version 9.3 (SAS Institute, Cary, NC) unless otherwise stated for specialized analysis. Demographic and summary data will be compiled and entered into the SAS research database by a

trained data manager. The database has been in use for 14 years; it will be adapted for data entry specific to the new project. The database is stored on SHC's dedicated network drive. The network is security- and backup- protected by SHC information systems on a daily basis. In addition, the individual study files are password protected. The programs are run by the statistician and verified by a research investigator. Prior to embarking on any analysis, variables will be checked for outlying values. Distributional properties of the continuous variables will be examined and any transformations necessary for analysis considered. Bivariate comparisons will follow, to look at differences in baseline variables between HT and control groups (ex. age, gender and race, also length of time and type of surgical procedure e.g. burn versus other reconstructive procedure). These latter variables are potential covariates for secondary analysis. Analysis of variance (ANOVA) or Kruskal-Wallis test and Chi-square analysis will be used for these comparisons. Similarly, the association between outcome variables and baseline variables will be examined; correlation and ANOVA or Kruskal-Wallis will be used as appropriate.

8.2 The first approach for a clinical trial is usually intent-to-treat analysis. In the case of a missing end-point, where possible, the subject will be assigned to the "worst" possible value. However, this is not feasible for our sleep outcomes. A second approach would be to include those subjects with outcome data, complete case analysis. Last observation carried forward is also commonly used, but this method can be biased, but will be examined. Multiple imputation (MI) methods have been proposed^{92,104,105} and may be superior, but are not without problems, mainly bias with respect to missing data. In case the missing mechanism is not missing completely at random,¹⁰⁶ we will conduct a missing data analysis to address the question of bias. If the missing mechanism depends on group assignment (HT, sham or one of the control groups) or other demographic variables, we will estimate the bias using logistic regression. Bias adjusted analyses would then be conducted using the inverse of the estimated probability of being missing as the weighting factor. We will be able to do this by applying a weighted generalized estimating equations (GEE) method.¹⁰⁷ Thus we will use MI or weighted GEE method as appropriate, as well as complete case analysis. In general, it will be appropriate to use generalized linear random effects mixed model for analysis. This will allow for repeated nature of the outcome variables, and specification of the appropriate link function, dependent upon the type of outcome variable. SAS PROC GENMOD may be used for these analyses and using PROC GLIMMIX would also allow invocation of the GEE method if required. As mentioned above, bivariate relationships between outcome variables and independent variables will be examined; this will also be in preparation for consideration of any secondary analyses incorporating covariates and confounders. Variables considered as potential covariates in an initial model will either be those considered clinically significant irrespective of the statistical association and those associated with the outcome and independent variable of interest at $p < 0.15$. Inclusion in final models will depend upon statistical significance ($p < 0.05$) or effect of removal of the variable on the beta coefficient ($> 10\%$ change) on the independent variable of interest. Age and gender will be considered clinically meaningful and will be retained in the model independent of statistical significance.¹⁰⁸

8.3 Primary Study Endpoints

8.3.1 Statistical Analysis (Primary Objective)

The primary treatment endpoint for Aim 1 will be generated from PSG. Group comparisons will be made for total sleep time, sleep efficiency, REM, WASO and spectral analysis of C3/C4 delta waves, using a generalized linear random effects model. Secondary analyses will involve adding appropriate covariates to the

model. Age and gender will be retained. Potential covariates include prior experience with HT, medication usage, frequency of random disturbances (such as parents or other caregivers entering the room, cell phones) and number of prior surgical procedures. The same approach will be used to examine hormones, anesthesia emergence, anxiety, and pain scales (Aim 2), the advantage is that the appropriate link function may be applied and we can account for the repeated nature of the design.

Power Analysis

Variable Median (25 th , 75 th percentile)	Healing Touch night N=15	Non-Healing Touch night N=15	p-value
TST minutes	400 (302, 442)	366 (287, 396)	.09
Sleep efficiency %	80 (61, 90)	78 (56, 82)	.07
WASO minutes	72 (47, 160)	85 (82, 181)	.60
REM minutes	86 (62, 93)	63 (40, 97)	.30

The measures targeted are TST, sleep efficiency, REM sleep and WASO. This Table shows data from a pilot cross-over study (median and 25th and 75th percentile) for the sleep variables of interest for 15 study subjects. In order to see the HT group with longer TST than the other groups, we will need a sample size of 50 per group for 80% power to detect a difference of 35 minutes, standard deviation of 70, assuming a 2-sided test and type I error rate of 0.016 to account for multiple testing. Similarly for sleep efficiency, we hypothesize a difference of 2% whereas in a previous study we observed a difference of 10%.³¹ Using the sample size of 50 per group we would be able to detect a difference of 7% with a standard deviation of 15, 2-sided test and type I error rate of 0.016, to account for comparing HT to the 3 control groups. Because the percentages depend upon another time dependent variable, the power is based on REM minutes. Using REM minutes, 50 subjects per group would enable us to detect a 15 minutes difference in REM sleep, assuming a standard deviation of 30, power of 80% and a 2-sided test. For WASO, with an assumed standard deviation of 50, a type 1 error rate of 0.016, a power of 80% and a 2-sided test, a difference of 25 minutes will require 50 subjects in each group, producing a total sample size of 200 subjects.

8.3.2 Statistical Analysis (Aim 2)

Analysis will follow the general approach and then the same specific approach as described for Aim 1, looking at differences in outcomes among groups utilizing generalized linear models. Using this methodology we will be able to examine the differences over time baseline to post recovery, examining the change between time points adjusting for baseline and the interaction between time and group. The secondary approach would examine the difference among groups adding covariates,

accounting for age, gender and other potential covariates such as number of prior surgeries, length of time in surgery and type of surgery (burn related or other).

Using our validation information for the OPAS pain assessment scale¹⁰⁷ with 48 subjects per group, we have a power of $\geq 80\%$ to detect a reduction in pain scale of 0.4 given the standard deviation of 0.52, using a type I error rate of 0.016 (to account for the multiple testing) and 2-sided test. Given the 0.3 difference in pain reduction between preverbal and nonverbal in the validation study, the expected difference appears reasonable. Similarly using prior work performed at our hospital¹⁰³ which examined the rate of postoperative nausea and vomiting after reconstructive burn surgery, with 46 subjects per group we would have 80% power to detect a difference of 69% in the control versus 40% in the HT group with a 2-sided test and type I error rate of 0.05. However after accounting for the multiple testing, using type I error rate of 0.016, the power is reduced to 70% with the 50 subjects per group estimated for the proposed study. Turner et al²⁰ reported on pain after dressing change in older adolescents and adults. In their randomized trial of therapeutic touch; a 23% decrease in anxiety was detected in the intervention group. If we assume that we will see this level of decreased anxiety in the HT group compared to the control and also assume an effect size of 0.7 and a type I error of 0.16, the 50 subjects per group (estimated for Aim 1) would yield 85% power for our analysis of anxiety.

8.3.3 Statistical Analysis (Aim 3)

The data analytic plan will follow that established for Aims 1 and 2 using a general linear model and use of the appropriate link function dependent upon outcome. Satisfaction variables are notoriously skewed in distribution and so may need to be dichotomized for analysis. Data analysis will be performed in a blinded fashion with regards to the subject and any group assignment. The analysis of cost will include examination of cost to charge ratio (CCR). Because cost fluctuates over time, the annual cost to charge ratio (obtained from Shriners Headquarters) will be used to calculate and apply CCR to charges pertinent to this study in order to determine if the expense of a 1 hour HT session translates to a change in dollars expended in PACU care, total length of hospital stay and morbidity treatment costs (ex. anxiety/pain/itch/anti-nausea medication expense). Cost-benefit analysis comparing those with HT versus no HT and by group will be conducted. An expert in health cost/economics will be consulted where necessary for the latter analysis.

Unfortunately we have no published data with respect to satisfaction or cost analysis. We will be able to detect an effect size of at least 0.66 with a sample size of 50 per group and accounting for multiple testing, with a 2-sided test, a type 1 error rate of 0.016 and power is 80%. A power of 80% could be maintained with correlations as low as $r=0.20$.

9.0 Study Finance

9.1 Funding Source

This study is financed through a grant from the Shriners Hospitals for Children, North America.

9.2 Participant Stipends or Payments

A gas card valued at \$20 will be provided to study participants (or families) as compensation for time or travel.

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