Title: Electro-acupuncture (EA) in Children Undergoing Procedures for Congenital Heart Defects.

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Research plan

Background

Managing the child with congenital heart disease has become increasingly complex. The goal is to not only have the child survives, but has him or her recover with *comfort* and preservation of the heart and other vital organs through *reduced complications*. Despite optimal pharmacologic management, these problems continue to occur. Additionally, recent concerns about the crisis surrounding opiate use/abuse have had an effect reducing the use of these drugs even in situations where they are indicated.

Moving beyond pharmacologic strategies is one way to consider reaching the goal of increased comfort and reduced complications. Acupuncture has been used for centuries to diagnose and treat a variety of medical conditions and is the practice of using certain anatomical points to achieve well-being in the patient. Conventional acupuncture techniques involve needle manipulation at a specific anatomical point, but this approach may be difficult, if not impossible, to use in the operating room (OR) because of physical access and time constraints.

Electro-acupuncture (EA) can achieve the results of standard acupuncture with less time and utilizes electric current instead of needle manipulation to achieve its effects. The electric stimulation is provided through an acupuncture needle or a small electrode pad, and can be transmitted using different wave forms. These waveforms have the following theorized advantages[1]: Continuous and/or a dense-disperse wave for analgesia, and dense-disperse wave for blood circulation.

With electro-acupuncture, the stimulation frequency plays an important role in the release of naturally occurring analgesics. Evidence suggests that lower frequencies(2 Hz) result in the release of enkephalins and endorphins, whereas higher frequencies (100 Hz) result in the release of dynorphins.[2] Varying between high and low frequencies (continuous plus dense-disperse) endogenous opioid peptides should release resulting in their synergistic interaction.

There is controversy about the optimal current. Most studies have used current in the milliampere range and adjusted the current to be just below the threshold where electrically stimulated movement is observed, or typically in the mid-range (1-14mA). In contrast, there is a belief that the optimal current utilized should be in the microampere range. The Arndt-Shultz Law postulates that weak currents increase physiologic activity while strong current inhibit it. Adherents believe that micro currents (50 microamps -1000 microamp (1 Milliamp)) increase ATP concentrations while currents above 1000 micro amp do not increased ATP production and higher currents 5000 microamps may decrease ATP. Micro current techniques have been shown to increase microvascular blood flow, enhance circulation, reduce edema, and stimulate the growth of new blood vessels which significantly increases angiogenesis and tissue perfusion. [3].

Current literature discussed below identifies a number of points that experienced acupuncturist have found effective in dealing with issues encountered during cardiac surgery. The only recent pediatric cardiac acupuncture study was a randomized control trial done by Ni X et al.[4] Their study looked at 70 non-complex congenital heart patients age 2-12 that underwent cardiopulmonary bypass (CPB) with an aortic cross clamp. They stimulated point pericardial 6 (PC 6) bilaterally for 30 min using a dense-disperse wave at a frequency of 2 Hz. The mean amplitude used was 14±3mA. Lower troponin and C-reactive proteins were observed in children receiving stimulation. Shorter ventilation times, shorter PICU stays, higher levels of naturally occurring pain killers (β-endorphin) and lower levels of stress hormones (serotonin levels (5-HT)) were seen in the EA group.

Other adult cardiovascular studies have found similar advantages of stimulation of the PC-6 point. Ma et al. found that EA stimulation at PC 6 for 30 minutes before and during cardiac valve replacement had a positive effect on ischemic re-perfused myocardium by alleviating oxidative stress injury.[5] The patients receiving EA at PC 6 had higher superoxide dismutase levels and lower troponin levels than the control group.[4] Yang et al. stimulated PC 6 along with LieQue lung (LU) 7 and Yunmen LU 2 at 0.8-1.9 mA and frequency of 5 and 30 Hz for 30 minutes for 5 days before valve surgery. The EA group had shorter ICU stays and significantly lower troponin I levels at 6, 12 and 24 hours after cross clamp removal. Inotropic scores were also significantly lower at 12, 24 and 48 hours after ICU arrival.[6]

To optimize the effects of EA, there is a question as to when the EA should be initiated and how long it should be continued into the postoperative period. Adult studies have employed preoperative treatments from one hour to 3 days in advance of the procedure, then intraoperative therapy followed by post-operative therapy. Chen et al. performed EA at 30 minutes prior and continued their therapy postoperatively every 12 hours for 3 days. Their treatment group had lower serotonin levels, less nausea, required less analgesics, and had higher β-endorphin levels at 24, 48 and 72 hours post-operative than the sham EA group.[7]

Not only is the comfort of the patient increased, but acupuncture techniques have been shown to decrease complications. Qiang et al. added PC 4 to PC 6. They stimulated for 30 minutes one to two hours prior to the procedure. Compared to their control group that did not get EA, the EA treatment group (stimulated with 2 and15 Hz at 7-11mA) had a decreased incidence of major adverse cardiac and cerebrovascular events (odds ratio 0.327, 95% CI 0.140–0.767, *P*

= 0.010) at 24 months. They also found significant reduction in myocardial infarctions based on in serum troponin levels at 24 hours after percutaneous coronary intervention.[8]

The effects of EA do dissipate, but these techniques do not necessarily need to be started before the incision or insult. Syuu et al. looked at the effects of EA at PC 6 in a hemorrhaging dog model. EA was started 30 after the hemorrhage was initiated. This study illustrated that stimulation of PC 6 prevented the fall in left ventricular performance and rise of plasma vasopressin. Improved left ventricular performance was also noted as long as EA was maintained. Once the stimulation was stopped, the effects dissipated over 120 minutes. This confirmed that stimulation of the point can be initiated after incision or insult, and that the effects of EA dissipate over time.[9]

Though stimulation at PC-6 has been done by many investigators, other points have been used as well for cardiovascular surgery. Zhou et al. studied 100 patients with standard general anesthesia and 100 patients with combined acupuncture plus midazolam.[10] Those in the acupuncture group had significantly less opiate use, fewer pulmonary infections, shorter ICU stays, and lower cost. The points stimulated for this study were ZhongFU (Lung 1), Lung 7 and PC 4.[10] Points used by Chi et al. included Lung 1, Chize (Lung 5) and PC 4.[10]. Their acupuncture group needed significantly less blood transfusion, less antibiotics for pulmonary infections, and had shorter duration of hospitalization, shorter ICU stays and lower medical costs. They stimulated their points at 3-4 Hz and 2.0-2.2 mA for 20 minutes .[11] A common point in these papers was stimulation at PC 4 and PC 6. Another advantage of these points is that they are distal to the surgical field and usually readily accessible.

Stimulation at PC 6 has advantages in the kidney as well. Fifty percent of children undergoing cardiovascular surgery develop at least stage 1 acute kidney injury (AKI). It is speculated that this AKI is related to activation of sympathoexcitatory inputs modulated through renal afferent nerves. Recent studies have tried to decrease this incidence by modulation of the renotubular feedback loop with adenosine receptor antagonism [11] This has been able to decrease the need for renal replacement therapy after CPB, but has not been shown to prevent the development of AKI.[12] EA can affect sympathoexcitatory inputs. Yu et al. stimulated rabbits in an AKI model and found stimulation at PC 6 and ST 36 using a dense disperse wave at 2 and 15 Hz with 1 mA reduced morphologic renal damage and attenuated renal tubular apoptosis.[13]

A special consideration during cardiac surgery is that organ blood flow is also often affected by non-pulsatile flow or hypotension. Lele et al., in a controlled hypotension model in dogs, found that EA helped maintain better blood flow to the stomach and kidney, resulting in reduced apoptosis in those organs. Further, the apoptosis that was observed in the control animals' brains did not occur in the animals receiving EA. Points used were large intestine (LI)-4, ST-36 spleen (SP)- 6 and LI-11 stimulated bilaterally at 2 Hz with 3-5 mA.[14]

Research Plan:

This study will help to identify whether electroacustimulation is a beneficial anesthesia adjunct in children undergoing procedures on their congenital heart defects.

Electroacustimulation is a technique with minimal risks, which enhances the body's innate abilities to deal with the stresses and pain of surgery. Our goal is to optimize care for those patients with congenital heart disease by increasing *comfort* and *reducing complications*. This study will examine comfort using age appropriate pain scoring systems. The complications this study will focus on are myocardial injury which will be assessed by measuring Troponin levels, and renal injury assessed using AKIN criteria

Treatment Groups:

Subjects will be randomized. Randomization will be done using block randomization with block sizes between 4 and 8. The sham procedure will use the identical set up as the treatment group, but those participants in the sham group will not receive the electro-stimulation.

Group 1: Will have electrodes placed at Pericardial 4 and 6, Large Intestine 4, and Stomach 36 and receive electroacustimulation (treatment) frequency will be at 2Hz and 100 Hz the amplitude will be 1000mA.

Group 2: Will have electrodes placed at Pericardial 4 and 6, Large Intestine 4, and Stomach 36 and receive sham electroacustimulation (control) will not have stimulation.

Duration of Treatment:

The duration of treatment (stimulation or sham) for subjects will be length of surgical procedures on their congenital heart defects. Patients will be followed for 6 hours to collect data on myocardial injury and48 hours to collect data on pain, and renal injury.

Objectives:

Primary Objective:
The primary objective of this study is to identify whether electroacustimulation is a beneficial anesthesia adjunct in children undergoing procedures on their congenital heart defects. Does it decrease myocardial injury and or need for myocardial support. Differences between the groups Troponin I levels pre-operative and six hours postoperative will be evaluated.

Secondary Objectives:
1) Evaluate the incidence discomfort in the post- operative period.

To evaluate the incidence and severity of pain assessed by using age appropriate West Virginia University Hospital approved nurse guided pain scoring the Neonatal/Infant Pain Scale (NIPS) (children age birth to 2 months) FLACC (2 months to 7 years or unable to communicate, or VAS(age 8-18) every 2 hours for 48 hours post procedure.

2) Determine the incidence of Acute kidney injury (AKI) between these two treatment groups. Acute Kidney Injury will be evaluated by AKIN criteria. Creatinine and urines will be measured at 6, 12, 24 and 48 hours after bypass.

Need for post-operative myocardial support:

To assess the need for myocardial support an inotropic score will be used and compared between the two groups. The Inotropic score will be evaluated every 6 hours for 48 hour between the 2 groups
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Study Design:

This is a single site, randomized, blinded, sham controlled, parallel group study to identify whether electroacustimulation is a beneficial anesthesia adjunct in children undergoing procedures on their congenital heart defects.

Study subjects age's birth to eighteen years, undergoing cardiac surgery for their congenital heart lesions will be considered for entrance into the study. The randomized subjects will receive either electrostimulation or sham during their surgery for CHD. Subjects are expected to remain in the hospital 48 hours post procedure. Standard of care blood samples will be obtained pre-operative and post-operative. The only study specific blood sample will be Troponin I levels which will be obtained presurgically after the lines have been placed and a 6 hours post bypass/aortic clamp removal. Urine samples will be obtained pre-surgically after placement of the Foley and every 6 hours post bypass for 48 hours while the Foley catheter is still in place .

Number of Subjects planned:
Approximately 108 patients, over the two years, with randomization of 54 allocated to each group.
- Electroacustimulation (treatment) frequency will be at 2Hz and 100 Hz the amplitude will be 1000mA.
- Sham electroacustimulation (control) will not have stimulation

Study Population:
Inclusion criteria:
Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1) Patients 0-18 years of age undergoing procedures on their congenital heart defects.
   Additionally, patients with coarctation of the aorta for repair will be considered as a separate group and eligible for enrollment.
2) Willing to provide written Assent/Consent in English.

Exclusion criteria:
Subjects will be excluded if they fulfill any of the following exclusion criteria:

1) Patients with skin lesion over more than 50% of acupuncture sites.
2) Patients in renal failure.
3) Patients on chronic opioid therapy.
4) Unwilling to provide written Assent/Consent in English.

Concomitant Treatment:

All subjects will receive a standard anesthetic of propofol, remifentanil and dexmedetomidine at doses needed to maintain a stable BIS number and lack of movement. When possible neuromuscular blocking agents will not be used. A morphine infusion will be used for postoperative pain control based on need. Those allergic to morphine will receive a substitute opiate by continuous infusion.

Study Procedures:

Screening:

Review of consent form- Subjects that provide written assent/consent and meet all inclusion and no exclusion criteria will be included into the study. Subjects may withdraw consent to participate at any time. Participation in the study is voluntary. Adverse events will be recorded after informed assent/consent obtained.

Surgery: Treatment/Sham

Eligible subjects will undergo blood sampling (3.5cc) and urine sample (0.5-2cc) will be obtained prior to stimulation/sham.

All subjects will have electroacustimulation pads applied at four points bilaterally: pericardial 4 (PC 4), pericardial 6 (PC 6), large intestine 4 (LI 4) and stomach 36 (ST 36). No needles will be used. (Appendix A; 1)

Subjects will be randomized. Randomization will be done using block randomization with block sizes between 4 and 8. The sham procedure will use the identical set up as the treatment group, but those participants in the sham group will not receive the electro-stimulation. Stimulation/sham will begin as soon as possible after induction of anesthesia and obtaining baseline laboratory samples of urine and blood.

Group 1: Receive electroacustimulation (treatment) frequency will be at 2Hz and 100 Hz the amplitude will be 1000mA.

Group 2: Receive sham electroacustimulation (control) will not have stimulation.
Subjects will undergo procedures on their congenital heart defects.

Blind:

The anesthesia provider will be blinded as to whether the electroacustimulation device is actually turned on or not. The research coordinator will hold the blind. The electroacustimulation machine will be placed in an opaque bag to secure the blind. The current is below the threshold to stimulate the muscle so that no movement will be visible. It is also below the sensory threshold so that it will not produce any discomfort in the subjects.

Stimulation/Sham will be continued until the patient is ready for transport to the PICU.

Post-Operative: PICU

Stimulation/Sham will be discontinued.

PICU care givers will be blinded as to which group the patients were randomized.

Subject comfort will be assessed using age appropriate West Virginia University Hospital approved nurse guide pain scoring based on Universal Pain Assessment Tool or the Neonatal/Infant Pain Scale (NIPS) will be recorded in the electronic medical record (EMR) every 6 hours for 48 hours.

The amount of opiate infused, Nausea, Vomiting, and urine output will be assessed every 6 hours for the first 48 hours and recorded in the EMR.

Research blood samples for troponin I will be obtained at 6 hours post surgery. Total amount of 7cc of blood will be

obtained for this study. WVUH lab will process samples.

Research urine samples (.05-2cc) will be collected at 6, 12, 24, and 48 hours after bypass. The urine samples will be stored in a -80 degree freezer and analyzed by ELISA testing at the end of the study for Superoxide dismutase, Neutrophil gelatinase – associated lipocalcin (NGAL), WNT4.

AKIN criteria will be used to evaluate AKI every 6 hours. Inotropic score will be recorded every 6 hours.

Daily chest x-ray will be used to assess pulmonary status.

The AKIN criteria, inotropic scores, chest x-ray and creatinine levels, (used for AKIN), are standard of care measurements and the data will be collected for this research project.

An Electrostimulation Documentation Guide has been developed for the staffing. (Appendix A2)

Tool/Instruments to be used in data collection:
Tools and instruments for data collection: secured Excel data base; Neonatal/Infant Pain Scale (NIPS); AKIN stage; Inotropic Scores; RACHS categories (Appendix A3-6).

Variables:
Detailed descriptions of the variables are given in Appendix B. The information collected for each patient will include the following variables. *Outcomes*: Pain score; inotropic score; Narcotic use; renal laboratory values: creatinine, neutrophil gelatinase-associated lipocalin (NGAL), WNT4, AKIN score; superoxide dismutase; indicator for pneumonia; time-to-extubation (intubation time, extubation time); length of pediatric intensive care unit (PICU) stay (arrival time, discharge time). *Other variables*: Age, sex, cardiac defect, cyanosis, RACHS score, cardiopulmonary bypass time (CPB), cross clamp time and surgery start and end time, occurrence of nausea, vomiting event, urine output, number of lobes with atelectasis.

Analytic methodology
Randomization: Eligible participants will be randomized to the acupuncture treatment or control group using a randomly varying block randomization method to ensure equal distribution among treatment groups.[22] The project statistician, who will have no contact with the participants or any of the personnel assessing the patients, will generate a randomized assignment master list and provide this information only the study personnel who will be setting up the acupuncture device. Each participant will be assigned a unique number that will follow the patient through the study. The study number and participant's name will be retained on a secure electronic database; this information will be linked to the randomization assignment to create a crosswalk file. It will be stored in a separate password-protected database. At the end of the study, the cross-walk file will be used to link the patient data and treatment allocation.

Sample size:
Predicated on the primary aim, the sample size for this pilot study we used a two-sided two-sample t-test with unequal variance t-test with an alpha level of 0.05 and power of 80%. A morphine equivalent dose of 0.71 mg/kg was used for the control group and 0.57 mg/kg for the acupuncture group. This represents a conservative 20% change between the control and acupuncture group. The standard deviation of the control group was estimated to be 0.3 mg/kg for the control group and 0.2 for the experimental group. The **total estimated sample size is 108 patients, over the two years, with 54 allocated to each group.** Historically, we would have had a potential enrollment and retention of approximately 74 patients per year accounting for a 25% non-consent rate and a 2% drop-out rate. This project is well powered for statistical significance and feasibility for a 2-year study.

Data collection:
The data will be retrieved from the EMR and imported or entered into a secured EXCEL database.

Statistical analysis plan:
For all aims, univariate statistics (e.g. mean, median, standard deviation, min, max and skew) will be used to describe the collected data. Parametric approaches (e.g. t-test, Pearson's correlation, and chi-squared test) will be used when the data satisfy the required statistical assumptions; they will be used to compare the demographic and clinical characteristics between treatment and control. If the distributional assumptions are untenable, then the Mann-Whitney test, Spearman

correlation, and Fisher's exact test will be used. We will use the Box-Cox or the exponential transformation when the absolute value of skew is greater than 0.4.

To address the overall difference between the control and the acupuncture group, we will look at the score changes between baseline and 48 hours. For the continuous outcomes, a t-test based on the difference in outcome will be used to compare the two treatment groups. For the categorical outcomes, a logistic regression model (generalized linear model with binary or multinomial outcome) will be used to compare the two treatment groups' at baseline and 48 hours. The generalized linear hypothesis methodology will be used to contrast the two time points. This approach will provide consistency of modeling methodology for the secondary analyses. Adjusted models will be considered (e.g. glm regression with identity and/or logit links) to account for any data imbalances, potential confounders, etc. Minimally, a RACHS score adjustment will be assessed for its relevance.

A secondary analysis will be used to describe the longitudinal (repeated measures) outcome trends. A generalized linear mixed-effects regression model will be used for longitudinal data. Both unadjusted and adjusted trends will be assessed. We will account for both heteroscedasticity and autocorrelation variance-covariance structures. The generalized linear model approach will permit trend characterizations for either continuous or categorical outcomes under the same generalized linear model framework.

All results, predicated on formal hypothesis testing methodology, will use an alpha-level of 0.05 for statistical significance. Bonferroni or Scheffe adjustments will be used, when appropriate, to retain the family-wise alpha level of 0.05 when performing multiple tests under the same global hypothesis or construct. Every effort will be used to ensure all relevant information is collected. In the event of missing data, generalized estimating equations for longitudinal analysis will be used. All statistical analysis will be done using the most recent version of the R language for statistical computing and graphics.

Tentative time table: Approximately 2 years to enroll 108 subjects.

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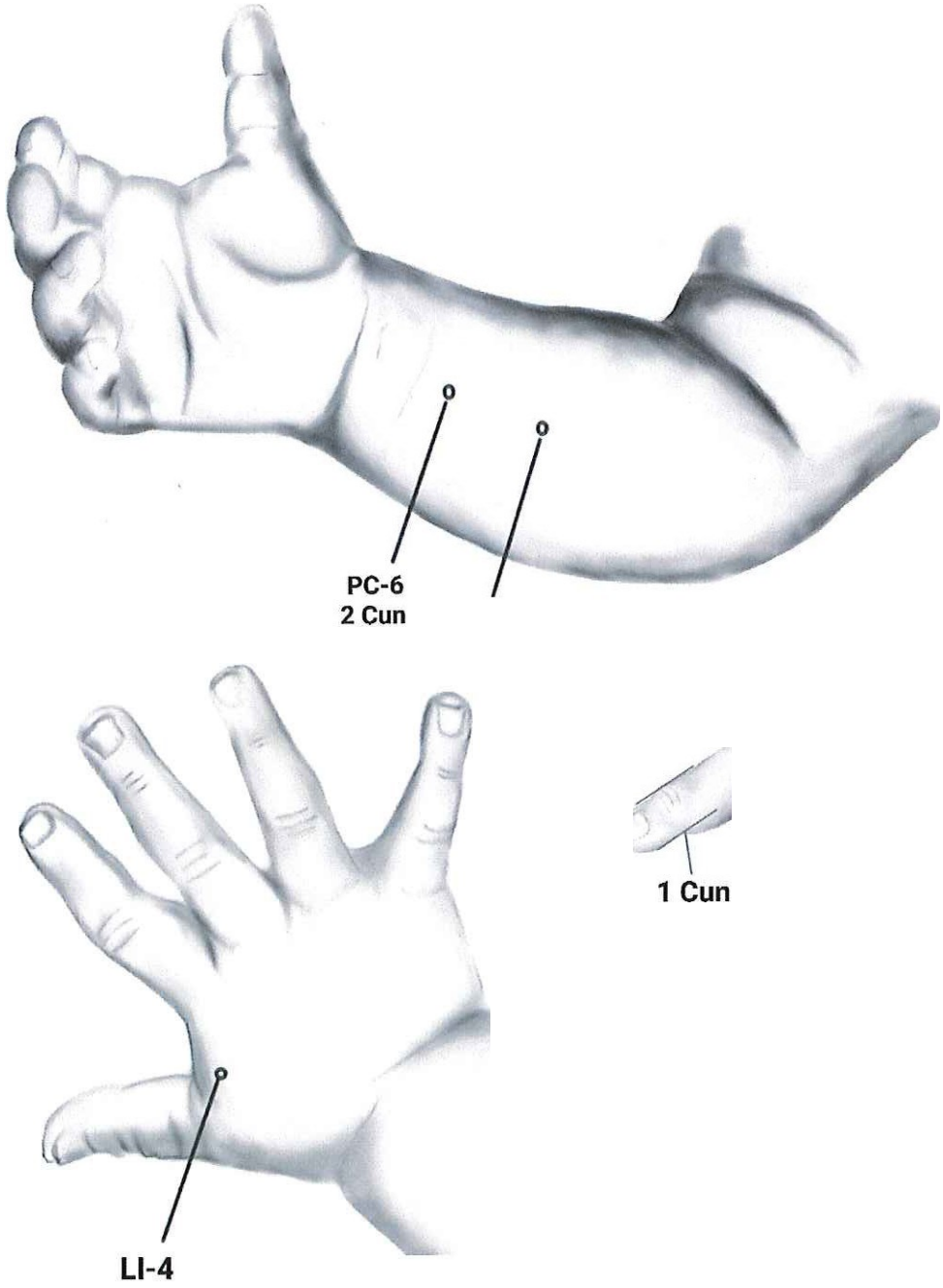
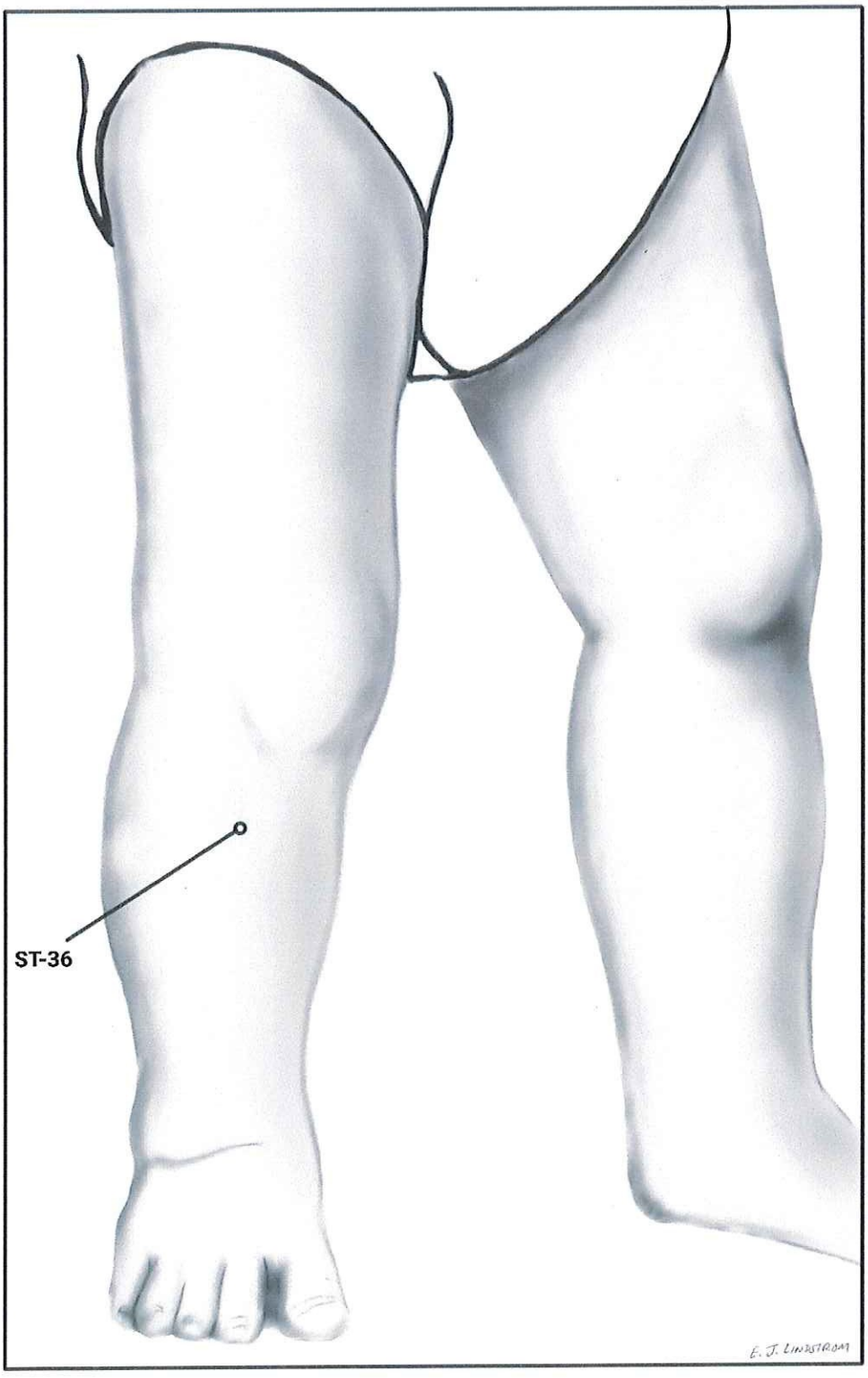
Appendix A 1




ST-36
E. J. LINDSTROM

Appendix A. 2

Acupuncture Study Documentation Guide (record in EMR)

Baseline (pre- acupuncture/sham)

Procedure/Lab	Date/Time
Creatinine	
Urine sample	
RACHS score	
Cyanosis: yes or no	

Acupuncture/sham	Date/Start time	Date/End time
Pre-surgery		
Post-surgery		

Aortic clamp removed date/time:

CPB end date/time:

PICU:

Times post CPB	Date/Time	Pain scale Number 0-10	Nausea (Yes/No)	Vomiting (number of episodes)	Urine output
6 hours:					
12 hours:					
18 hours					
24 hours					
30 hours					
36 hours					
42 hours					
48 hours					

Labs:

Times post CPB	Date/Time	Creatinine	Urine Sample
6 hours:			
12 hours:			
24 hours			
48 hours			

Scores:

Times post CPB	Date/Time	AKIN/AKI	Inotropic
6 hours:			
12 hours:			
18 hours			
24 hours			
30 hours			
36 hours			
42 hours			
48 hours			

*Daily chest x-ray

Appendix 3

Neonatal/Infant Pain Scale (NIPS)

(Recommended for children less than 1year old) A score greater than 3 indicates pain.

Pain Assessment		Score
Facial Expression		
0 - Relaxed Muscles	Restful face, neutral expression	
1- Grimace	Tight facial muscles; furrowed brow, chin, jaw (negative facial expression – nose, mouth brow)	
Cry		
O - No cry	Quiet, not crying	
1- Whimper	Mild moaning, intermittent	
2 - Vigorous cry	Loud scream; rising, shrill, continuous (Note: Silent cry may be scored if baby is intubated as evidenced by obvious mouth and facial movement	
Breathing Pattern		
0 - Relaxed	Usual pattern for this infant	
1- Change in breathing	Lndrawing.n,irregular, faster than usual ;gagging,, breath	
Arms		
0 - Relaxed/Restrained	No Muscular rigidity; occasional random movements of arms	
1- Flexed/Extended	Tense, straight arms; rigid and/or rapid extension, flexion	
Legs		
0 - Relaxed/Restrained	No Muscular rigidity; occasional random movements of legs	
1- Flexed/Extended	Tense, straight legs; rigid and/or rapid extension,flexion	
State of Arousal		
0 - Sleeping/Awake	Quiet, peaceful, sleeping or alert, random leg movements	
1- Fussy	Alert, restless and thrashing	

Appendix 4

The AKIN classification/staging system of acute kidney injury

Stage	SCr	UO
1	↑ SCr ≥26.5 μmol/L (≥0.3 mg/dL) or ↑SCr ≥150- 200% (1.5 - 2×)	<0.5 mL/kg/h (>6 h)
2	↑ SCr >200- 300% (>2 - 3×)	<0.5 mL/kg/h (>12 h)
3	↑ SCr >300% (>3×) or if baseline SCr ≥353.6 μmol/L (≥4 mg/dL) ↑SCr ≥44.2 μmol/L (≥0.5 mg/dL)	<0.3 mL/kg/h (24 h) or anuria (12 h)

Appendix A 5

Inotrope Score (IS) =

Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 100 x Epinephrine dose (mcg/kg/min)

Vasoactive-Inotropic Score (VIS) =

IS + 10 x Milrinone dose (mcg/kg/min) + 10,000 x Vasopressin dose (units/kg/min) + 100 x Norepinephrine dose (mcg/kg/min)

Classification system based on inotropic score

Group[†]	IS or VIS 1st 24 hours	IS or VIS 24–48 hours
1	<10	<5
2	10–14	5–9
3	15–19	10–14
4	20–24	15–19
5	≥25	≥20

[†]Group assignment based on highest support level in either time period.

(Example: Patient with maximum IS 22 in first 24 hours, and 14 in the subsequent 24 hours, would be classified as group 4. Similarly, a patient with maximum IS 10 in the first 24 hours and maximum IS 25 in the second 24 hours would be classified as group 5.)

Michael G. Gaies, MD,[1,2] Howard E. Jeffries, MD,[3] Robert A. Niebler, MD,[4] Sara K. Pasquali, MD,[1,2] Janet E. Donohue, MPH,[2] Sunkyung Yu, MS,[2] Christine Gall, MS,[5] Tom B. Rice, MD,[4] and Ravi R. Thiagarajan, MD[6] Vasoactive-Inotropic Score (VIS) is Associated with Outcome After Infant Cardiac Surgery: An Analysis from the Pediatric Cardiac Critical Care Consortium (PC[4]) and Virtual PICU System Registries. Pediatr Crit Care Med. 2014 Jul; 15(6): 529–537.

Appendix A.6

RACHS category 1:

1. Secundum ASD
2. Aortopexy
3. PDA (> 30 days of age)
4. Coarctation (> 30 days of age)
5. PAPVR repair

RACHS category 2:

1. Aortic valvuloplasty (> 30 days of age)
2. SubAS resection
3. Pulmonary valvuloplasty or replacement
4. RV infundibulectomy
5. RVOT augmentation
6. Coronary fistula repair
7. ASD & VSD repair
8. Primum ASD repair
9. VSD repair
10. Tetralogy repair
11. VSD closure with PA band removal
12. Repair of unspecified septa! defect
13. TAPVR repair (> 30 days of age)
14. Glenn shunt
15. Vascular ring surgery
16. A-P window repair

17. Coarctation repair (:5 30 days of age)

18. PA stenosis repair

19. Common atrium closure

20. LV-RA shunt repair

RACHS category 3:

1. AVR

2. Ross procedure

3. LVOT patch

4. Ventriculomyotomy

5. Aortoplasty

6. Mitra! valvuloplasty or replacement

7. Tricusp id valvuloplasty or valvectomy or replacement

8. Tricuspid valve repositioning (Ebstein's) (> 30 days of age)

9. Anomalous coronary artery repair with or without intrapulmonary tunnel (Takeuchi)

10. Closure of semilunar valve (aortic or pulmonary valve)

11. RV-PA conduit

12. LV-PA conduit

13. DORV repair with or without RV obstruction

14. Fontan

15. AVSD (complete or transitional) repair with or without valve replacement

16. PA banding

17. Tetralogy with Pulm. Atresia repair

18. Cor triatriatum repair

19. Systemic-Pulmonary artery shunt

20. Atrial switch operation

21. Arterial switch operation

22. Pulmonary artery reimplantation

23. Annuloplasty

24. Coarctation & VSD repair

25. Cardiac tumor excision

RACHS category 4:

1. Aortic valvuloplasty (:::; 30 days of age)

2. Konno procedure

3. Complex defect (Single ventricle) repair with VSD enlargement

4. TAPVR repair (:::; 30 days of age)

5. Rastelli procedure

6. Atrial switch with VSD closure

7. Atrial switch with subpulmonary stenosis repair

8. Arterial switch with PA band removal

9. Arterial switch with VSD closure

10. Arterial switch with subpulmonary stenosis repair

11. Truncus repair

12. Repair of ... or interrupted aortic arch with or without VSD repair

13. Unifocalization ... Tetralogy-PA

14. ...

RACHS category 5:

1. Tricuspid valve repositioning for neonatal Ebstein's (:S 30 days of age)

2. Truncus with Interrupted aortic arch repair

RACHS category 6:

1. Norwood operation

2. ...

Appendix B: Variable descriptions.

Variable	Description	Measurement times	Measurement scale
Outcomes			
Pain score	Age appropriate WVUH approved Nurse guided pain scoring. The pain scale score will be recorded in the electronic medical record.	Every 2 hours for 48 hours	Tool: NIPS score, FLACC score or Visual analog scale Scale: 0-10; 0=none, 10=worst pain
Inoptropic score	IS or VIS 1st 24 hours IS or VIS 24-48 hours	Every 6 hours for the first 48 hours of observation	Group 1-5
Narcotic use	Opiate use will be its own variable as well as a surrogate for pain as comfort will be maintained at a score less than 40% of the max possible score for the pain scoring system used.	Every 2 hours for 48 hours	mcg/kg/hr
Creatinine/Urine	Assessment of AKI-renal complication	Baseline, 6, 12, 24, and 48 hrs post CPB	Creatinine mg/dl Urine ml/kg/hr
Neutrophil gelatinase-associated lipocalin (NGAL)	Renal biomarker-urine sample collected and frozen-renal complication	Baseline, 6, 12, 24, and 48 hrs post CPB	ELIZA
WNT4	Renal Biomarker-urine sample collected and frozen-renal complication	Baseline, 6, 12, 24, and 48 hrs post CPB	ELIZA
AKIN score	Acute kidney injury (AKI)-renal complication	Every 6 hours for the first 48 hours of observation (EMR)	Stage 1-3
Superoxide dismutase	Renal Biomarker-urine sample collected and frozen-cardiac injury-complication	Baseline,6, 12, 24, and 48 hrs post CPB	ELIZA
Pneumonia	complication	Daily (Chest x-ray)	Indicator: 0=No, 1=Yes
Intubation time	The date and time of intubation as part of surgery prep.	Obtained from patient's EMR	Date and time
Extubation time	The date and time of extubation as part of surgery prep.	Obtained from patient's EMR	Date and time
PICU arrival	The date and time of arrival in the PICU	Obtained from patient's EMR	Date and time
PICU discharge	The date and time of discharge from the PICU	Obtained from patient's EMR	Date and time
Other variables			
Age	Age of the patient	Baseline	In days
Sex	Sex of the patient	Baseline	Indicator: 0=Male, 1=Female
Cardiac defect	Type of CD	Baseline	Diagnosis

Cyanosis	Blueness of skin- based on room air oxygen level less than 90% sat-guide for opiate amount-complication	Baseline	1=yes 2=no
RACHS score	Randomization Guide	Baseline	Categorical: 1 through 6
CPB start time/ Aortic clamp time	Cardiopulmonary bypass (CPB) start time/ Placement of artic clamp	Obtained from patient's EMR	Date and time
CPB end time/Removal of aortic clamp	Cardiopulmonary bypass (CPB) end time/ removal of aortic clamp	Obtained from patient's EMR	Date and time
Surgery start time	Surgery start time	Obtained from patient's EMR	Date and time
Surgery stop time	Surgery stop time	Obtained from patient's EMR	Date and time
Nausea	Occurrence of nausea within a 6 hour period	Every 6 hours for the first 48 hours of observation (EMR)	Indicator: 0=No, 1=Yes
Vomiting	Number of episodes in a 6 hour period	Every 6 hours for the first 48 hours of observation (EMR)	Count of occurrences
Urine output	AKI	Every 6 hours for the first 48 hours of observation (EMR)	ml/kg/hr
Atelectasis	Graded by number of lobes with atelectasis.	Daily (Chest x-ray)	Count of the number of lobes