DOCTOR OF NURSING PRACTICE

HOW DOES STANDARD USE OF A RECTAL ACETAMINOPHEN/INTRAVENOUS (IV) OPIOID COMBINATION COMPARE TO IV OPIOID ALONE IN IMPROVED COMFORT LEVELS AND DECREASED OVERALL OPIOID USE IN FULL-TERM INFANTS POST OPEN HEART REPAIR?

A Capstone Project Proposal Presented to
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by
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ABSTRACT

Pediatric cardiothoracic surgical patients experience varying degrees of pain in the immediate post-operative period. Multiple analgesic modalities can be utilized to effectively manage pain in this specific patient population. Routinely, IV opioid only is prescribed post-operatively to manage acute pain needs in this select group of patients. However, standard use of rectal acetaminophen as an adjunct to IV opioid to improve comfort levels and decrease overall opioid use in the immediate post-operative period in this select population has not been examined. This retrospective, 18-month, quantitative study was conducted at a large urban children’s teaching hospital incorporating electronic medical inpatient chart review. The study was designed to compare comfort levels (as measured by the Face, Legs, Activity, Cry, and Consolability [FLACC] Behavioral Pain Assessment Scale) and overall opioid use in male and female full-term infants (36 0/7 weeks or greater gestation as of the date of surgery) with congenital heart disease (CHD) who were less than or equal to 30 days of age and within 24 hours or less post open heart repair. The comparison groups included infants standardly prescribed rectal acetaminophen in conjunction with IV opioid and infants prescribed IV opioid only. A total of 203 participants were identified as meeting inclusion criteria; 129 participants were excluded due to exposure to confounding variables; 53 infants received standardly prescribed rectal acetaminophen in conjunction with IV opioid; and twenty-one infants received IV opioid only. Infants standardly prescribed rectal acetaminophen in conjunction with IV opioid had no significant difference in comfort levels as compared to infants who received IV opioid only ($p < 0.08$), but had a statistically significant ($p < 0.01$) decrease in overall opioid exposure (0.11mg/kg/day) as compared to infants prescribed IV opioid alone (0.28mg/kg/day).
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How Does Standard Use of a Rectal Acetaminophen/Intravenous (IV) Opioid Combination Compare to IV Opioid Alone in Improved Comfort Levels and Decreased Overall Opioid Use in Full-Term Infants Post Open Heart Repair?

Optimizing pain management modalities for pediatric patients remains a priority for practitioners and researchers alike. Prior difficulties providing appropriate pain management therapies for this unique group of patients were due to concerns for opioid-induced side effects, lack of clinical knowledge, and research (Verghese & Hannallah, 2010). However, with the validation and development of pain assessment tools specific to pediatric patients, treatment and accurate assessment of pain in this specific population has improved over the last decade (Verghese & Hannallah, 2010).

Providing pharmacologic combination therapy for evidence of maximum analgesic benefit, with minimal to no side-effect at lowest administrable dose should be the standard for practice and implementation for pediatric patients with post-operative pain management needs (Chiaretti et al., 2013; Kokinsky & Thornberg, 2003; Rosero & Joshi, 2014; Verghese & Hannallah, 2010). However, managing pain effectively in pediatric patients post-operatively poses its own unique challenges and quandaries for providers and caregivers as well. Acute pain needs coupled with potential post-surgical complications including bleeding, fluid shifts, and hemodynamic instability lends itself to judicious use of analgesics in the post-operative setting.

The application and pursuit of this research in the form of a Doctor of Nursing Practice Capstone Project that will compare and analyze overall opioid use and analgesic benefit in pediatric post-operative patients who received pharmacologic combination versus monotherapy will add to the existing body of knowledge in pediatric pain management. In addition, research findings may promote development of practice guidelines that support
judicious use of post-operative analgesics utilizing combination therapy maximizing analgesic benefit improving patient care and patient care outcomes.
PROBLEM STATEMENT

Overview

Pediatric cardiothoracic surgical patients experience varying degrees of pain in the immediate post-operative period. Multiple analgesic modalities can be utilized to effectively manage pain in this specific patient population. Routinely, IV opioids are prescribed post-operatively to manage acute pain needs in this select group of patients. However, standard use of rectal acetaminophen as an adjunct to IV opioids to improve comfort levels and decrease opioid use in the immediate post-operative period in this select population has not been examined.

Statement of the Problem

Standard use of rectal acetaminophen as an analgesic adjunct with IV opioids to improve comfort levels and decrease overall opioid use in full-term infants with CHD who are less than or equal to 30 days of age and within 24 hours or less post open heart repair has not been examined.

Inquiry Question(s)

How does standard use of a rectal acetaminophen/IV opioid combination compare to IV opioid alone in improved comfort levels and decreased overall opioid use in full-term infants post open heart repair?
OBJECTIVES AND AIMS

Overall Objective

The overall objective of this retrospective, 18-month, quantitative study was to compare comfort levels and overall opioid use among two groups of full-term infants with CHD who were less than or equal to 30 days of age and within 24 hours or less post open heart repair: one group received standardly prescribed rectal acetaminophen in conjunction with IV opioid and the other group received prescribed IV opioid alone.

Specific Aims

A specific aim of this retrospective, 18-month, quantitative study was to accurately identify, document, and analyze comparison findings specific to comfort levels and overall opioid use in male and female full-term infants with CHD who were less than or equal to 30 days of age and within 24 hours or less post open heart repair and who received standardly prescribed rectal acetaminophen in conjunction with IV opioid versus prescribed IV opioid alone. An additional aim of this retrospective, 18-month, quantitative study was to stimulate development and implementation of a practice change protocol based on interpretation and application of data analysis findings.
BACKGROUND AND SIGNIFICANCE

A review of the literature examining the concept that rectal acetaminophen utilized as an analgesic adjunct with IV opioids has opioid-sparing effects that decrease overall opioid consumption and improve comfort levels will be presented. Secondly, a review of the literature demonstrating accurate measurement and assessment of comfort levels in male and female infants (36 0/7 weeks or greater gestation as of the date of surgery) with CHD who are less than or equal to 30 days of age can be accomplished by use of age-appropriate pain assessment and measurement tools will be described as well.

The initial review of the literature incorporated the key terms Tylenol, pediatric analgesia, infant, acetaminophen, cardiac, pain, Paracetamol, Visual Analog Scale (VAS), and comfort scale. The literature search was further refined utilizing Boolean Operators associated with concepts to be examined in this study. These included pediatric pain management and Tylenol (23 studies), pediatric analgesia or Tylenol (74,006), pediatric analgesia and Tylenol (2), acetaminophen or infants and cardiac (773), infants and pain and cardiac (32), pain analgesics and infants and Paracetamol (4), rectal Paracetamol or infants and pain (70), analgesics or postoperative pain and pediatrics (17,673), rectal Tylenol and morphine-sparing (5), Paracetamol and morphine sparing (2), morphine and pediatrics and post-operative pain (2), clinical efficacy of rectal Tylenol (11), VAS in pediatrics (67), COMFORT scale in children (261), and FLACC scales and pediatrics (2).

Data bases that were subject-focused, concept-specific, and scholarly were searched within the last 15 years applying key terms and Boolean Operators. These included Cumulative Index to Nursing and Allied Health (CINAHL) Plus, Google Scholar, PubMed, and Medline. Applicable research suitable for review was found in fields of medicine,
nursing, and psychology. A majority of the literature initially identified was not specifically relevant to all concepts considered in this particular research design. Narrowing of research studies applicable for review was accomplished by controlling for the following indices: most recent, most conceptually pertinent, and most significant. Forty-four article abstracts were examined from the initial literature search and narrowed down to 25 articles for literature review. Six articles eventually came from Google Scholar, seven articles came from Medline, and twelve articles from CINAHL Plus.

**Double-Blind Randomized Controlled Clinical Trials**

The review begins with an examination of empirical literature that demonstrates a causal relationship between adjuvant use of rectal acetaminophen with IV opioids producing an opioid-sparing effect which decreases overall opioid consumption and improves comfort levels. Korpela, Korvenoja, and Meretoja (2006) in a double-blinded, placebo-controlled study randomized 120 children (ages 1-7 years) to receive placebo, 20mg/kg, 40mg/kg, or 60mg/kg doses of rectal acetaminophen after anesthetic induction for an elective day-case surgical procedure. These patients were followed post-procedure after arrival to the Post-Anesthesia Care Unit (PACU) for 2 hours and assessed for opioid requirement and comfort level. Demographic data of patients, operative procedures, and anesthetic utilized were controlled-for and similarly distributed in the randomized groups. Comfort levels were assessed using behavioral and physiologic indicators and documented by means of a VAS. Kruskal-Wallis analysis, Mantel-Cox, Mann-Whitney U-tests, the exact chi-square test, and analysis of variances were used for statistical analysis and a $p$-value of less than 0.05 was considered significant (Korpela et al., 2006).

A statistically significant finding ($p < 0.001$) demonstrated that dose dependent acetaminophen had an opioid-sparing effect on a percentage of children in the PACU (Korpela et al., 2006). Improved comfort levels and decreased overall morphine
consumption was demonstrated in children who received 40mg/kg and 60mg/kg doses of rectal acetaminophen. Children who received placebo or 20mg/kg dose of rectal acetaminophen had statistically significant pain and required increased morphine dosing PACU (Korpela et al., 2006). Limitations of this study included exclusion of children less than 1 year of age, relationship of dose dependent acetaminophen to comfort levels and opioid-sparing, and singular use of the VAS for pain assessment.

In another double-blinded, placebo-controlled study, Dashti, Amini, and Zanguee (2009) recruited 104 children (ages 7-15 years) for randomization to receive placebo or 40mg/kg dosing of rectal acetaminophen after anesthetic induction for adenotonsillectomy. Evaluation of opioid requirements and comfort levels post-operatively were followed every 2 hours up until 6 hours post-operatively. Rescue analgesic requests were documented at 24 hours post-surgery. The VAS assessment tool was used to document comfort levels. An independent samples t-test was used to analyze differences between the study groups and chi-square testing was used for non-parametric results. A p-value less than 0.05 was considered statistically significant (Dashti et al., 2009).

Controlling for age, weight, and sex between the groups, there was a statistically significant finding (p < 0.002) in regards to comfort levels in the acetaminophen group upon arrival to the PACU and at 2 hours, 4 hours, and 6 hours post-procedure. The patients who received acetaminophen had less pain, had a 62% opioid dose-sparing effect, and were more comfortable than the placebo group (Dashti et al., 2009). In addition, the number of patients who required more opioid overall in the 24 hour study period were control group participants compared to acetaminophen group participants (p < 0.001) (Dashti et al., 2009). Limitations of this study included that children less than 1 year of age were excluded from the study, documentation of comfort levels was only for 6 hours instead of 24 hours, study participants
only received one dose of rectal acetaminophen in a 24 hour period, and singular use of the VAS for pain assessment in older children.

Using an adult population, Cobby, Crighton, Kyriakides, and Hobbs (1999) studied the morphine-sparing effect of rectal paracetamol (Tylenol) and diclofenac during the first 24 hours post-hysterectomy in 72 women in a randomized placebo-controlled, double-blinded study. All women were randomized to receive rectal paracetamol, placebo, or diclofenac after wound closure in the operating room and then at 6 hours and 8 hours post-procedure. In addition, study participants received patient-controlled analgesia (PCA) with morphine post-operatively as an adjuvant to their pain management plan. Suppositories were blinded by the hospital pharmacy and controlled study variables included patient data, intra-operative anesthetic and opioid requirement, sedation, and nausea scores. Data were analyzed using analysis of variance (ANOVA), chi-square, and Kruskal-Wallis tests. Comparisons were examined using Student’s-t and Mann-Whitney U-tests. Comfort levels were documented using the VAS assessment tool. A p-value less than 0.05 was considered statistically significant (Cobby et al., 1999).

Patients who received rectal paracetamol and diclofenac used less morphine overall than patients who received placebo (p < 0.05) (Cobby et al., 1999). Morphine-sparing was similar in both the paracetamol group (36%) and the diclofenac group (40%). Documented pain scores in the diclofenac group were less compared to the paracetamol group (p < 0.008) and placebo group (p < 0.08) (Cobby et al., 1999). Limitations of this study included analgesic efficacy of standard rectal paracetamol in the first 24 hours post-operatively in adults which may be improved by using higher doses (1.3 grams/dose used in each patient), using a lipophilic base for emulsion in suppositories, and only adult female patients studied.

A total of 160 children (ages 1-6 years) undergoing adenoidectomy with or without myringotomy were studied using a randomized double-blind, placebo controlled protocol by
Viitanen, Tuominen, Vaaraniemi, Nikanne, and Annila (2003). Study participants were randomized to receive either 40mg/kg per dose of rectal acetaminophen, 15mg/kg per dose of rectal ibuprofen, a combination of both, or placebo after anesthetic induction. Comfort levels, opioid requirements, sedation scores, recovery times, and adverse events were recorded up to the first 24 hours post-procedure. ANOVA with Bonferroni corrections was used for analysis of normally distributed data. Kruskal-Wallis analysis, Mann-Whitney U-test, and Fisher’s exact-test were used where appropriate. Comfort levels were documented using the Objective Pain Scale. A $p$-value less than 0.05 was considered statistically significant (Viitanen et al., 2003).

Controlling for variables associated with recovery times, duration of anesthesia, and patient characteristics, opioid-sparing was statistically significant for study groups inclusive of acetaminophen ($p < 0.03$), ibuprofen ($p < 0.001$), and combination ($p < 0.002$) (Viitanen et al., 2003). Overall, opioid consumption was highest in the placebo group ($p < 0.008$). Of note, it was reported that participants who received acetaminophen alone were more sedated than those receiving ibuprofen alone, and ibuprofen participants were discharged sooner due to less sedative effects. Comfort levels were equianalgesic in acetaminophen and ibuprofen groups (Viitanen et al., 2003). Limitations of this study included children less than 1 year of age not included, 40mg/kg sole-dosing of rectal acetaminophen was compared to ibuprofen, and combination therapy regimens were utilized and compared.

Capici et al. (2008) compared intravenous acetaminophen to rectal acetaminophen and its post-operative effect on duration of analgesia (first analgesic request) and comfort levels in children post-adenotonsillectomy. Fifty children with four exclusions (ages 2-5 years) were studied using a randomized observer, blind-controlled trial. Participants either received 15mg/kg IV acetaminophen or 40mg/kg of rectal acetaminophen after anesthetic induction. Controlled variables included age, weight, type of surgery, surgical time,
intraoperative agents, wake-up time, and post-operative agitation. Comfort levels, analgesic requirements, agitation levels, and any adverse events were recorded up to the first 24 hours post-procedure. Children and Infant’s Postoperative Pain Scale (CHIPPS) and Aldrete scoring, a scoring system used to assess how a patient is recovering from anesthesia (Abdullah & Chung, 2014), were used for pain, sedation, and recovery measurement. Median and inter-quartile ranges, X2 analysis, and Kaplan-Meier Curves were utilized to document result outcomes. A $p$-value less than 0.05 was considered statistically significant (Capici et al., 2008).

Children who received rectal acetaminophen demonstrated longer analgesic effectiveness compared to participants who received the IV formulation ($p < 0.01$). The first analgesic request was longer in participants who received rectal acetaminophen (10 hours) versus those participants who received the IV formulation (7 hours). Children who received rectal acetaminophen had a 78% global comfort score of 4 or less versus 61% of children who received IV acetaminophen (Capici et al., 2008). Differences in comfort were most notable 6-10 hours post-initial dosing. Overall, participants who received rectal acetaminophen were comfortable longer and rescue analgesic need was less (Capici et al., 2008). Limitations of this study included children less than 1 year of age were excluded from study, opioid-sparing and overall opioid consumption were not measured, rectal premedication of midazolam and atropine may have increased absorption of rectal acetaminophen, and skewed results.

In 2014, Haddadi et al. conducted a double-blinded, randomized-controlled clinical trial comparing the effectiveness of IV versus rectal acetaminophen on controlling pain in post-adenotonsillectomy patients. Ninety-six children (ages 4-10 years) were randomized to receive either IV or rectal acetaminophen after anesthetic induction and were followed post-operatively for 24 hours. Post-operative pain was assessed using the CHIPPS criteria. Data
analysis testing included chi square and t-tests. A p-value less than 0.05 was considered significant (Haddadi et al., 2014).

A significant relationship was demonstrated between the two study groups. Forty-three percent of children who received rectal acetaminophen post-induction reported no pain immediately post-operatively as compared to 10% of patients in the IV acetaminophen group. In addition, post-operative pain scores at 4 hours and 6 hour post-procedure were lower in children who received rectal acetaminophen versus IV acetaminophen ($p < 0.05$). Rescue analgesic post-procedure was less in the rectal acetaminophen group than in the IV formulation group ($p < 0.0001$) (Haddadi et al., 2014). Limitations of this study include that children less than 1 year of age were not studied and comparison of efficacy began post-induction as compared to post-operatively.

Zavras et al. (2014) randomly assigned 106 males (ages 2-12 years) who were scheduled for elective circumcision to either receive either rectal paracetamol at 30mg/kg or ring block with levobupivacaine 0.25% with rectal paracetamol at 30mg/kg post-induction of anesthesia and prior to surgical incision. Children were assessed 48 hours post-operatively for pain, surgical and post-anesthetic complications, and total rescue analgesic doses received. Pain-free periods were documented as well. Statistical Analysis was performed using t-tests, one-way ANOVA, and chi-square. A p-value less than < 0.05 was considered significant (Zavras et al., 2014).

Age and weight distribution between studied groups were relatively similar. Duration of anesthesia and surgical times were closely related as well. Time to first analgesic request was identified as the pain-free period. Children who received combination levobupivacaine 0.25% with rectal paracetamol at 30mg/kg post induction of anesthesia had a longer post-procedure pain-free period than controls ($p < 0.001$). The combination group also reported longer times to first analgesic rescue requests and lower pain scores than patients who
received rectal paracetamol alone (Zavras et al., 2014). Limitations of this study include children less than 1 year of age not studied, sole rectal acetaminophen dosing was limited to 30mg/kg, and only males were studied.

**Measurement and Assessment of Comfort in Infants**

The empirical literature demonstrates that accurate measurement of comfort levels in infants can be accomplished by utilization of age-appropriate pain assessment tools. Franck, Ridout, Howard, Peters, and Honour (2010) in their single descriptive, quantitative study compared indices of pain in critically-ill newborns post-cardiac surgery. Eighty-one full-term newborns were studied post-operatively for 48 hours. Physiologic parameters and urine and serum cortisol levels were measured and compared utilizing four pain separate measurement scales. These scales included: Premature Infant Pain Profile (PIPP), COMFORT Scale, CHIPPS, and C--Crying; R--Requires increased oxygen administration; I--Increased vital signs; E--Expression; S—Sleeplessness (CRIES). Regression models were used to compare relationships between physiologic parameters, pain assessment scales, procedural intensity, opioid dose and cortisol levels. A $p$-value less than 0.05 was considered significant (Franck et al., 2010).

The COMFORT pain assessment tool produced a 27% score difference between procedures causing pain and those that did not ($p < 0.001$) (Franck et al., 2010). Of all pain indices studied, including cortisol levels measured and controlling for variances in behavioral and physiologic components, the COMFORT pain assessment tool remained significant in accurately assessing pain in critically-ill newborns(Franck et al., 2010). Limitations of the study include observer reporting bias and post-cardiac surgery sequela, which could result in physiologic parameter changes that could be misinterpreted as pain variances.

McNair, Ballantyne, Dionne, Stephens, and Stevens (2004) compared the validity of the PIPP and CRIES pain assessment scales to the VAS in the first 72 hours immediately
after surgery utilizing a prospective, correlational-observational design study. Pain was assessed in 51 neonates (ages 28-42 weeks) post-operatively in a level-three neonatal intensive care unit. Control variables were inclusive of gestational age, surgical procedure, and absence of neurological impairment. In addition, the neonates were furthered stratified into two groups based on infant development related to gestational age for more accurate pain assessment and measurement. Convergence validity and intraclass correlation profiles were examined to assess differences among measurement scales and pain indicators. Classification of correlation categories was used to measure correlation indices. A correlation value greater than 0.21 was considered significant (McNair et al., 2004).

The intraclass correlation profiles revealed moderate correlation between assessment scales (correlation value =0.62) until 24 hours post-operatively (McNair et al., 2004). Fair correlation continued to as far as 72 hours post-operatively with minor variance after that time (McNair et al., 2004). Prior to this study, the CRIES pain assessment scale had been validated for use only in term infants and the PIPP scale in term and preterm infants. This study supports the CRIES and PIPP scales as valid measurements of pain in term and preterm neonates. The data from this study supports comparable efficacy and accuracy of the CRIES and PIPPP scales to the well-researched VAS measurement tool (McNair et al., 2004).

Limitations of this study include etiology of correlational variances after 72 hours, subjectivity of VAS observational measurements, moderate sample size, and generalizability.

Hummel, Puchalski, Creech, and Weiss (2007) in a prospective, single correlational-observational design study examined the clinical reliability and validity of the Neonatal Pain, Agitation, and Sedation Scale (N-PASS) in neonates who were mechanically ventilated and had prolonged pain. Forty-six infants (ages 23-40 weeks) were observed for a total of 46 observations. Two observers conducted the study simultaneously and independently before and after pharmacologic intervention. Comparison of the N-PASS to the PIPP for
correlation, internal consistency, and construct validity was measured. Indices for measurement included Spearman’s rank, Cronbach’s alpha, and Wilcoxon signed-rank test. A correlation value greater than 0.21 was considered significant. A \( p \)-value of less than 0.05 was considered significant (Hummel et al., 2007).

Based on Spearman’s rank (correlational coefficient) of 0.83, Cronbach’s alpha of 0.82 and 0.87, and Wilcoxon signed-rank test \( (p < 0.001) \), the N-PASS is a reliable pain/agitation assessment tool for post-operative infants (ages 23 weeks and older) (Hummel et al., 2007). Limitations to this study include moderate sample size and generalizability to a singular NICU.

Voepel-Lewis, Zanotti, Dammeyer, and Merkel (2010) evaluated the FLACC pain assessment tool for accuracy and validity in adults and children before analgesic administration and during painful procedures. They compared the FLACC tools’ efficacy and correlational relativity to the 0-10 Numerical Pain Rating and COMFORT scales respectively. Statistical analysis used to study correlational relationships included \( k \)-statistics and exact-agreement, intraclass correlation coefficients, and Cronbach’s alpha. FLACC scores reported in studied patients indicated a highly correlational relationship with the 0-10 and COMFORT pain scales values \( (p=0.963 \text{ and } p=0.849) \) (Voepel-Lewis et al., 2010). Cronbach’s alpha supported excellent internal consistency 0.882 with excellent interrater reliability expressed by correlation coefficients of 0.67-0.95 (Voepel-Lewis et al., 2010).

In 2012, Bai, Hsu, Tang, and van Dijk piloted a repeated-observation study examining specificity, sensitivity, and validity of the VAS,COMFORT, and FLACC pain scales in post-operative pediatric cardiothoracic surgical patients (ages 0-7 years). One hundred and seventy children were assessed with the FLACC and COMFORT pain scales over a 3-day period at 18 specific fixed-time periods. Concurrent validity between pain assessment tools was calculated by correlation coefficients. Positive correlations distributed between 0.31-
0.86 were reported between the VAS, COMFORT, and FLACC assessment tools (Bai, et al., 2012). The FLACC pain assessment and measurement tool showed the highest sensitivity (98%) and strong specificity (88%) as compared to the COMFORT pain assessment tool (sensitivity 86% and specificity 83%)(Bai et al., 2012). The FLACC pain assessment and measurement tool demonstrated valid and reliable indicators for adequate measurement of pain in pediatric patients post-cardiac surgical repair (Bai et al., 2012).

After reviewing the empirical literature for evidence of a relationship between adjuvant use of rectal acetaminophen with IV opioids having an opioid-sparing effect that decreases overall opioid consumption and improves comfort levels, identification of research studies that corroborated these findings were identified. Identified studies validated rectal acetaminophen as an excellent analgesic adjuvant to IV opioid when dosed appropriately and emulsion composition ideal. Rectal acetaminophen worked well in children and adults, yet studies were limited in newborns. Opioid-sparing was statistically significant as was decrease in overall opioid consumption when rectal acetaminophen was adjuvantly utilized in conjunction with IV opioids to manage pain in adult and pediatric post-operative patients. Comfort levels were improved as evidenced by lowered documented pain scores and reporting indices.

Further examination of the empirical literature supported that pain assessment and measurement can be accurately and reliably documented in premature and term newborn infants utilizing well-established, reliable, and valid pain assessment and measurement scales. Several pain assessment and measurement scales currently exist that consistently and accurately assess pain in premature and term newborns. These include the COMFORT, CRIES, PIPP, N-PASS, VAS, and FLACC scales. Of note, Dorfman et al., (2014) in their systematic review of measurement instruments utilized to identify and quantify pain, distress, analgesic and sedation adequacy in critically-ill pediatric patients, identified the modified
FLACC scale as one of the most applicable pain rating scales available for assessment and measurement of pain in pediatric patients.

This review of the literature supports the theoretical underpinnings of a retrospective, quantitative study implemented at an urban children’s hospital that compares comfort levels and overall opioid use in male and female full-term infants (36 0/7 weeks or greater as of the date of surgery) with CHD who are less than or equal to 30 days of age and within 24 hours or less post open heart repair and who receive standardly prescribed rectal acetaminophen in conjunction with IV opioid to prescribed IV opioid alone.

**Conceptual Model**

The Neuman Systems Model (Neuman, 1995) is based on systems theory (Snowden, Donnell, & Duffy, 2014). Systems Theory has been described as a principle where components may be cooperative or communicate in some way. The Neuman Systems Model is comprised of two specific components, stress and the reaction to stress by a client system (Neuman, 1995). A client system can be an individual or a group. Each client system is unique but share common characteristics. Environmental stressors disrupt a system’s stability to a certain degree. Each system responds differently to stressors, but when defenses are inadequate, the client can be affected negatively or positively. Resistance factors inherent to each client system stabilize and direct the system towards health. Nursing interventions affect a systems ability to move towards health by adjusting the environment in response to stressor effect. System stability is the goal of patient care (Neuman, 1995). Optimizing secure and stabilizing relationships within and around the client system is the goal of The Neuman Systems Model of Nursing (Neuman, 1995).

Neuman supported that a revitalization of a system occurs when stability is achieved (Neuman, 1995). The major elements of the model include basic structure with system variables, energy resources, client variables, lines of resistance, normal and flexible lines of
defense, environment, stressors, health, reaction, prevention, reconstitution, and nursing (Neuman, 1995). Survival factors make up the basic structure of a system and include variables pertaining to physiologic, psychological, sociologic, developmental, and spiritual parts. Energy resources stabilize the system and react and respond to system instability by surging to counterbalance the disturbance within the system. Lines of resistance activate and protect the basic structure from stress when normal lines of defense are permeated by environmental stressors. The flexible line of defense, accordion-like in its response, acts as a buffer between a client’s normal state and the normal line of defense. The larger the gap, the more protected the client becomes to environmental stress and strain. The environment is affected by internal, external, or created factors and the client responds to these influences in either a positive or negative way. Stressors may cause system instability and can occur inside or outside the system (Neuman, 1995).

A client’s state of health is described as dynamic, with changing levels of normal across the life span. Outcomes or reactions are either negative or positive depending on the client systems response. System balance is optimized utilizing primary, secondary, or tertiary preventive measures (Neuman, 1995). Reconstitution aids in stabilization of energy resources when stressors invade. Most importantly, nursing care supports system stability by providing linkage between the client system, health, and the environment.

The internal consistency/reliability of The Neuman Systems Model for nursing is strong (Fawcett & Desanto-Madeya, 2012). Client systems may include individuals, families, groups, or communities. This nursing model can be utilized as an appropriate base for deductive and inductive research methods using quantitative and qualitative design methods (Fawcett et al., 2012). The Neuman Systems Model is one of the most widely used nursing models for nursing research and is an appropriate theoretical underpinning to the research proposed in this study.
Stabilization of the patient environment in response to pain stressors with standard use of rectal acetaminophen in conjunction with intravenous opioids in the immediate post-operative period is a clear example of moving the client system towards a state of constancy and eventual health. Promotion of system stability by assessing the impact of a stressor and helping the client adjust to the environment via a secondary prevention intervention is a true caveat of the Neuman Systems Model (Neuman, 1995).

The Neuman Systems Model focuses on stability of a client system in response to environmental stressors. Nursing interventions affect a systems ability to move towards health by adjusting the environment in response to stressor effect. System stability is the goal of patient care. Optimizing comfort levels while utilizing the least amount of opioid necessary with standard use of rectal acetaminophen in conjunction with IV opioids in post-operative infants will help stabilize the client system environment, reduce internal and external stressors, and promote a rapid return to wellness. The Neuman Systems Model is an excellent theoretical underpinning to this study.
PROJECT DESIGN AND METHODS

Project Design

This retrospective, 18-month, quantitative study was conducted at a large urban children’s teaching hospital using electronic medical inpatient chart review. The study was designed to compare comfort levels (as measured by the FLACC Behavioral Pain Assessment Scale) and overall opioid use in male and female full-term infants (36 0/7 weeks or greater gestation as of the date of surgery) with CHD who were less than or equal to 30 days of age and within 24 hours or less post open heart repair. The comparison groups included infants who were standardly prescribed rectal acetaminophen in conjunction with IV opioid and infants who were prescribed IV opioid only. Anticipated enrollment of approximately 100 participants was identified as sufficient to capture moderate to large effect.

Retrospective chart reviews are a valuable source of data for outcomes research, clinical practice trends, and treatment patterns (Solem et al., 2014). Utilizing this methodological approach for this study provided a unique data base source specific to the question of inquiry. Advantages of this methodological design specific to this study included its feasibility and applicability for rapid completion.

An independent samples $t$-test was the statistical method of choice to compare means of normally distributed, interval-dependent variables for two distinct groups (Hollander, Wolfe, & Chicken, 2013). Comparison of FLACC Behavioral Pain Assessment scores between both participant groups was analyzed by independent samples $t$-test in order to compare the means between normally distributed, interval-dependent variables for two distinct groups.
To accurately compare overall opioid use among the two participant groups queried, the Wilcoxon rank-sum test was used as an appropriate data analysis method to determine statistical significance between the two participant groups.

The Wilcoxon rank-sum test is a non-parametric test that can be used to compare two sample groups that are independent, vary continuously or ordinally, and contain abnormally distributed data (Hollander, Wolfe, & Chicken, 2013).

**Setting**

The study was conducted at a single investigative site in the United States. The setting of this study was a large urban children’s teaching hospital.

**Population and Study Sample**

The population of interest for this study included male and female full-term infants (36 0/7 weeks or greater gestation as of the date of surgery) with CHD who were less than or equal to 30 days of age and within 24 hours or less post open heart repair. Anticipated enrollment was to have been approximately 100 participants. Of the 100 participants, there was to have been two groups of 50 participants each.

**Sample Size**

Recruitment was to have stopped when 100 participants (50 in each group) were identified and met inclusion criteria. Fifty participants in each study group, power set at 80% and 0.05 identified as two-sided significance level, would yield the probability of 0.66 that an observation in group one (the acetaminophen and opioid combination group) was less than an observation in group two (the opioid only group) using a Wilcoxon rank-sum test. A two-sided, independent samples t-test with a sample of 50 in each group would have had a 50%
power to detect a 40% reduction in opioid use assuming the coefficient of variation is one.
The significance level was set at 0.05.

**Inclusion Criteria**

All male and female full-term infants (36 0/7 weeks or greater gestation as of the date of surgery) with CHD and who were less than or equal to 30 days of age and who (a): underwent open-heart repair within 24 hours or less; (b) received IV opioids (both comparison groups); and (c) received rectal acetaminophen (test of change group).

**Exclusion Criteria**

Participants who met the following conditions were excluded from the study:

1. Received or were receiving any mechanical support device inclusive of Extracorporeal Membrane Oxygenation (ECMO), Left Ventricular Assist Device (LVAD), or Right Ventricular Assist Device (RVAD).
2. Received or received paralytic agents, benzodiazepines, dexmedetomidine, propofol, ketamine, barbiturates, anti-epileptics, antidepressant, or IV or oral acetaminophen within 24 hours or less post open heart repair.
3. Known or acquired neurologic dysfunction, hepatic dysfunction, or renal insufficiency.
4. Had a known allergy to or intolerance of acetaminophen or opioid.
5. All pre-term infants (35 and 6/7 weeks of age or less as of the date of surgery) and infants greater than 30 days of age.
6. Had an equal to or greater than 25% increase in baseline creatinine post-operatively (Gelot & Nakhla, 2014).
Selection of Sample/Recruitment

The study was designed to measure comfort levels and opioid needs (measured mg/kg or calculated mg/kg totals in morphine equivalents) between two study groups of participants. The first study group consisted of male and female full-term infants (36 0/7 weeks or greater gestation as of the date of surgery) with CHD who were less than or equal to 30 days of age and within 24 hours or less post open heart repair prescribed rectal acetaminophen (ordered mg/kg consistent with the large urban children’s teaching hospital Formulary Guidelines) in conjunction with IV opioids (ordered mg/kg consistent with the large urban children’s teaching hospital Formulary Guidelines) in the immediate post-operative period. The second comparison group consisted of male and female full-term infants (36 0/7 weeks or greater gestation as of the date of surgery) with CHD who were less than or equal to 30 days of age or within 24 hours or less post open heart repair prescribed IV opioid alone (ordered mg/kg or calculated mg/kg morphine equivalents consistent with the large urban children’s teaching hospital Formulary Guidelines).

Existing electronic medical records (EMRs) were used to identify initial participants in the appropriate age range who meet inclusion criteria. Further potential participants were identified by existing operative records located within cardiac patient-specific databases at the large urban children’s teaching hospital where EMRs were stored for surgeries on patients who underwent open-heart repair in the specified time frame (November 1, 2012 to April 29, 2014).
Sources of Data

Retrospective chart reviews inclusive of information garnered from EPIC were queried for demographic data, pain score(s), serum creatinine(s), and medication(s) administered (type, route, dose, total amount). Retrospective chart review inclusive of potential participants were identified by existing operative records in Cardio Access and Cardio IMS for surgeries on patients that underwent open heart repair in the specified time frame (November 1, 2012 to April 29, 2014). Existing EPIC electronic medical records were then used to identify participants in the appropriate age range who met inclusion criteria.

Collection of Data

Access to existing medical records was obtained after institutional IRB review and approval of study. Potential participants were identified based on existing operative records (Cardio Access and Cardio IMS) for surgeries on patients that underwent open-heart repair in the specified time frame (November 1, 2012 to April 29, 2014). The EMR was queried for demographic data, pain score(s), serum creatinine levels, and types of medication administered. Data were collected and logged using an Excel spread sheet during the chart review process. Data collection was to stop when all potential participants who met inclusion and exclusion criteria during the specified period of inquiry were identified.

Data Analysis Strategies

The FLACC Behavioral Pain Assessment scores for the two study groups were compared utilizing independent samples t-tests. Total milligrams per kilogram of opioid administered over a 24 hour period were compared utilizing Wilcoxon rank-sum testing. Based on the concept of comparing two related sample groups to detect a moderate to large
effect, 100 participants in each study group was to be examined. The assumption of 80% power and 0.05 two-sided significance level will detect a probability of 0.66 that an observation in group one (the acetaminophen and opioid combination group) was less than an observation in group two (the opioid only group) using a Wilcoxon rank-sum test. A two-sided, independent samples $t$-test with a sample of 50 in each group was to have a 50% power to detect a 40% reduction in opioid assuming the coefficient of variation is one. The significant level is set at 0.05.

**Ethics and Human Subjects Issue/Risks and Benefits**

Identification of all participants was protected by utilizing medical record numbers (MRN) solely as means of participant identification. There were no potential participant risks due to study design. Study benefits identified included similar levels of comfort and less overall opioid use in male and female full-term infants (36 0/7 weeks or greater gestation as of the date of surgery) with CHD who were less than or equal to 30 days of age and within 24 hours or less post open heart repair receiving standardly prescribed acetaminophen in conjunction with IV opioid as compared to opioid alone in the immediate 24 hour post-operative period. All personal identifiable participant information was protected by keeping a master list containing PHI and MRN number separate from the data collection forms that only had a sequential study ID number (not derived from patient MRN or other PHI) on a secure, password-protected data-base. The master list was stored on a separate password-protected computer. In the event of the computer malfunction resulting in loss of data, a password-protected copy was stored on the pulmonary service secure server. All personal identifying information will be destroyed at the completion of the data analysis and study publication. The remaining coded data will be saved on a password-protected computer.
All data and records generated during this study were kept confidential in accordance with Institutional policies and HIPAA standards. No personal health information (PHI) was stored on paper records. Study personnel did not use the collected data and records for any purpose other than conducting this study. All PHI was coded and stored in a secured location and on a password protected computer to ensure minimal risk to the subjects. The data obtained in the course of the investigation were stored in a secure location and kept in such a manner that potential risk of breach of confidentiality if the data protection plan was breached is minimal. The benefits of this research far outweighed the risks, as the risk associated with this retrospective chart review was minimal.

**Data Analysis**

A total of 203 participants were identified as meeting inclusion criteria during the date range of study. Of the total participants identified, 9 patients were excluded due to lack of documented pain scores in the EMR. Ninety-three patients were excluded due to exposure to confounding variables including additional medications with analgesic or sedative properties. Seven patients were excluded due to need for mechanical support and 20 patients were excluded due to poor creatinine clearance post-operatively. Of the total 129 participants excluded, 74 participants met all inclusion and exclusion criteria during the time period queried and were compared for comfort levels and overall opioid exposure within 24 hours or less post open heart repair.

In total, 53 infants received standardly prescribed rectal acetaminophen in conjunction with IV opioid and 21 infants received IV opioid only. Comparison of demographic and clinical variables between the two participant groups queried identified no clinically significant variance (see Table 1, for Comparison of Demographic and Clinical Variables).
Comparison of overall opioid exposure between the two participant groups identified a statistically significant difference ($p < 0.01$) between infants who received standardly prescribed rectal acetaminophen in conjunction with IV opioid versus infants prescribed IV opioid alone (see Table 2, for Comparison of Overall Opioid Exposure). Infants who received IV opioid alone used more opioid overall, with a concomitant increase in overall opioid exposure, than infants who received standardly prescribed rectal acetaminophen with IV opioid in the first 24 hours post open heart repair. The median value of opioid usage was 0.28mg/kg/day in infants who received IV opioid only versus 0.11mg/kg/day in infants who received rectal acetaminophen with IV opioid in the first 24 hours post open heart repair.

Comparison of pain scores utilizing the FLACC Behavioral Pain Assessment Scale between the two participant groups studied did not identify a statistically significant difference ($p < 0.08$) in comfort levels between infants who received standardly prescribed rectal acetaminophen in conjunction with IV opioid versus infants prescribed IV opioid alone within the first 24 hours post open heart repair (see Figure 1, for Comparison of the Outcomes: Pain Scores). Interestingly, both groups experienced similar levels of comfort despite infants in the rectal acetaminophen with IV opioid group receiving less overall opioid in mg/kg/day in the first 24 hours post open heart repair as compared to the infants who received IV opioid only.

Final data analysis methodology compared pain scores between the two participant groups studied with a total of 53 participants receiving rectal acetaminophen with IV opioid and a total of 21 participants receiving IV opioid alone. With the assumption of mean pain scores of 1.7 and 1 in the rectal acetaminophen with IV opioid group and the IV opioid only group respectively, the Poisson regression achieved a 72% power at a level of 0.05 significance.
**Timeframes**

Date range of the study was between October 1, 2012 through April 30, 2014. These dates encompassed initial surgeries between November 1, 2012 and April 29, 2014. Follow-up information through April 30, 2014 was included, as well as 30 days prior to the initial date of surgery (October 1, 2012) to evaluate subject inclusion.

**STRENGTHS AND WEAKNESSES OF THE STUDY**

**Strengths**

Utilizing dedicated cardiothoracic surgical, anesthetic, nursing, and respiratory care teams to manage care protocols for study participants queried, lends itself to the development of similar care practices between the two groups studied. Studying and comparing comfort levels and overall opioid use and exposure between two similar pediatric populations with similar post-surgical acute pain needs were also strength of this study. Participants of both groups, despite surgical procedure, had similar acute pain needs post-operatively as evidenced by a median sternotomy incision, chest tube, arterial or umbilical line, peripheral IV line, absence or presence of an endotracheal tube and nasogastric tube.

Clearly defining inclusion and exclusion criteria for study participants helps to support research findings and to reduce the possibility of investigative error (Hulley, Cummings, Browner, Grady, & Newman, 2013). Limiting data gathering to a single individual also helped to reduce data recording error related from EMR review. A final strength of this study was that this author and consultants utilized in the design and implementation of this study had prior experience and a knowledge base in regards to this population and interest of study.
Weaknesses

An identified weakness of this study is the lack of generalizability or external validity of data findings due to sampling from a single investigative site. Findings would need to be replicated or reproduced under similar conditions in related populations for generalizability of data findings to be applicable. An additional limitation of this study may be narrowing of participant population to only include full-term infants with CHD post open heart repair. Examining alternative infant participant populations may add to the body of knowledge this study provided.

An additional weakness of this study may be the designated time period of study. By limiting the period of study to 18 months, sufficient participants demonstrating a moderate to larger effect greater than 72% may have identified a statistically significant difference in comfort levels between infants who received standardly prescribed rectal acetaminophen in conjunction with IV opioid versus infants prescribed IV opioid alone within the first 24 hours post open heart repair. For instance, by increasing the designated time period of study from 18 to 24 months, a potential increase in participants from 21 to 29 infants who received IV opioid only may have been identified. By comparing 29 infants who received IV opioid only to 53 infants who received rectal acetaminophen with IV opioid, a power of 80% with a significance level of 0.05 may have detected a statistically significant difference in comfort levels between the two participant groups.
CONCLUSIONS AND RECOMMENDATIONS

Pediatric cardiothoracic surgical patients experience varying degrees of pain in the immediate post-operative period. Multimodal pain management therapies have been found to optimize pain needs in post-operative patients (Manworren, 2015). This retrospective, 18-month, quantitative study, completed at a large urban children’s teaching hospital, compared comfort levels and overall opioid use in full-term infants with CHD who were less than or equal to 30 days of age and within 24 hours or less post open heart repair. Fifty-three infants received standardly prescribed rectal acetaminophen in conjunction with IV opioid and 21 infants received IV opioid only. There was no reported statistically significant difference in comfort levels between both groups. Interestingly, infants who received IV opioid alone used more opioid overall, with a concomitant increase in overall opioid exposure, than infants who received standardly prescribed rectal acetaminophen with IV opioid in the first 24 hours post open heart repair.

Based on the results, future practice recommendations would include adjuvant use of rectal acetaminophen with IV opioid to reduce overall opioid exposure post-operatively in infants post open heart repair. Reduced overall opioid exposure may lead to fewer mu-mediated side effects, decreased recovery times, shorter hospital stays, and decreased costs related to care conditions. Additional recommendations would include utilizing lipophilic emulsion composition of suppositories for superior absorption (Prasanna, Deepthi, & Rao, 2012). Dosing recommendations for rectal acetaminophen at 40mg/kg have demonstrated an improvement in comfort levels and decreased overall morphine consumption in children postoperatively (Capici et al. 2008; Dashti et al., 2009; Korpela et al., 2006).

Additional practice recommendations would include clinical pathways that incorporate not only adjuvant use of rectal acetaminophen with IV opioid post-operatively in
infants, but use of valid and accurate pain assessment tools in the post-operative period. A final recommendation would be a multi-center study trial replicating this study or studying alternative or selective infant populations with CHD to determine if adjuvant use of rectal acetaminophen with IV opioid as compared to IV opioid only improves comfort levels and decreases overall opioid use in infants post open heart repair.
REFERENCES


### APPENDIX A: FLACC BEHAVIORAL PAIN ASSESSMENT SCALE

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Face</strong></td>
<td>No particular expression or smile</td>
<td>Occasional grimace or frown, withdrawn, uninterested</td>
<td>Frequent to constant quivering chin, clenched jaw</td>
</tr>
<tr>
<td><strong>Legs</strong></td>
<td>Normal position or relaxed</td>
<td>Uneasy, restless, tense</td>
<td>Kicking, or legs drawn up</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td>Lying quietly, normal position, moves easily</td>
<td>Squirming, shifting, back and forth, tense</td>
<td>Arched, rigid or jerking</td>
</tr>
<tr>
<td><strong>Cry</strong></td>
<td>No cry (awake or asleep)</td>
<td>Moans or whimpers; occasional complaint</td>
<td>Crying steadily, screams or sobs, frequent complaints</td>
</tr>
<tr>
<td><strong>Consolability</strong></td>
<td>Content, relaxed</td>
<td>Reassured by occasional touching, hugging or being talked to, distractible</td>
<td>Difficult to console or comfort</td>
</tr>
</tbody>
</table>

APPENDIX B: COMPARISON OF DEMOGRAPHIC AND CLINICAL VARIABLES

Table 1

Comparison of Demographic and Clinical Variables

<table>
<thead>
<tr>
<th></th>
<th>Opioid Alone (n=21)</th>
<th>Rectal acetaminophen with Opioid (n=53)</th>
<th>( p ) value (( p &lt; 0.05 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in weeks</td>
<td>39.2 (1.7)</td>
<td>39.5 (1.3)</td>
<td>( p &lt; 0.33 )</td>
</tr>
<tr>
<td>Weight in Kilograma(kg)</td>
<td>3.3 (0.6)</td>
<td>3.4 (0.6)</td>
<td>( P &lt; 0.38 )</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=46)</td>
<td>17 (81%)</td>
<td>29 (55%)</td>
<td>( P &lt; 0.06 )</td>
</tr>
<tr>
<td>Female (n=28)</td>
<td>4 (19%)</td>
<td>24 (45%)</td>
<td></td>
</tr>
<tr>
<td>Intubated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=59)</td>
<td>18 (86%)</td>
<td>41 (77%)</td>
<td>( P &lt; 0.53 )</td>
</tr>
<tr>
<td>No (n=15)</td>
<td>3 (14%)</td>
<td>12 (23%)</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* Mean (Standard deviation) were reported for continuous variables. Count (Frequency) was reported for categorical variables. Two samples \( t \)-test were used to compare continuous variables. Fisher’s exact tests were used to compare the categorical variables.

*Interpretation: There is no statistical difference between the two study groups.*
APPENDIX C: COMPARISON OF OVERALL OPIOID EXPOSURE

Table 2

Comparison of overall Opioid Exposure

<table>
<thead>
<tr>
<th></th>
<th>Opioid Alone (n=21)</th>
<th>Rectal acetaminophen with Opioid (n=53)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Milligrams per kg per day (24 hours)</td>
<td>0.28 mg/kg/day (0.16,0.32)</td>
<td>0.11mg/kg/day (0.06,0.21)</td>
</tr>
</tbody>
</table>

Notes. Median (Q1, Q3) and p value for Wilcoxon rank-sum test were reported. Infants who received IV opioid alone used more opioid overall, with a concomitant increased overall opioid exposure, than infants who received standardly prescribed rectal acetaminophen with IV opioid in the first 24 hours post open heart repair. The median value of opioid usage is 0.28mg/kg/day in the opioid alone group. The median usage of the opioid with rectal acetaminophen group is 0.11mg/kg/day. Interpretation: There is a statistically significant difference in opioid usage between the two study groups (p < 0.01).
APPENDIX D: COMPARISON OF THE OUTCOMES: PAIN SCORES

Figure 1

Comparison of the outcomes: Pain Scores

*Figure 1.* Frequency in percentages of number of pain scores ≥ 4 occurring between the two groups with 24 hours post open heart repair. *Interpretation: There is no statistically significant difference between the two study groups in pain scores (p < 0.08).*
APPENDIX E: NEUMAN CONCEPTUAL MODEL