Randomized prospective study comparing variable Gabapentin dosages for postoperative analgesia following open thoracotomy

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1.0 Background

Thoracic surgery, particularly open thoracotomy, is considerably stressful and painful for patients. Enhanced recovery after surgery (ERAS) protocols have been designed to decrease this stress and pain for patients via multimodal analgesia, strict fluid balancing, and patient optimization preoperatively, intraoperatively, and postoperatively (1). Effective ERAS protocols, for many surgeries including thoracotomy, have been shown to decrease opioid exposure, improve outcomes, and decrease hospital length of stay (LOS) (2-4, 14). Other studies have shown conflicting evidence, that ERAS protocols may not have significant improvements in the previously stated items (5-6, 15-16). Gabapentin is a common medication used preoperatively and postoperatively as part of multimodal analgesia for ERAS protocol. Recent studies have shown concern that gabapentin may not decrease opioid use postoperatively and that it may lead to increased postoperative pulmonary complications and impaired cognition (6-9). The purpose of this study is to determine the effectiveness of various dosages of gabapentin, as part of an ERAS protocol, for postoperative analgesic control after open thoracotomy and additionally determine if there is a correlation of the dosage of gabapentin with pulmonary complication and impaired cognition postoperatively.

ERAS protocols in thoracic surgery have experienced a variety of iterations and are often still institutionally dependent. These protocols include several components including patient education, intraoperative anesthesia management, perioperative pain control, chest tube management, nutrition, IV fluids and Foley management, and mobilization. Among these, pain control methods are still actively debated and there is considerable variety between institutions (4-5, 10-12). Many institutions use gabapentin preoperatively and postoperatively in varying amounts. Given the widespread use of gabapentin and the huge variability in dosing, our study aims to simplify ERAS protocols for thoracotomy by figuring out the optimal dosing of gabapentin and whether its use overall decreases postoperative opioid consumption and complications.

Our hypothesis is that higher doses of gabapentin will correlate with decreased pain at the incision and chest tube sites and decreased opioid consumption.

2.0 Rationale and Specific Aims

The specific aim of the study is to compare the difference in the postoperative use of no gabapentin, 300 mg gabapentin 3x daily, or 300 mg gabapentin once at night
The primary endpoint of this study will be incision and chest tube site pain scores.

The secondary endpoint includes opioid consumption, pain scores, sedation, falls, time to first opioid request, pulmonary complications, hospital LOS, presence of visual disturbance, dizziness, and delirium., antiemetic usage and patient satisfaction will also be recorded. The IV and PO opioid doses will be quantified at every 24 hours after completion of surgery up to 96 hours. Sedation will be quantified via the 11-point numeric rating scale (NRS) (0= no sedation and 10 = worst sedation imaginable; subjective rating by patients) every 24 hours up to 96 hours after completion of surgery (13). Incidence of falls will be quantified for up to 96 hours after completion of surgery. Pulmonary complication will be defined as respiratory rate (RR) <8 breaths per minute and oxygen saturation either below 92% or a decrease of

more than 5% from baseline in patients with a baseline $SP0_2$ <90% and will be quantified up to 96 hours after the completion of surgery (17). Oxygen saturations will be recorded in Cerner by nursing staff. Delirium will be defined as a patient screening positive during any of their daily CAM (Confusion Assessment Model) assessments performed by nursing staff in the ICU and/or on the floor up to 96 hours after the completion of surgery.

All patients will receive a phone survey 6 months after surgery to assess for chronic post-surgical pain and opioid use.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria:

- Pt undergoing open thoracotomy at Indiana University Hospital
- ASA 1,2,3 or 4
- Age 18 or older, male or female

Exclusion criteria:

- History of substance abuse in the past 6 months which would include heroin, marijuana or any other illegal street drugs
- Patient on home dose of gabapentin or pregabalin
- Patient staying intubated after surgery
- Patient above 70yo
- Patient (home dose) taking more than 30mg PO morphine equivalent (PME) per day
- Known allergy or other contraindications to the study medications, which include gabapentin
- Patient unable to receive post-op epidural
- BMI above 40
- Creatinine clearance less than 30

4.0 Enrollment/Randomization

All open thoracotomy cases scheduled by thoracic surgeons at IU Health University Hospital will be identified. The subjects will be contacted initially face-to-face by thoracic surgeons in their clinics prior to their scheduled surgery date. They will be given a copy of the consent and authorization form explaining this study. The subjects will again be contacted face to face in POCU on the day of surgery and the study will be explained in detail and all questions will be answered. If participation is agreed, written consent will be taken and a signed copy of both the authorization and consent will be given to the participant.

A total of 120 subjects will be randomized by the computer program Research Randomizer into three groups (40 per group): The primary investigator will inform the PACU physician and the physician assuming care of the patient while inpatient postoperatively as to which group the patients are randomized to. All patients will receive acetaminophen and gabapentin preoperatively per usual ERAS protocol.

1. No postoperative gabapentin
2. 300 mg gabapentin 3x daily postoperatively

3. 300 mg gabapentin once a day at night postoperatively

5.0 Study Procedures

All patients will receive 1gm of acetaminophen and 600mg of gabapentin preoperatively per usual ERAS protocol. General anesthesia will be induced in the operating room and the patient will be placed in the lateral position for the open thoracotomy procedure. All patients will receive intraoperative lidocaine and ketamine which is used to decrease opioid use after surgery and is being used as part of ERAS protocol. The patients will be intubated with dual lumen endotracheal tubes and placed on one-lung ventilation for the procedure. All patients will receive an epidural (patient-controlled epidural analgesia, PCEA) post-operatively for pain. They will also be scheduled on PO acetaminophen. PRN dilaudid will be given for breakthrough pain and PO oxycodone PRN will be started on POD 1 once patients tolerate diet. Patients will be encouraged to ambulate on postoperative day 1 under supervision.

Pain scores will be measured and recorded by a member of the research team using Visual Analog Scale (VAS) at 1, 24, 48, 72 and 96 hours after surgery.

Opioid usage at 1 ,24, 48, 72, and 96 hours after the surgery will be recorded by a member of the research team. Time to first opioid request will also be recorded. Sedation scores will also be assessed by a member of the study team using the 11-point numeric rating scale (NRS) (0= no sedation and 10 = worst sedation imaginable; subjective rating by patients). All these parameters will be measured at 1, 24, 48, 72, and 96 hours after the procedure. Incidence of falls will be quantified up to 96 hours after the completion of surgery. Pulmonary complication will be defined as respiratory rate (RR) <8 breaths per minute and oxygen saturation either below 92% or a decrease of more than 5% from baseline in patients with a baseline $SP0_2$ <90% and will be quantified for up to 96 hours after the completion of surgery (17). Hospital LOS will be recorded when each patient is discharged from the hospital. CAM assessments (to screen for delirium) are to be performed approximately once every 24 hours as an inpatient by nursing staff. If a patient screens positive for any of these assessments, that patient will be considered to have experienced delirium. If a subject is unable to provide a pain score due to delirium, the subject will be withdrawn from the study. Visual disturbance and dizziness will be assessed by research nurse using yes or no questions at 24, 48, 72, and 96 hours.

All patients will receive a phone call 6 months after surgery for assessment for chronic post-surgical pain. Patients will be assessed by a member of the research team over the phone. They will be assessed on their pain score and narcotic usage by using the Brief Pain Inventory. Study participation will conclude after the 6 month follow questionnaire has been completed.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Patients will be monitored by the primary team during the postoperative period which is after surgery, through hours 1, 24, 48, 72, and 96 hours. We will also follow up in 6 months with a telephone call to

complete a questionnaire which will conclude all study participation. Any adverse events or unanticipated problems that are reported to the acute pain anesthesia resident who is not listed on the study will contact the Principal investigator or one of the study personnel and all events will be addressed immediately. All adverse events or unanticipated problems that meet the criteria for prompt reporting will be reported to the IRB within 5 business days.

7.0 Study Withdrawal/Discontinuation

The patient can withdraw from the study at any time by contacting the research team or acute pain anesthesia resident.

8.0 Statistical Considerations

Primary outcome: VAS score at 24 and 48 hours
Primary Research Hypothesis: Higher gabapentin dose will correlate with decreased VAS score and reduced opioid consumption.

Secondary outcomes: Opioid usage after 1, 24, 48, 72, and 96 hours. Pain scores using VAS at 1, 72, and 96 hours. Sedation scores at 1, 24, 48, 72, and 96 hours. Time to first opioid request will be recorded at the time of request. Falls will be recorded as they occur. Pulmonary complication will be defined as respiratory rate (RR) <8 breaths per minute and oxygen saturation either below 92% or a decrease of more than 5% from baseline in patients with a baseline $SP0_2$ <90% and will be quantified upon occurrence up to 96 hours after the completion of surgery (17). Hospital LOS recorded as each patient is discharged from the hospital. The presence of delirium will be assessed approximately every 24 hours up to 96 hours after the completion of surgery by reviewing the patient's CAM assessment recorded by nursing staff in Cerner. The presence of visual disturbance and dizziness will be assessed at 24, 48, 72, and 96 hours.

Statistical analysis will be performed using a standard statistical program (SAS). All data will be summarized (either means and standard deviations or medians and quartiles for continuous variables; frequencies and percentages for categorical variables) by group. Demographic data will be compared between the three groups using ANOVA or Kruskal–Wallis Test as appropriate for continuous variables, and chi-square tests or Fisher's exact test for categorical variables as appropriate. The primary outcome, VAS at 24 and 48 hours, along with secondary outcome, VAS at 1, 72, and 96 hours , as well as opioid consumption, will be compared between the groups using Mixed effect Model Repeat Measurement (MMRM); the model will include fixed effects for group, time, and the group by time interaction with a random intercept effect. The mixed model is flexible enough to accommodate different variance structures across time and groups. Nausea, sedation, and satisfaction scores will be compared between groups at each time point using Mantel-Haenszel chi-square tests for ordered categorical data. Time to first opioid request and hospital length of stay will be compared between the three groups using ANOVA or Kruskal–Wallis Test as appropriate. Finally, incidence of pulmonary complication, dizziness, delirium, falls, and presence of visual disturbance will be compared between the three groups using chi-square tests or Fisher's exact test. Distributions of the continuous variables will be examined, and a transformation of

the data (e.g. natural logarithm) or nonparametric tests will be used as necessary. A 5% significance level will be used for all comparisons.

Based on prior studies, the coefficient of variation for the VAS score at 24 and 48 hours is estimated to be 0.70. Working with a feasible sample size of 30 per group (40 with an assumed dropout rate of ~20%) and using a power of 80%, 5% significance level, and employing a two-sided test, the study will be able to detect a difference of 59% in VAS score between any two groups. Here we used a "Tests for the Ratio of Two Means" using sample size software PASS 2019.

9.0 Statistical Data Management

Primary data will be collected via face to face interview and stored electronically in REDCap. The storage location will be backed up automatically. There are no outside data sources for this study. Quality assurance steps will include testing of database by study team prior to moving to production mode. The following quality control methods will be used: double entry of data with random checks of accuracy.

10.0 Privacy/Confidentiality Issues

All study papers containing patient identifiers will be kept in each subjects confidential study file accessible to only the research team. All records will be kept in a locked room in a locked cabinet that only authorized staff enters. Collected data from each enrolled participant will be recorded on Redcap which is a secure web-based data collection tool. Three years after completion of the study, all electronic information and paperwork containing patient identifiers will be deleted or shredded.

11.0 Follow-up and Record Retention

The study will start in March 2021 and will end when a sample size of 120 subjects is achieved. The estimated time frame to enroll 120 study subjects is 24 months. After 120 subjects have been enrolled, the study will be stopped and the data collected will be analyzed using statistical methods.

The study will follow IU's policy on research record retention. HIPAA authorizations will be maintained for 6 years and only data without any patient identifiers will be retained by the research team for an indefinite time.

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