Opioid Free vs. Standard Perioperative Pain Regimen for Anterior Cervical Discectomy and Fusion (ACDF) Surgery

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1.0 Background

Historically, opioids have been the mainstay of pain management after spine surgery. Inadequately controlled postoperative pain is a common patient complains and is also a common reason for readmission after spine surgery (7,8). The Joint Commission guidelines, Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) surveys, and outcome-based and bundled payment models have placed a strong emphasis on adequate postoperative pain control and decreased readmission rates.

While opioids are an effective means of short-term pain control, their use is associated with a number of detrimental effects including respiratory depression, altered cognition, urinary retention, gastrointestinal dysfunction, and chronic opioid use. Over the past two decades, overdoses and deaths from opioids have reached epidemic proportions in the United States and prescription opioids are a major cause of opioid addiction and opioid-related overdose deaths. From 1999–2018, almost 450,000 people died from an overdose involving opioids in the United States (1).

With increased focus on the opioid epidemic, there has been a movement away from traditional pain control protocols towards multimodal analgesic regimens developed to reduce opioid consumption and associated adverse effects. Common medications utilized as part of these regimens include Nonsteroidal Anti-inflammatory Medications (NSAIDS), steroids, neuromodulatory agents, acetaminophen, and local anesthetics. NSAIDS are an area of intense debate among spine surgeons. While the evidence supports their use on low doses, many spine surgeons have been reluctant to adopt NSAIDs for perioperative pain management in patients undergoing spinal fusion because of concern for pseudarthrosis and postoperative bleeding (9-14). In addition to decreased opioid related postoperative complications, the potential benefits of non-opioid pain regimens also potentially include lower rates of chronic opioid use. Chronic opioid use has been shown to be associated with worse patient reported outcomes after spine surgery (15). The proposed study aims to directly compare opioid and non-opioid postoperative pain regimens in patients undergoing ACDF in a randomized clinical study. Successful utilization of an opioid-free postoperative pain regimen in patients undergoing ACDF may spur the utilization of such regimens for other types of spine surgery including posterior cervical and lumbar spine surgeries.

2.0 Rationale and Specific Aims

Over the past two decades, overdoses and deaths from opioids have reached epidemic proportions in the United States. From 1999–2018, almost 450,000 people died from an overdose involving opioids (1). Prescription opioids are a major cause of opioid addiction and opioid-related overdose deaths in the United States. In 2016, more than 11.5 million Americans reported misusing prescription opioids in the past year (2).

Despite the well-documented clinical benefits of spine surgery, recent evidence suggests a high incidence of new chronic opioid use following spine surgery. The incidence of

chronic opioid use after anterior cervical discectomy and fusion (ACDF) is reported between 11% to 39% in patients with no-preoperative opioid-use (3-5). With increasing awareness of the opioid epidemic, there will be greater emphasis on developing strategies to ensure that spine surgery patients remain opioid-free in the long-term after elective spine surgery. In the present study, we aim to evaluate the use of an opioid-free postoperative pain regimen after ACDF and its effect on new chronic opioid use, postoperative pain control, opioid-related postoperative complications, and postoperative clinical outcomes.

Aim 1: Evaluate whether utilization of a non-opioid postoperative pain regimen after ACDF results in equivalent postoperative pain scores in the early postoperative period.

> We hypothesize that utilization of a non-opioid postoperative pain regimen after ACDF leads to equivalent postoperative pain scores in the early postoperative period when compared with postoperative pain regimens utilizing opioids

Aim 2: Evaluate whether utilization of a non-opioid postoperative pain regimen after ACDF leads to equivalent clinical outcomes when compared with postoperative pain regimens utilizing opioids at 3 months.

> We hypothesize that utilization of a non-opioid postoperative pain regimen after ACDF leads to equivalent clinical outcomes when compared with postoperative pain regimens utilizing opioids

Aim 3: Evaluate whether utilization of a non-opioid postoperative pain regimen after ACDF leads to fewer postoperative complications when compared with postoperative pain regimens utilizing opioids.

> We hypothesize that utilization of a non-opioid postoperative pain regimen after ACDF leads to fewer postoperative complications when compared with postoperative pain regimens utilizing opioids

Aim 4: Evaluate whether utilization of a non-opioid postoperative pain regimen after ACDF leads to lower rates of new chronic opioid use when compared with postoperative pain regimens utilizing opioids.

> We hypothesize that utilization of a non-opioid postoperative pain regimen after ACDF leads to lower rates of new chronic opioid use when compared with postoperative pain regimens utilizing opioid

3.0 Animal Studies and Previous Human Studies

As mentioned previously, while the evidence supports their use on low doses, many spine surgeons have been reluctant to adopt NSAIDs for perioperative pain management in patients undergoing spinal fusion because of concern for pseudarthrosis and postoperative bleeding (9-14). Despite the well-documented clinical benefits of spine

surgery, recent evidence suggests a high incidence of new chronic opioid use following spine surgery. The incidence of chronic opioid use after anterior cervical discectomy and fusion (ACDF) is reported between 11% to 39% in patients with no-preoperative opioid-use (3-5). Chronic opioid use has been shown to be associated with worse patient reported outcomes after spine surgery (15). Successful utilization of an opioid-free postoperative pain regimen in patients undergoing ACDF may spur the utilization of such regimens for other types of spine surgery including posterior cervical and lumbar spine surgeries.

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

- Radiographic evidence of degenerative cervical spine disease
- Failure of conservative therapy
- Age ≥18 years
- Skeletal maturity

Exclusion Criteria:

- Preoperative chronic opioid use as determined by self-report
- History of chronic kidney disease
- Undergoing revision cervical spine surgery or concurrent posterior cervical fusion
- Spinal infection
- Tumor
- Traumatic fracture or dislocation
- Age less than 18 years
- Non-English-speaking patients
- Incarceration
- Intolerance to NSAIDs
- Any preexisting health condition the study physician believes will be exacerbated by participating in this study

5.0 Enrollment/Randomization

This investigation will be conducted as a multi-site trial, with patients being enrolled at both Vanderbilt University Medical Center and University of Pittsburgh Medical Center. Research personnel at each institution will screen their respective patients for eligibility based on the surgery schedule posted in their respective EMRs. Study personnel will then approach patients during a preoperative clinic visit. No flyers or brochures will be utilized. A phone script will be used by the study staff to recruit participants over the phone if we are unable to recruit in person. A VUMC department letter will be sent to participants that study personnel are unable to see in clinic prior to study personnel reaching out over the phone.

The patient's doctor will approve each patient for the research study prior to the research personnel approaching or contacting the patient.

Once the patient has been consented and completed the baseline assessment, the patient will be randomized electronically. The randomization scheme will frequency-match patients in a 1:1 ratio in blocks of assignments stratified by age and number of levels (i.e., 1 or 2 vs. 3 levels). Block sizes will be 2 and 4 with the patient as the unit of randomization.

6.0 Study Procedures

All patients will undergo standard preoperative evaluation prior to surgery and will be seen by an anesthesiologist on the morning of surgery.

Postoperative Phase (Hospital and/or Discharge – 2 weeks)

Non-Opioid Group:
These patients will receive no opioids. Pain will be managed with Acetaminophen 1000mg q8 hours, Ketorolac 10mg every 6 hours (for 5 days), Gabapentin 300mg q8 hours or Pregabalin 75mg twice daily, and a muscle relaxer (Methocarbamol 750mg BID or Cyclobenzaprine 5-10 mg TID) all to be taken as scheduled for the first 2 weeks (except Ketorolac – 5 days) postoperatively as side effects permit. Other NSAIDS (Naprosyn 500 mg BID or Ibuprofen 800 mg TID) may be utilized if contraindications to Ketorolac exist. Famotidine (20mg BID) or Omeprazole (20mg daily) will be prescribed along with NSAIDS for GI prophylaxis. Alternative muscle relaxers (Metaxalone 800 mg TID or Tizanidine 2-6 mg TID) may be utilized if contraindications to methocarbamol and cyclobenzaprine exist.

Opioid Group:
These patients will be provided a prescription for low dose opioids for 5 days postoperatively (Hydrocodone/Acetaminophen 5/325mg or Oxycodone/Acetaminophen 5/325mg) to be taken every 6 hours as needed for pain. Refills may be provided (Hydrocodone/Acetaminophen 5/325mg or Oxycodone/Acetaminophen 5/325mg) if requested by the patient at the providers discretion. In addition, patients will also be prescribed Gabapentin 300mg q8 hours or Pregabalin 75mg twice daily and a muscle relaxer (Methocarbamol 750mg BID or Flexeril 5-10 mg TID) as needed for spasms. Alternative muscle relaxers (Metaxalone 800 mg TID or Tizanidine 2-6 mg TID) may be utilized if contraindications to methocarbamol and cyclobenzaprine exist.

Both groups will receive postoperative patient questionnaires on postop day 1, postop day 7, and postop day 14 to assess their level of pain and medication use.

Postoperative Phase (2 weeks – 6 weeks)

Non-Opioid Group:
These patients will receive no opioids. Patients will be given instructions to discontinue use of ketorolac at 5 days postoperatively.

Acetaminophen, Gabapentin 300mg q8 hours or Pregabalin 75mg twice daily, and muscle relaxers (Methocarbamol 750mg BID or Cyclobenzaprine 5-10 mg TID) may be continued as needed between 2 and 6 weeks with instructions to discontinue use by 6 weeks postoperatively.

If pain control remains poor at 6 weeks postoperatively, patients will be referred to pain management at our institution.

Opioid Group:
Opioid prescriptions between 2 and 6 weeks postoperatively will not be provided unless requested by the patient and will be at the providers discretion. Patients will not be provided with any prescriptions for opioids by the treating surgeon beyond 6 weeks postoperatively.

Acetaminophen, Gabapentin 300mg q8 hours or Pregabalin 75mg twice daily, and muscle relaxers (Methocarbamol 750mg BID or Cyclobenzaprine 5-10 mg TID) may be continued as needed between 2 and 6 weeks with instructions to discontinue use by 6 weeks postoperatively.

If pain control remains poor at 6 weeks postoperatively, patients will be referred to pain management at our institution.

7.0 Risks

The risk to human subjects of participation in this study is minimal due to the nature of the interventions being compared. Both standard opioid-containing postoperative pain regimens and non-opioid postoperative pain regimens are acceptable standards of care, and both are currently utilized at our institution. The risks of opioid pain medication use include sedation, nausea / vomiting, constipation, respiratory depression, physical dependence, and overdose. The short-duration, low dose regimens proposed for use in this study pose minimal risk for serious adverse events. The risks of non-opioid postoperative pain regimens depend on the medications used. The medications proposed for use in the study include propofol, ketamine, lidocaine, dexmedetomidine, ketorolac, acetaminophen, gabapentin, pregabalin, methocarbamol, and cyclobenzaprine as well as other medications that may be utilized for pain control in the perioperative period at the discretion of the provider. These medications are all commonly used in the care of postoperative spine patients undergoing ACDF and therefore do not represent departures from the standard of care.

There is a small risk of breach of confidentiality, but the data for this study will be secured in a password-protected database. Access to this database will be limited to the PI, study coordinator, and study staff at VUMC and UPMC. Data will be deidentified for data analysis and interpretation.

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

AE's, unanticipated problems and protocol deviations will be reviewed by the PI and study staff on a weekly basis. The principal Investigator will notify the Institutional Review Board (IRB) of a serious adverse event according to institutional policy. However, based on the nature of the intervention the investigators don't expect any AE's.

9.0 Study Withdrawal/Discontinuation

Participants can withdraw from the study at any time. If any of the participants wish to withdraw from the study for any reason, the investigators will not use their data for analysis. All information will be destroyed on that participant.

10.0 Statistical Considerations

Data collected at VUMC and UPMC will be compiled into one dataset. Descriptive statistics will be used to describe participant characteristics across the two groups and to summarize feasibility. The acceptability analyses for outcomes will be intent-to-treat. Descriptive statistics will be used to summarize the outcome measures pre and post-intervention for the two groups. Between and within group comparison will be conducted using 2X2 Mixed ANOVA. The effect size will also be determined using a partial eta square value. Missing observations due to drop-out and other reasons not related to the treatments will be handled with multiple imputation methodology. This method will allow us to use data with some missing values and avoid the information loss that is inherent in a complete case analysis. All the data will be explored graphically and numerically to observe the effects.

11.0 Privacy/Confidentiality Issues

The study's data will be stored in a VUMC REDCap folder, a password protected database, and any paper study forms will be stored in a locked room of the admin offices of the Department of Orthopaedics at either VUMC or UPMC. Only the PI, study coordinator, and research staff from VUMC and UPMC will have access to this database. Participant identifiers will be removed from all study forms and the database before analysis. The link between the data and subjects' identifying information will be found in a REDCap form that will be password protected and only accessible by the PI and research coordinator. Once the study is complete, the code list will be destroyed, and all other identifiable data or information not part of the limited data set will be destroyed at the expiration of the project.

12.0 Follow-up and Record Retention

Participants will be enrolled in this study for a period of 12 months. Enrollment is expected to last 18-24 months. The total duration of the study is expected to last 3 years.