Protocol Title: Pain Control in Pediatric Posterior Spine Fusion Patients: The Effect of Gabapentin on Post-operative Opioid Use and Patient Satisfaction

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Primary Investigator: Matthew F. Halsey, MD

Primary Aims:

To evaluate the pain control efficacy of gabapentin when added to a standard postoperative protocol in pediatric patients undergoing posterior spinal fusion for idiopathic or neurogenic scoliosis, using the visual analog scale (VAS - Appendix 1) and total dose/kg of opioid used during the postoperative period to determine differences in pain.

Secondary Aims:

To evaluate the effects of adding gabapentin on instances of opiate related side effects, duration of hospitalization, the amount of narcotics used postoperatively and overall family satisfaction with efforts to control postoperative pain.

Introduction:

Surgery for the correction of pediatric spine deformity results in significant post-operative pain that is challenging to the patients, their families and the staff caring for them. Numerous studies have tried to identify the best methods to control this pain including the use of opioid PCA, intravenous acetaminophen, epidural morphine, intravenous ketorolac and multimodal therapies. [1,2,3,4,5] These efforts have produced some successes yet there remain problems with poorly controlled pain and substantial adverse effects associated with each of these modalities.

Recently, attention has turned to the use of gabapentin as a potential agent to improve peri-operative pain control and to decrease the use of opioids.[6] Originally used as an anticonvulsant medication, gabapentin is now commonly used to treat chronic, centrally-mediated neuropathic pain syndromes.[8] It's mechanism of action is to suppress spontaneous central neuronal firing thereby decreasing the pain associated with the central sensitization brought about by the peripheral tissue injury.[7]

The impetus for this study is to re-evaluate the effectiveness of gabapentin in a randomized, double-blinded, controlled fashion similar to that used by Rusy et al[8] but in the context of a more robust multi-modal postoperative pain management milieu.

Methods:

This will be a prospective, randomized, controlled and double-blinded study. Study candidates will be identified in clinical encounters which evaluate or diagnose idiopathic or neurogenic scoliosis in patients aged 10-19. Written, informed assent from each patient and consent from parents will be obtained at pre-operative visits in which posterior spinal fusion is the planned procedure. Inclusion criteria will be patients of age 10-19 with an ASA patient classification of I to III. Patients will be excluded

from the study if they have a body mass index greater than or equal to 35.0, will require a surgical approach or technique differing from posterior spinal fusion, and/or have allergies to any of the standardized or experimental study medications: acetaminophen, gabapentin, hydromorphone, ketorolac or oxycodone. Patients who cannot effectively use the PCA alone will be included in the study for analysis but will not be counted towards the calculated number of patients per study arm due to difficulty comparing their hydromorphone use with that of other patients. Many of these patients are projected to be neuromuscular patients, and to build on a relative parity of literature about post-operative pain control in neuromuscular scoliosis RNCA will be used and all data recorded as with patients who can communicate their pain level.

If patients choose to participate in the study, they will be randomized into either the experimental or control group using the following computer randomization applet:
<www1.assumption.edu/users/avadum/applets/applets.html>
Patients, caretakers and providers will be blinded to the group assignments. An electronic copy of the group assignments will be retained by researchers uninvolved in patient care, and patients will be known by an alphanumeric code in research files to maintain privacy of information.

Medications and Patient Care Protocols:

Following pre-operative hospital admission, all patients will be asked to record their initial pain level with the VAS tool prior to receiving standardized pre-operative medications. The VAS has been well verified in pediatric patients as a valid pain measure patients are capable of understanding and using reliably. Patients in both groups will receive one 12.5 mg/kg dose of IV acetaminophen. Additionally, patients in the experimental group will receive one 15 mg/kg dose of gabapentin while the control group will receive a placebo. Each time the gabapentin or placebo is administered it will be prepared by the OHSU research pharmacists so that providers will remain blinded to treatment assignment. These medications will be administered on a regimen so that each group and patient receive them approximately the same amount of time prior to surgery. The placebo will be compounded by the research pharmacy and both the gabapentin and placebo will be in liquid form.

Several intraoperative anesthetic medications will be protocolized including IV ketamine at 5mcg/kg/min for 120 minutes and IV Ketorolac 0.5mg/kg up to 15mg(at the conclusion of the case), while propofol infusions and IV hydromorphone are titrated to desired effect. Two surgeons, Dr. Matthew Halsey MD and Dr. Ronald Turker MD will perform all of the surgeries in this study, and all patients considered in this study will undergo a posterior spinal fusion procedure.

Post-operative medication administration will also be protocolized. Ketorolac will be continued at 0.5mg/kg up to 15mg IV q6 for twelve total doses (including the intraoperative dose). Once the Ketorolac doses are complete, the patient will receive Ibuprofen 10mg/kg up to 600mg PO q6 scheduled. Hydromorphone PCA will be set at a basal dose of 0.002mg/kg/hr and demand dose of 0.004mg/kg with an 8 minute lockout; the basal PCA dose will be administered for 24 hours. Once basal PCA is discontinued, administration of oxycodone 0.1-0.2mg/kg PO up to 15mg PO q4h as needed will be

used in conjunction with the PCA demand dose. If the patient is able to tolerate PO oxycodone without emesis, after 24 hours the PCA will be completely removed but a rescue dose of Hydromorphone 0.002mg IV q4 prn will remain. Other as needed medications will include Valium 0.15mg/kg up to 5mg PO q6h for muscle spasms, Ondansetron 0.1mg/kg up to 4mg IV q12h for nausea, and IV Acetaminophen 12.5mg/kg up to 1000mg q6h. Acetaminophen 12.5mg/kg up to 650mg PO q6 hours will be administered after the patient's IV is removed. All patients will receive 1 Senokot-S tablet and Miralax 0.8 g/kg up to 17g daily for bowel regimen.

The dosing for Gabapentin, the study medication, is 10mg/kg PO q8h, beginning when the patient is admitted to his or her floor bed postoperatively. This will be administered through postoperative day four. Patients in the control group will receive equivolume doses of a placebo medication at the same administration intervals.

For the entirety of hospitalization, nursing staff will regularly assess and monitor vital signs and POSS sedation using current protocols to ensure patient comfort and safety (POSS tool- Appendix 2).[9] Any POSS score of 3 or greater will be considered unacceptable and require specific actions including but not limited to closely monitoring respiratory status, sedation level, decreasing opioid dose, and administering naloxone. All rounding residents and doctors will have a checklist of the most common and most adverse gabapentin drug reactions when assessing patients. The most common reactions include peripheral edema, nausea/vomiting, viral disease, ataxia, dizziness, nystagmus, somnolence, hostile behavior, fatigue and fever. The most adverse reactions include Stevens-Johnson syndrome, drug hypersensitivity reactions, drug induced coma/seizure, and suicidal thoughts. These reactions will result in the gabapentin or placebo being stopped at the clinicians' discretion. Nursing staff will also assess patient pain using the VAS, instructing patients to mark the laminated scale with a vertical line using a dry-erase market at the point which best corresponds to their pain level at that time. Nursing staff will be instructed on proper measurement, in millimeters from 0, or "no pain," and will record the measured pain score in the patient's electronic medical record. The VAS scale used in this study is a 10 cm line with anchors of "no pain" and "worst pain imaginable." The use of a VAS scale in pediatric pain management has been well verified.[10,11,12,13] The assessment of pain level will be performed a minimum of once per 4 hour period from 06:00 until 22:00 for the duration of hospitalization and recorded as the highest VAS score during each 4 hour period (6-10, 10-14, 14-18, 18-22). A minimum of 4 daily VAS score values will be recorded per patient.

Patients will be discharged from the hospital upon meeting the following criteria: adequate PO intake, Foley catheter removal without urinary retention, ability to perform independent bed to toilet transfer and adequate pain control on oral medications defined as acceptable to the patient and family. (Upon discharge patients will be prescribed oral narcotics which will be counted at their first follow up appointment two weeks later.)

Data Recording:

VAS scores will be collected by nursing staff as described above. These laminated sheets will be kept with the patients' charts. A nurse or doctor will also provide the parent or primary caregiver of each patient with a pain control satisfaction survey (Appendix 3) on the day of discharge to assess their overall understanding and satisfaction with the pain control efforts and efficacy in the hospital. These surveys will be collected prior to discharge and also kept with the patient chart. Documents will be collected daily by researchers and stored in a secure office on OHSU campus, in a building separate from any in which study patients will be receiving care. Upon discharge, all paper documents will be scanned into an electronic file.

Each patient will have their own individual file kept on OHSU campus computers in the OHSU secured network with password permissions applied so that only study researchers have access to the information. All medication data will be obtained post-discharge by a review of the electronic medication administration report (MAR). PCA hydromorphone syringes used and syringes wasted will be counted and recorded. Patient weight, date of transition to oral pain medications, dates of admission, operation and discharge, episodes of documented nausea/emesis, instances of urinary retention requiring replacement of a catheter after removal or POSS ≥3 recorded in flow sheets will all also be retrieved from patients' electronic medical records by study researchers uninvolved in patient care. VAS scores measured in millimeters from the start point and uploaded into electronic medical records by nursing staff will be collected. Furthermore, patients will be asked to bring their prescribed postoperative outpatient narcotics to their first follow up appointment after discharge for a pill count to determine the amount of medication used, and that count will conclude their participation in the study. Further follow up appointment data will not be collected. A data collection tool (Appendix 4) has been created to record study data in each patient's electronic study file, and as mentioned above all patients will have an alphanumeric code assigned to their information instead of name for data analysis.

Statistical Considerations and Analysis:

Sample size (n) was calculated using a two-sided continuous outcome superiority trial model; $n = f(\alpha/2, \beta) \times 2 \times \sigma^2 / (\mu_1 - \mu_2)^2$ where μ1 and μ2 are the mean outcome in the control and experimental group respectively, σ is the standard deviation; $f(\alpha, \beta) = [\Phi\text{-}1(\alpha) + \Phi\text{-}1(\beta)]2$; Φ-1 is the cumulative distribution function of a standardized normal deviation. Data will be collected for a minimum of a total of 50 total patients, with an equal number of patients in both the control and trial groups. Based on past history at OHSU Doernbecher Children's Hospital and the number of annual operative scoliosis cases of the two participating surgeons it is estimated that it will take approximately 2 years to accumulate this number of study subjects. This n was reached by calculating a statistical study power β of 0.8 and α of 0.05. The study has been powered to compare VAS scores, mg/kg of opiate use, and duration of hospitalization post-operatively.

Calculations were designed to detect a difference in mean VAS score $(\mu_1 - \mu_2)^2$ of 2 between study groups with a standard deviation σ of 2.5, which was calculated from the standard deviations in VAS score reported by Rusy et al.[8] These values were chosen to reflect a clinically significant difference

in pain. Prior studies have stated that variability of 12mm or less constitutes no clinical difference in patient pain, and that reduction in pain level of 20% correlates with mild improvement or minimal clinically important difference and 30% with notable improvement of patient pain. [12,14] It has also been documented that requests and use of additional analgesia increase as patients move through different stratifications of pain scores, with those having a score under 30mm rarely requesting additional medication and those with a score above 70mm requesting additional pain medication frequently.[15] Instances of severe pain, defined as a pain score of greater than 70mm will be recorded and compared between groups as well.

The sample size of 55 patients was confirmed as a valid choice for this study using a continuous equivalence calculation to exclude a difference of VAS means of greater than 2.1 with a standard deviation of 2.5, β of 0.8 and α of 0.05. Additionally, calculations were performed to power the study for amount of opiate used. Provided a sample size of 25 patients per group, β of 0.8, α of 0.05, and standard deviation of .0046 mg/kg/h of hydromorphone used based on morphine equivalents using a conversion factor of 6.67 as in a prior study by Dampier et al[16] this study will be able to detect a significant difference in hydromorphone use of .0037 mg/kg/h. Standard deviation estimates were used based on data from Rusy et al[8] and Turan et al[17] and morphine equivalents used to compare to those studies' findings regarding the total daily opioid sparing effects of gabapentin and the significance of a cumulative decrease in morphine use after spinal surgery.

The following previously developed and tested study power calculators were used:
<http://www.sealedenvelope.com/power/continuous-superiority/>
<http://www.sealedenvelope.com/power/continuous-equivalence/>

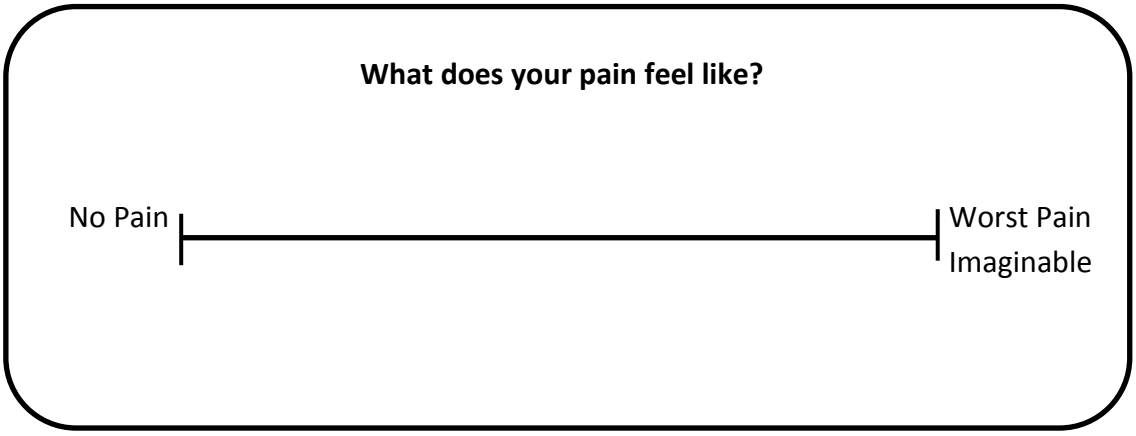
Paired T-tests will be used to evaluate the study outcomes and hypotheses. The null hypotheses are as follows:

1. There is no significant difference in pain control when adding gabapentin to a multimodal pain management protocol in pediatric post-operative posterior spinal fusion patients.

2. There is no significant difference in the amount of opiate medication required for pain control in pediatric post-operative posterior spinal fusion patients.

Appendix 1: VAS

Visual Analog Pain Scale



Appendix 2: POSS

Pasero Opioid-induced Sedation Scale (POSS)

S = Sleep, easy to arouse
Acceptable; no action necessary; may increase opioid dose if needed

1. Awake and alert
Acceptable; no action necessary; may increase opioid dose if needed

2. Slightly drowsy, easily aroused
Acceptable; no action necessary; may increase opioid dose if needed

3. Frequently drowsy, arousable, drifts off to sleep during conversation
Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50% or notify prescriber or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing non-opioid, such as acetaminophen or an NSAID, if not contraindicated.

4. Somnolent, minimal or no response to verbal or physical stimulation
Unacceptable; stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.

*Appropriate action is given in italics at each level of sedation.
[1]Opioid analgesic orders or a hospital protocol should include the expectation that a nurse will decrease the opioid dose if a patient is excessively sedated.
[2]For example, the physician, nurse practitioner, advanced practice nurse, or physician assistant responsible for the pain management prescription.
[3]Mix 0.4 mg of naloxone and 10 mL of normal saline in syringe and administer this dilute solution very slowly (0.5 mL over 2 minutes) while observing the patient's response (titrate to effect) (Source for naloxone administration: Pasero, Portenoy, McCaffery M. Opioid analgesics, in *Pain: Clinical Manual* [ed 2]. St. Louis, MO, Mosby 1999, p. 267; American Pain Society [APS]. *Principles of Analgesic Use in the Treatment of Acute Pain and Chronic Cancer Pain* [ed 5], Glenview, IL, APS, 2003.)
[4]Hospital protocols should include the expectation that a nurse will administer naloxone to any patient suspected of having life-threatening opioid-induced sedation and respiratory depression.

Appendix 3: Parental Pain Perception Assessment Survey

Study #_____ Interview Date_____ Surgery Date_____

PARENT INFORMATION
Sex: Male ☐ Female ☐ **Age in years:** 16-25 ☐ 26-30 ☐ 31-39 ☐ 40-49 ☐ 50-59 ☐ 60-69 ☐
Race/Ethnicity: Black ☐ White ☐ Hispanic ☐ Other ☐
Highest Level of Education: Less than high school ☐ High school/GED ☐ Some college ☐ College graduate ☐ Advanced Degree ☐
Marital Status: Single ☐ Married ☐ Divorced ☐ Partnered ☐ Widowed ☐
Relationship to Child: Mother ☐ Father ☐ Stepmother ☐ Stepfather ☐ Grandparent ☐ Foster parent ☐ Other ☐
***Child's* Health Status:** Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor ☐ Does your child have any disabilities?
ADMISSION
The following questions apply to when your child was admitted to the hospital
Was your child in pain when admitted to the hospital? Yes ☐ No ☐
On admission, did your nurse ask you or a family member about how your child shows pain? Yes ☐ No ☐
Does your child have a history of chronic pain? Yes ☐ No ☐
PAIN HISTORY
The following questions apply to previous hospitalizations
Has your child been hospitalized before? Yes ☐ No ☐
If yes, did your child experience pain during the hospitalization? Yes ☐ No ☐
Was the pain related to a procedure? Yes ☐ No ☐
Was the pain following surgery? Yes ☐ No ☐
During that hospitalization, how satisfied were you with your child's pain control? Very dissatisfied ☐ Somewhat dissatisfied ☐ Somewhat satisfied ☐ Very satisfied ☐
PARENTAL PRESENCE
The following questions apply to this hospitalization
During the past 24 hours, have you been able to be with your child… None of the time ☐ Some of the time ☐ Half of the time ☐ Most of the time ☐ All of the time ☐

During the past 24 hours, if you were able to be with your child was it… During the day ☐ During the evening ☐ During the night ☐ All ☐

CURRENT PAIN HISTORY
The following questions are general questions related to pain during the hospitalization.
How often did your child have pain in the past 24 hours? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
On a scale of 0-10, zero meaning no pain and 10 meaning the worst pain imaginable, how often did your child experience a pain score of 4 or greater (this is considered moderate to severe pain)? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did the nurse promptly identify that your child was in pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did your child receive pain medication? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
From your perspective, what type of pain medication did your child receive? Pain Pump ☐ IV Medication ☐ Oral Medication ☐ Other ☐
How often was the pain relieved with the medication? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did someone discuss different options to treat the pain when your child had pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did you receive enough information to understand the pain treatment plan? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often were you or a family member included in decisions to change treatment of your child's pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often was there a prompt response to your worries or concerns regarding your child's pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often was there prompt treatment of your child's pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did the nurse help calm and soothe your child using methods other than pain medication or involve child services? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did the nurse demonstrate caring behaviors to help you and your child with their pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did the nurse show they had adequate knowledge and skills to help your child with their pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did someone explain the pain relief plan when your child had pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often did someone take the time to answer all your questions about treating pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐

What information would you have liked to receive or not receive? How often were you or a family member included in decisions on how best to treat your child's pain? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
How often was management of your child's pain to your satisfaction? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
SATISFACTION
The following questions relate to your level of satisfaction with pain management and any recommendations for improvement.
In the past 24 hours, how often were you satisfied with the providers' communication with you? None of the time ☐ Some of the time ☐ Most of the time ☐ All of the time ☐
For the past 24 hours, how satisfied are you with the overall management of your child's pain? Very dissatisfied ☐ Somewhat dissatisfied ☐ Somewhat satisfied ☐ Very satisfied ☐
Overall, how satisfied were you with pain control in the hospital? Very dissatisfied ☐ Somewhat dissatisfied ☐ Somewhat satisfied ☐ Very satisfied ☐
Is there something we could have done differently to better manage your child's pain?
Other comments: *Thank you for your participation!*

Appendix 4: Data Collection Tool

Pt. Identification Code										
Study Group #										
Pt. Name										
MRN										
Parental Survey ID #										
Sex										
Age										
Weight (Kg)										
Admit Date										
Discharge Date										
Days Hospitalized										
Pre-Op. Diagnosis										
Operative Technique										
# Days Using PCA										
	Operative Day	PO Day 1	PO Day 2	PO Day 3	PO Day 4	PO Day 5	PO Day 6	PO Day 7	Total	Avg./Day
VAS Pain Score 1 (02:00-06:00)										
VAS Pain Score 2 (06:00-10:00)										
VAS Pain Score 3 (10:00-14:00)										
VAS Pain Score 4 (14:00-18:00)										
VAS Pain Score 5 (18:00-22:00)										
VAS Pain Score 6 (22:00-02:00)										
Avg. VAS Pain Score										
IV Hydromorphone use (mg/kg)										
Hydromorphone syringes used (#)										
Hydromorphone syringes wasted (#)										
Oxycodone use (mg/kg)										
IV Acetaminophen use (mg/kg)										
P.O. Acetaminophen use (mg/kg)										
Total Acetaminophen use (mg/kg)										
Gabapentin use (mg/kg)										
IV Ketorolac use (mg/kg)										
Zofran use (mg/kg)										
Episodes of Emesis										
Reports of Nausea										
Instances of POSS score ≥ 3										
Urinary Catheter in place (Y/N)										
Date of First Recheck Appt:										
Days Outpatient (#)										
Narcotic Prescribed on Discharge (Name)										

Narcotics Prescribed on Discharge (#)										
Narcotics Remaining at First Recheck (#)										
Narcotics Used Post Discharge (Total mg)										
Avg. Daily Narcotic Use (mg)										

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