Version: 7.2.18

Gabapentin Premedication to Reduce Postoperative Pain for Pediatric Tonsillectomy/Adenoidectomy: Randomized Control Trial

Study Personnel: Principal Investigator Margaret Gettis DNP, CPNP-PC and Co-Investigator James Thomsen MD

I. Background and Purpose

Tonsillectomy is one of the most common surgeries in children and is associated with significant postoperative pain. When pain is inadequately managed, a cascade of complications can ensue including difficulty swallowing, poor hydration and food intake as well as sleep disturbances and secondary bleeding. The current standard of care for pain management of young children having tonsillectomy/adenoidectomy (T/A) is Tylenol and Motrin. Adolescents having T/A receive a postoperative prescription for narcotics. However, both management modalities present challenges. Tylenol and Motrin became the de facto standard for young children upon discharge after the 2013 FDA's safety warning about codeine use and serious sequelae (FDA, 2013).However, studies have indicated even intravenous use of acetaminophen provides less pain relief than opioids and may increase the need for other analgesia (Amani & Abedinzadeh, 2015). In addition, chronic opioid usage after receiving opioids for surgery is well documented. It has been reported that in 2014, there were almost 500,000 teens using pain relievers for nonmedical use and of those adolescents, nearly a third would meet criteria for a use disorder (Knipper, Banta-Green & Jimenez, 2017). Few studies have compared acute surgical pain in the pediatric population and even fewer have evaluated the use of non-narcotics such as gabapentin to limit pain response.

Gabapentin is FDA approved for neuropathic pain in adults and it is often used off label in pediatric patients. Gabapentin has been used successfully for pain relief in other surgeries in the pediatric population. In spinal fusion surgery, gabapentin's suppression of spontaneous neuronal firing in response to tissue injury has been shown to be effective in treating pain (Rusy, Hainworth, Nelson, et al., 2010). In adult patients, two studies have described the use of gabapentin preoperatively in ACL surgery (Mardini-Kivi, Mobarakeh, & Motlgh, 2013; Menigaux, Guignard, Sessler, & Chauvin, 2005). Both studies concluded preoperative gabapentin was effective in decreasing pain intensity and reducing the use of postoperative analgesia. In addition, Mardini-Kivi et al (2013), found additional benefits as gabapentin improved preoperative anxiety as well as early knee mobilization after surgery.

Gabapentin (Neurontin) was originally developed as a gamma-aminobutyric acid (GABA)-mimetic compound to treat spasticity. Early studies found Neurontin also had anticonvulsive activity that led to initial approval for use in patients with partial seizure disorders. (Taylor, 1993; Satzinger, 1994). Later, it showed promise in the treatment of chronic and neuropathic pain syndromes, and was successfully used to treat neuropathic pain (Gustoff, Wahlin, & Spacek, 2002; Rosenberg, & Harrel, Ristic, 1997; Backonja, & Glanzman, 2003).

Although the mechanism of action of gabapentin in the treatment of pain is not completely understood, the drug appears to have a unique effect on voltage-dependent calcium ion channels at the postsynaptic dorsal horns and may interrupt the cascade of events leading to

the experience of neuropathic pain. Gabapentin also appears to be effective at relieving allodynia, pain due to a stimulus not normally provoking pain as well as hyperalgesia, an exaggerated reaction to a normally painful stimulus (Rose & Kam, 2002). Lastly, several studies have shown gabapentin to have a positive opioid sparing effect in adult surgical patients (Menigaux, Adam, & Guignard, et al., 2005; Fassoulaki, Patris, Sarantopoulos, & Hogan, 2002).

Gabapentin has been used as adjunct therapy in a variety of adult surgical procedures. In a 2006 meta-analysis, seven studies utilized gabapentin as adjunctive treatment for procedures including abdominal and vaginal hysterectomies, mastectomies, cholecystectomies, lumbar discoidectomies, and spinal surgeries (Seib, & Paul, 2006). In addition, it is a first line agent for the treatment of neuropathic pain including pain arising from diabetic neuropathy, post-herpetic neuralgia and central neuropathic pain (Attal, Cruccu, Baron et al, 2010).). Gabapentin is approved by the Federal Drug Administration (FDA) and has been used off label as adjunct therapy for pain in spine surgery and treatment of neuropathic pain in children. (Mayell, Srinivasan, & Campbell et al, 2014; Rusy, Hainsworth, Nelson, et al, 2010; Butkovic, Toljan, & Mihovilovic-Novak, 2005).

Purpose: The purpose of this pilot study is to: 1) to examine the use of gabapentin in reducing pain postoperatively including the total amount of narcotics and Tylenol/Motrin mg/kg given 2) to record the time to first analgesic postoperatively and 3) to compare Wong Baker and scaled 1-10 pain scores at 12, 24 and 48 hours postoperatively.

Hypothesis: We hypothesize one 15mg/kg (up to 600mg) dose of gabapentin will decrease mean narcotic amounts mg/kg compared to participants who do not receive preoperative gabapentin and will demonstrate a decreased mean time to first analgesic as well as to lower mean pain scores for each age group at 12, 24 and 48 hours. Tylenol and Motrin use will be recorded for participants not taking narcotics as well as any medication requested for "break through" pain.

Conclusion: Gabapentin may represent a low cost and effective modality to reduce acute pain after T/A in the pediatric population. Due to the current opioid crisis as well as the lack of studies validating alternative pain management strategies, the study may yield compelling information.

II. Summary of Procedures

This double blinded randomized control pilot study will enroll 50 participants age 3-18 years, undergoing T/As in the Scottish Rite Day Surgery at Children's Healthcare of Atlanta. Participants will be receiving either gabapentin or placebo preoperatively. The cost of the medication will be paid out of study funding; no expense will be incurred by the participant. Both control and test group will receive the standard narcotic regimen intraoperatively.

During the preoperative phase, the participants will be asked to consider enrolling in the study at the preoperative visit with the attending surgeon. A brochure explaining the study will be provided and the surgeon will be available to answer questions. Written informed consent will be obtained at the preoperative visit by a member of the research study team. The study team member will enter the participant's participation into the REDCap database. REDCap is a secure database approved for use by Children's IRB. A CHOA hospital pharmacist will randomize the subjects to the gabapentin group or placebo group. The PI will be responsible for insuring the participant's randomized medication is available at the surgery site. The

medications will be administered by mouth in liquid form with identical appearance and taste for drug and placebo. Patients will be randomized to either a single dose of 15mg/kg up to 600 mg of gabapentin or a placebo equivalent at a 1:1 ratio. The method for the randomization will be the creation of a sequence of sealed envelopes containing assignment information for a dose of up to 600 mg of gabapentin or placebo. Additionally, children age 3-12 years will receive instruction for Tylenol and Motrin postoperatively while teenagers age 13-18 years will receive a narcotic prescription. Outcome measurements collected from the medical record by the study team will include the mean time to first analgesic as well as Tylenol mg/kg, Motrin mg/kg and narcotic mg/kg use. All data collected from the medical record will be recorded into REDCap. In addition after discharge, the study participants receive an email for three days to fill out pain diary information via a secure link to REDCap. A research study team member may call to remind study participants to fill out the pain dairy three times. The pain diary will document medication use, pain scores and side effects. These outcome measurements will give a more comprehensive description of the postoperative experience and test gabapentin's opioid sparing effect. Due to the paucity of literature on alternative pain methods in the pediatric population, this study could provide evidence of the effectiveness of gabapentin as a standard of care in pediatric pain management.

III. Risks

Possible risks for study participation include physical harm or discomfort from unanticipated drug side effects, and minor psychological or emotional distress. Benefits could include access to a potentially beneficial intervention for pain relief and monetary gain through study financial incentives.

Participation in the RCT is completely voluntary. The participants will be instructed during consent that they may withdraw at any time with no changes in their treatment.

Study IDs will be assigned for each participant and patient PMI will remain confidential. Study papers will be kept in a locked file drawer and electronic data storage will be in the IRB approved secure site RedCap, in password protected files. After study completion, all data will be destroyed at the designated time per Children's Healthcare of Atlanta requirements,

Gabapentin is generally well tolerated with few serious adverse effects. However, in less than 20% of the time potential adverse events could include somnolence, dizziness, ataxia and fatigue and most seriously in less than 1% of the time, convulsions (Ramsey, Levy, Mattson, & Meldrum, 1995). Patients will be closely monitored for these side effects. The FDA finds that Gabapentin should be used carefully in patients with renal impairment due to possible accumulation and toxicity (Federal Drug Administration, 2015). For this reason, patients with renal insufficiency are not eligible to participate.

A safety plan is in place for the study. The research study team member will screen for side effects during each phone call. The PI will file a monthly report of side effects in the Note to File section in the study binder.

IV. Potential Benefits

Benefits could include access to a potentially beneficial intervention for pain relief.

V. Inclusion and Exclusion Criteria

Participants scheduled for Tonsillectomy/Adenoidectomy will be screened for eligibility. Eligible participants will be approached at the attending surgeon's office during their preoperative visit and consented at the preoperative visit or the day of surgery by a member of the research study team.

Inclusion criteria include participants age 3-18 years with an ASA class 1 or 2 scheduled for elective Tonsillectomy/Adenoidectomy in the outpatient setting without regard to race or ethnicity. Exclusion criteria include a BMI >40, history of renal insufficiency, chronic pain or allergy to gabapentin. Participants will receive a $25.00 gift card after providing information during brief phone interviews at 12 hours, 24 hours and 48 hours after surgery.

VI. Informed Consent Process

During the preoperative phase, participants scheduled for Tonsillectomy/Adenoidectomy repair will be screened for eligibility by the attending surgeon and the participants will be asked to consider enrolling. A brochure explaining the study will be provided and the surgeon will be available to answer questions. Written informed consent will be obtained at the preoperative visit by a member of the research study team. The language to be used by the research study team will be English. However, if the language understood by the participant and family is different, accommodation will be made by offering the written informed consent in the participant and family's native language on the Children's approved short forms or with an interpreter. Likewise, an interpreter will be used to assist the research study team with postoperative phone calls. Per Children's policy, written informed consent for study participation will be obtained from a parent or legal guardian. Additionally, written assent to participate will be obtained from participants age 11-17 years. Verbal assent will be obtained from participants 6-10 years of age.

VII. Other Protocol Elements to Consider

Provisions to protect the privacy interests of participants include the following: participants will be approached at the attending surgeon's office during their preoperative visit which will be conducted in a private setting. The participants will be consented at the preoperative visit by a member of the research study team in a private room. All study paperwork discussed with the participants and family will be signed and a duplicated copy given to them. Data will be input into the REDCap database at the time of consent in the privacy of the room. REDCap is a secure database approved for use by Children's IRB.

Study IDs will be assigned for each subject and participant PMI will remain confidential. Study papers will be kept in a locked file drawer and electronic data storage will be in RedCap, the IRB approved secure site in password protected files. After study completion, all data will be destroyed at the designated time per Children's Healthcare of Atlanta requirements.

To balance the effects of age and type of surgery, we will utilize a stratified block randomization. Subject will be randomized according to their age (3-5, 5- 12 and 13-18) and surgery type (tonsillectomy alone, tonsillectomy + adenoidectomy). The combination of age and surgery type will create 6 different strata. Within each strata, randomization assignments will be generated

using random permuted blocks of size 2 and 4 subjects. Subjects will be randomized to receive either Gabapentin or Placebo at a 1:1 ratio.

Descriptive statistics will be calculated for all variables of interest and include means and standard deviations, medians and ranges, or counts and percentages, when appropriate. Normality of continuous outcomes (postoperative pain scores, time to first analgesic) will be assessed using histograms, density plots and the Shapiro Wilk-Test for normality. Normalizing transformations will be applied or nonparametric analyses will be utilized instead. Categorical and continuous demographics and surgical characteristics will be compared between treatment groups Chi-square tests and two-sample t-tests, respectively. Cross sectional outcomes will be compared between treatment groups using generalized linear models. These models are flexible class of exponential models that allow for the modeling of different outcomes measurements (i.e., count data, binary data and continuous data) through the use of different distributions and link functions. In addition, these models will allow control for other clinical characteristics that may affect the outcome measures and include: ASA status, age, sex, and weight. Total amounts of opioids mg/kg given will be calculated over the 3 day period and compared using similar methods as described above.

For measurements followed repeatedly over time (i.e., pain, daily opioid consumption and side effects) the statistician will use generalized linear mixed models to compare outcomes among treatment groups with random intercepts for each patient. These models account for the correlation arising from repeated measurements made on the same study subject and allow for participants to have different baseline postoperative measurements. Cross-sectional comparisons between groups at specific time intervals will be made using a post-hoc multiple comparison procedure to control the type I error rate. Within group comparisons will be made using paired t-tests or a nonparametric equivalent. Non-linear models will also be considered. A $p< 0.05$ will be considered statistically significant and analyses will be conducted using SAS 9.3.

A safety plan is in place for the study. The research study team member will screen for side effects at each phone call. The PI will file a monthly report of any side effects in the Note to File section in the study binder.

References

Amani, S., Abedinzaheh, M.R. (2015). Effects of oral gabapentin, local bupivacaine and intravenous pethidine on post tonsillectomy pain. *Iranian Journal of Otorhinolaryngology.* 27 (5): 342-347.

Amin, S.M. (2014). Evaluation of gabapentin and dexamethasone alone or in combination for pain control after adenotonsillectomy in children. *Saudi Journal of Anesthesia.* 8 (3): 317-322.

Attal, N., Cruccu, G., Baron, R. (2010). EFNS guidelines on the pharmacological treatment of neuropathic pain. European Journal Neurology, 17 (9), 1113.

Backonja, M., Glanzman, R.L. (2003). Gabapentin dosing for neuropathic pain: evidence from randomized, placebo controlled trials. Clinical Therapeutics, 25, 81-104.

Butkovic, D., Toljan, S., Mihovilovic -Novak, B. (2006). Experience with gabapentin for neuropathic pain in adolescents: report of five cases. Pediatric Anesthesia, 16, 325-329.

Fassoulaki, A., Patris, K., Sarantopoulos, C., Hogan, Q. (2002). The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesthesia Analgesia, 95,985-991.

Gabapentin official FDA information, side effects and uses. Retrieved from http://www.fda.gov.

Gustoff, B., Wahlin, G., Spacek, A. (2002). Gabapentin in the treatment of chronic intractable pain. Schmerz, 16, 9-14.

Harbaugh, C.M., Lee, J.S., Hu, H.M., McCabe, S.E., Voepel-Lewis, T., Englesbe, M.J., Brummett, C.M., Waljee, J.F. (2018). Persistent Opioid Use among pediatric patients after surgery. 141 (1): 1-9.

Hwang, S.E., Park, I.J., Cho, Y.J., Jeong, Y.M., Kang, J.M. (2016). The efficacy of gabapentin/pregabalin in improving pain after tonsillectomy: a meta-analysis. *The Laryngoscope.* 126:357-366.

Knipper, E., Banta-Green, C.J., Jimenez, N. (2017). Opioid use disorder and misuse: A review of the epidemiology and medical implications for pediatric anesthesiologists. Pediatric Anesthesia, (11), 1070-1076.

Mardini-Kivi, M., Mobarakeh, M.K., Keyhani, S., Motlagh, K.H., Ekhtiari, K.S. (2013, September). Is gabapentin effective on pain management after arthroscopic anterior cruciate ligament reconstruction? A triple blinded randomized controlled trial. The Archives of Bone and Joint Surgery, 1(1), 18-22.

Mayell, A., Srinivasan, I., Campbell, F., Peliowski, A, A. (2014). Analgesic effects of gabapentin after scoliosis surgery in children: a randomized controlled trial. Pediatric Anesthesia, 24, 1239-1244.

Menigaux, C, C., Adam, F., Guignard, B., Sessler, D.I., Chauvin, M. (2005). Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesthesia Analgesia, 100, 1394-1399.

Mohamed, M.H., Al-Sercy, H. (2014). Preoperative gabapentin decreases the incidence of postoperative vomiting and analgesic requirements after pediatric adenotonsillectomy. *The Egyptian Journal Otolaryngology.* 225-228.

Ramsey, R.E. (1995). Gabapentin toxicity. In: Levy, R.H., Mattson, R.H., Meldrum, B.S., (Eds.), Antiepileptic Drugs (pp.857-860). New York: Raven Press.

Rose, M.A., Kam, P.C.A. (2002). Gabapentin: pharmacology and its use in pain management. Anesthesia, 57,451-462.

Rosenberg, J.M., Harrel, C., Ristic, H. (1997). The effect of gabapentin on neuropathic pain. Clinical Journal of Pain, 13, 271-275.

Rusy, L.M., Hainsworth, K.R., Nelson, T. J., Czarnecki, M.L., Tassone, C., Thometz, J.G., Lyon, R. M., Berens, R.J., Weisman, S.J. (2010, May). Gabapentin Use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial. Anesthesia Analgesia, 110 (5), 1393-1398.

Satzinger, G., (1994). Antiepileptic from gamma-aminobutyric acid. Arneimittelforchung, 44, 261-266.

Seib, R.K., Paul, J.E. (2006). Preoperative gabapentin for postoperative analgesia; a meta-analysis. Canadian Journal of Anesthesia, 53, (5), 461-469.

Shea, K.G., Pfeiffer, R., Wang, J.H., Curtin, M., Apel, P.J. (2004). Anterior cruciate ligament injury in pediatric and adolescent soccer players: an analysis insurance data. Journal of Pediatric Orthopedics. 24, 623-628.

Taylor, C.P. (1993). Mechanisms of action of new antiepileptic drugs. In: Chadwick, D., (Ed), New Trends in Epilepsy Management: the Role of Gabapentin.

Thiels, C.A., Anderson, S.S., Ubl, D.S., Hanson, K.T., Berquist, W.J., Gray, R.J., Gazelka, H.M., Cima, R.R., Habermann, E. Wide variation and overprescription of opioids after elective surgery. *Annals of Surgery* 266 (4): 564-573.

U.S. Food and Drug Administration (2013). FDA Drug safety communication: *codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare but life threatening adverse events or death.* Retrieved from www.https:www.fda.gov/downloads/Drugs/Drug Safety/UCM339116.pdf