CLINICAL STUDY PROTOCOL

An Analysis of the Efficacy of a Pre-Emptive Multimodal Pain Regimen in Reducing Acute Post-Operative Pain and Narcotic Pain Medication Requirements in Spine Surgery

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Confidentiality Statement:

Study Personnel

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Synopsis

Primary Objective

Aim 1: Determine pain control post-operatively after elective spine surgery

Secondary Objectives

Aim 2: Determine patient variables significantly associated with post-operative pain control

Aim 3: Determine operative variables significantly associated with post-operative pain control

Aim 4: Determine long term outcomes and complication rates after pre-emptive MMA regimen implementation

Study Duration

Expected Duration: 2020 to 2022

Study Design

Prospective Cohort Study

Study Population

Adult patients undergoing elective spine surgery at NYU Winthrop Hospital

Number of Participants

At a significance level of 5%, in order to achieve 80% power for detecting a 1 point mean difference in VAS pain scores[1], we would need a sample of 31 patients to assess the primary outcome. Adjusting by approximately 5% to account for patients that are found ineligible retrospectively, the total sample size required is 33 patients for the primary outcome.

Furthermore, additional analyses to fulfill Aims 2-4 would require a larger sample size and would constitute separate studies based on final sample size achieved

[1] Using the reported control group VAS scores by Garcia et al. of 8.4 and standard deviation of 2

Number of Study Sites

The study will be conducted out of NYU Winthrop hospital as well as in the outpatient office settings.

Primary Outcome Variables

Aim 1: Determine pain control post-operatively after elective spine surgery

- Measure acute pain using the VAS pain scale in PACU
- Measure opioid sparing and rescue time as determined by the time interval from patient extubation to time when pain medication is first demanded in PACU
- Determine secondary outcomes: length of stay in PACU, opioid dose, drain output, transfusion rates, and hospital length of stay.

Secondary and Exploratory Outcome Variables

Aim 2: Determine patient variables significantly associated with above outcomes

- The following variables will be considered: age, gender, race, comorbidities, pain medication use prior to surgery (including dose and number of years used), history of

seeing a pain management physician, history of psychological illnesses, demographic history, use of ambulatory aids and activity level at baseline

Aim 3: Determine operative variables significantly associated with above outcomes

- The following variables will be considered: primary vs revision surgery, surgical site, number of spinal levels, length of surgery, use of intra-operative dexamethasone, blood loss, ASA score

Aim 4: Determine long term outcomes and complication rates after pre-emptive MMA regimen implementation

- Determine patient reported VAS pain scores at 3 , 6, and 12 months post-operatively
- Determine long term pain medication use at 3 , 6, and 12 months post-operatively
- Determine rate of surgical complications including surgical site infection, readmission, pseudoarthrosis/lack of fusion rates, hardware complication, revision surgery, neurological deficit

Visit Schedule Table (Optional)

Study Flow Chart (optional)

Abbreviations

Abbreviation	Explanation

Glossary of Terms

Glossary	Explanation

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1 - Introduction

1.1 Introductory Statement

Pain following surgery of the spine is a common complaint[9]. In addition, pain is the second leading cause of readmission[2]. Continued research for novel and improved methods for post-operative pain control is vital; especially given the recent rising healthcare urgency to limiting opioid use amidst the opioid abuse crisis. Historically, post-operative pain control regimens have relied heavily on opioid medications provided at intervals in response to as needed protocols[3]. However, several limitations exist to this model of pain control including poor pain control and a host of opioid induced adverse effects[35].

Recently significant interest has been brought to the utilization of multimodal analgesia (MMA)[15]. MMA takes advantage of the synergistic effect of multiple pain medications that act through different mechanisms of actions to target pain more effectively. Several studies have highlighted the efficacy of such regimens and have proven that these regimens are safe[5,6,8,12,15,24,31,37].

Furthermore, the pre-emptive administration of pain medications has been believed to be more efficacious in controlling post-operative pain[36]. Pre-emptive control of pain is thought to mitigate or halt central nervous system sensitization (which includes prolonged changes) as a result of noxious stimuli such as surgery[36]. Therefore, we sought to evaluate the efficacy of a pre-emptive MMA pain regimen in controlling post-operative pain in a community hospital setting.

2 - Background

2.1.1 Preclinical Experience

A wide range of pharmacological options are available for the effective amelioration of post spine surgery pain. Each analgesic choice possesses inherent advantages and disadvantages to its applicability[15].

Acetaminophen, one of the most commonly used non-opioid analgesics utilized exerts its effects though cyclooxygenase (COX) inhibition. Multiple studies have demonstrated improved pain control and reduced opioid use with acetaminophen use in patients undergoing orthopaedic procedures[29,33]. As such acetaminophen remains a cornerstone in most multimodal pain regimens.

Nonsteroidal anti-inflammatory (NSAID) medications are another commonly utilized analgesic choice. They exert their anti-inflammatory and analgesic effects via COX inhibition therefore blocking prostaglandin production. Although COX1 are ubiquitous throughout the body, COX2 enzymes are more specific to inflammatory tissues. Specific COX2 inhibitors were developed in order to minimize adverse effects of COX1 inhibition (ie gastric mucosa damage and platelet dysfunction). However, there has been controversy over the use of NSAIDs in spine surgery given concerns for nonunion, pseudoarthrosis, and bleeding/hematoma formation. A number of studies have shown higher nonunion rates in a dose dependent manner with the use of NSAIDs[19,39]. Nevertheless, recent studies highlight that COX2 inhibitors as well as NSAIDs used in lower doses prove to be efficacious for pain control and may not carry the same adverse effects as previously thought[10,11,21,27].

Gabapentin and pregabalin are neuromodulatory agents commonly used for neuropathic pain. They work by inhibiting calcium gated channels on presynaptic axons thereby reducing neuronal excitability. The efficacy of these neuromodulatory agents in post-operative pain control and reduction of opioid consumption is well documented in spine surgery with multiple level I studies presenting positive outcomes[7,20,34,38].

Oxycodone is a standard opioid pain medication that is widely accepted as part of a pain regimen for post-operative pain control[4]. The medication works by decreasing excitability of neurons by binding to mu, kappa, and delta receptors thereby inhibiting adenylyl cyclase signaling pathway[23].

Limited literature exists on the efficacy of these commonly used analgesics as part of a multimodal regimen especially one given pre-operatively. Therefore we sought to investigate the efficacy of a MMA regimen administered pre-operatively in terms of acute post-operative pain control and opioid pain medication requirements.

2.1.2 Clinical Experience

The use MMA regimens for controlling post-operative pain continue to gain acceptance and popularity[6,8,12,15]. The idea of MMA relies on the synergistic action of multiple agents working to inhibit pain through distinct mechanisms along the pain pathway. MMA prove to

improve pain control, reduce opioid consumption, decrease adverse effects, and facilitate recovery and rehabilitation. Furthermore, the use of analgesic agents prior to the insult of pain may prove to have further value by preventing pain and controlling pain before its onset thereby reducing sensitization. Limited studies have looked at MMA efficacy in spine surgery and very limited literature exists on its efficacy if given pre-emptively (ie pre-operatively)[1,13,14,16,36].

Garcia et al. report their findings of a preemptive MMA regimen with 22 patients undergoing lumbar laminectomy surgery[8]. In this randomized control trial (RCT), patients received either IV morphine only or MMA regimen consisting of 200 mg celecoxib pre-op and 100 mg post-op, 15 mg pregabalin pre-op, and 10 mg oxycodone extended-release given twice daily post-op. Medications were administered every 12 hours with first dose given pre-op. All patients were allowed to receive IV morphine post-op on an as needed basis. Pain levels were assessed using the VAS pain scale at 0, 4, 8, 12, 16, 24, and 48 hours post-op. IV morphine requirements were recorded 6,12, and 24 hours post-op. They found that compared to the IV morphine group, the MMA group had lower VAS pain scores at all time points, a 58% reduction in morphine consumption and earlier oral food intake. No difference in intra-operative blood loss was noted.

Another RCT by Kim et al. looked at preemptive MMA efficacy in single level lumbar fusion surgery in 80 patients[14]. Regimen consisted of 500 mg acetaminophen, 200 mg celecoxib, 75 mg of pregabalin, and 10 mg extended release oxycodone given 1 hour before surgery and then twice daily. IV morphine was used in the control group. They found improved VAS pain scores at all time points and lower Oswentry Disability Index scores at all time points except day 1 post-op. Of note they did not find a difference in acute complications or in fusion rates at 1 year. No difference in intra-operative blood loss was noted.

Lee et al. looked at a retrospective observational study of 393 patients undergoing lumbar spinal fusion from 17 hospitals sent a post-op questionnaire[16]. Only 79 of these patients were noted to have received preemptive analgesics; COX2 inhibitors with or without gabapentin/pregabalin. 363 patients received some form of MMA post-operatively. They did not find significant differences in outcomes with the post-op MMA protocols assessed. However, preemptive pain regimen group reported significantly lower self-administered PCA use post-op. Furthermore, EQ-5D activity, depression/anxiety, and self-care also improved significantly in the preemptive group at 2 weeks post-op. It is worth noting the retrospective and observational nature are limitations to the study as well as possibility of selection and recall bias.

A recent study by Kien et al. looked at the preemptive use of pregabalin and celecoxib in 60 lumbar spine fusion surgery patients in a prospective cohort study[13]. The patients were randomized to receive either the MMA regimen or placebo 2 hours pre-op. The MMA consisted of pregabalin 150 mg and celecoxib 200 mg. Post-op pain was managed with a morphine PCA. They noted VAS pain scores and morphine consumption to be significantly lower in the treatment group at 24 and 48 hours post-op.

Finally, Mathiesen et al. and Rajpal et al. are additional retrospective studies looking at primarly post-op MMA after spine lumbar fusion surgery in 85 and 200 patients respectively[22,26]. They also note improved pain control and lower opioid requirements in the intervention groups.

Unfortunately, the long term outcomes including fusion rates and complications such as pseudarthrosis were not found in our review to be reported by any of the studies.

2.2 Background/prevalence of research topic

3 - Rationale/Significance

3.1 Problem Statement

Increasing demand for elective spine surgery accentuates the importance of improving outcomes and lowering costs. One of the key challenges in spine surgery remains to be post-operative pain control. Pain leads to a number of adverse effects on physical, emotional, and social health as well as to short and long term outcomes[32].

3.2 Purpose of Study/Potential Impact

Adequate and effective pain control leads to lower risk of complications, greater patient satisfaction, and earlier mobility, rehab as well as recovery from surgery[17,18,25,31].

Traditionally pain control has focused on opioid pain medications utilized on an as pain occurs basis post-operatively[3]. However, recent advances in pain control research have brought up a shift in paradigm to targeting pain earlier[1,16,36]. Pain leads to a cascade of neuronal activation as well as some changes that may be long term in the central nervous system[36]. Therefore blocking the pain pathway earlier prior to prevent is thought to prevent central sensitization to pain and prevent these long term changes in the central nervous system. Furthermore, this paradigm of targeting pain before it occurs is thought to lead to more effective pain control as well as reduce the opioid dependency on post-operative pain control[1,16].

Utilizing multiple agents to control pain is conjectured to work in a synergistic manner, described as multimodal analgesia(MMA)[37]. This allows not only a strategy to target pain more effectively through numerous distinct pathways but also allows the use of lower doses of each individual analgesic therefore mitigating adverse effects of each medication[12,15,28]. A growing body of evidence supports the utility of MMA in spine surgery[30].

Therefore significant interest exists in optimizing MMA protocols especially prior to the onset of pain for treating patients undergoing spine procedures[12,15,16,37].

3.3.1 Potential Risks

Potential risks include any described adverse effects of the analgesic medications as well as undescribed effects of these medications on surgery or outcomes. However, since these medications are routinely used and common practice their effectiveness and safety have been thoroughly described previously in the literature. Furthermore, patients with health conditions that would put them at higher risk are excluded from the study. In addition, the medications to be used have been previously described to be safe in similar studies. For example, NSAIDs have been traditionally avoided due to risks on platelet function and operative blood loss. However, the use of celecoxib which has minimal effect on COX1 associated with platelet function. Celecoxib has also been described in a number of studies for pain control in spine surgery without any evidence of increased blood loss.

3.3.2 Potential Benefits

Some of the strengths of this study include its novel nature to assess pre-op MMA in all areas of spine, prospective nature, relatively large sample size, and the analysis of multiple patient and treatment parameters in the context of pain control.

Adequate and effective pain control leads to lower risk of complications, greater patient satisfaction, and earlier mobility, rehab as well as recovery from surgery[17,18,25,31].

The long term implications are promising in terms of patient care and future post-op pain control after spine surgery. This study will significantly add to better controlling pain in the post-op period, improving outcomes, and facilitating recovery after elective spine surgery.

4 - Study Objectives

4.1 Hypothesis

Multimodal pain regimen (consisting of acetaminophen, celecoxib, gabapentin, and oxycodone) administered pre-operatively before elective spine surgery significantly decreases acute pain post-operatively as well as decreasing requirements of post-op opioids for pain control in PACU as compared to patients undergoing elective spine surgery without a pre-operative pain regimen.

4.2 Primary Objective

Aim 1: Determine pain control post-operatively after elective spine surgery

4.3 Secondary Objectives

Aim 2: Determine patient variables significantly associated with post-operative pain control

Aim 3: Determine operative variables significantly associated with post-operative pain control

Aim 4: Determine long term outcomes and complication rates after pre-emptive MMA regimen implementation

5 - Study Design

5.1 General Design Description

A prospective cohort study with patients undergoing elective spine surgery at NYU winthrop will be recruited for participation based on described inclusion and exclusion criteria. A prospective study allows the implementation of the new pain control protocol while assessing outcomes.

The study subjects will be assigned to the defined pre-op MMA regimen with standard post-op oxycodone based pain control regimen given on an as needed basis. The treatment group outcomes will be compared to patients outside of the study including a historical control group (receiving only post-op pain regimen) prior to the implementation of the new regimen.

The studied treatment group will receive within 3 hours before surgery an oral MMA regimen consisting of:

- Acetaminophen 975 mg
- Celecoxib 200 mg
- Gabapentin 300 mg
- Oxycodone 10 mg Extended Release

Pain control post-op will be assessed by RN noted VAS pain scale scores in PACU. Furthermore, opioid sparing and rescue time as determined by the time interval from patient extubation to time when pain medication is first demanded in PACU[1]. In addition, variables and secondary outcomes noted in Aims 1-4 will be measured.

The potential to selection and recall bias will be significantly reduced by standardizing all patients to the new protocol. Additionally, patients recruited from multiple spine surgeons in a private practice model at a community hospital will recruit a wide range of patients with variety of pathologies and demographics. A measurement bias may be indicated depending on the RN verbally assessing pain, however utilizing a validated outcome measure such as the VAS pain scale would minimize this.

5.1.1 Study Date Range and Duration

The study will be conducted and continue from 2020 to 2022.

5.1.2 Number of Study Sites

The study will be conducted out of NYU Winthrop hospital as well as in the outpatient office settings.

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

Data will be collected using review of EPIC care electronic medical record (EMR) with notation of VAS score in RN documentation in PACU as well as EMR record of time of opioid administration if requested. The pre-op history and physical will be utilized for extracting demographic and clinical data. Finally, long term data will be requested from outpatient office patient records at defined time intervals. Pain medication usage will be reviewed with prescriptions given / noted in state (ISTOP) registries. Complication rates will be assessed using outpatient records as well as readmission/ER documentation in EMR.

Measurement reliability is dependent on accuracy of data reported in EMR and by patients in follow up visits. The use of standardized data collection procedures will limit any measurement bias that may be observed. Discretionary data outside the standardized collection criteria will not be collected. Potential confounders and effect modifiers are outlined in the study aims as the patient and treatment characteristics. Their influence will be statistically evaluated using stratified univariate and multivariate analyses.

5.2.2 Secondary and Exploratory Outcome Variables

5.3 Study Population

All genders and races will be included in the study. Children will be excluded based on differences in physiology and small sample size that would influence the outcome measures and therefore would skew the comparison of interest in the study.

5.3.1 Number of Participants

All patients undergoing elective spine surgery at NYU Winthrop hospital will be screened and assessed for potential inclusion into the study. Patients meeting the inclusion criteria and avoiding the exclusion criteria will be recruited into the study. Based on the power analysis atleast 31 patients would be needed for the primary outcome. However, in the recruitment period, the goal would be to include as many participants as possible (100-200) in order for the secondary and ancillary outcomes to be achieved for statistical subgroup analyses.

5.3.2 Eligibility Criteria/Vulnerable Populations

Eligibility Criteria will be assessed by the PI as well as the lead author on the study.

Inclusion Criteria:

- Undergoing elective spine surgery at NYU Winthrop
- Age over 18 years

Exclusion Criteria:

- History of neuromuscular disorders
- History of inflammatory arthropathies
- History of spine metastases or active cancer in spine
- Medical History including any of the following: renal dysfunction, gastric ulcers, hepatic dysfunction, coagulopathic/bleeding disorders, prior adverse or allergic reactions to any of the medications in the study
- Age less than 18 years

6 - Methods

6.1 Treatment - Drug

6.1.1 Identity of Investigational Product/New Drug

All drugs utilized are well established and FDA approved. They are also currently in common use.

- Acetaminophen (Tylenol)
- Celecoxib (Celebrex)
- Gabapentin (Neurontin)
- Oxycodone 10 mg Extended Release (Oxycontin)

6.1.2 Dosage, Admin, Schedule

The studied treatment group will receive within 3 hours before surgery an oral MMA regimen consisting of:

- Acetaminophen 975 mg
- Celecoxib 200 mg
- Gabapentin 300 mg
- Oxycodone 10 mg Extended Release

6.1.3 Method of Assignment/Randomization

6.1.4 Blinding and Procedures for Unblinding

6.1.5 Packaging/Labelling

Included in hospital inpatient pharmacy. Administration through nursing similar to all drugs in the inpatient setting. No special packaging or labelling will be utilized.

6.1.6 Storage Conditions

Stored by hospital pharmacy under appropriate conditions.

6.1.7 Concomitant therapy

No restrictions to concomitant therapy outside of allowances of maximum medication doses and adverse effects. Concomitant use will be monitored.

6.1.8 Restrictions

No restrictions of note.

6.2 Assessments

Pain control post-op will be assessed by RN noted VAS pain scale scores in PACU. Furthermore, opioid sparing and rescue time as determined by the time interval from patient extubation to time when pain medication is first demanded in PACU[1]. In addition, variables and secondary outcomes noted in Aims 1-4 will be measured.

Data will be collected using review of EPIC care electronic medical record (EMR) with notation of VAS score in RN documentation in PACU as well as EMR record of time of opioid administration if requested. The pre-op history and physical will be utilized for extracting demographic and clinical data. Finally, long term data will be requested from outpatient office patient records at defined time intervals. Pain medication usage will be reviewed with prescriptions given / noted in state (ISTOP) registries. Complication rates will be assessed using outpatient records as well as readmission/ER documentation in EMR.

6.2.1 Efficacy

Measurement reliability is dependent on accuracy of data reported in EMR and by patients in follow up visits. The use of standardized data collection procedures will limit any measurement bias that may be observed. Discretionary data outside the standardized collection criteria will not be collected. Potential confounders and effect modifiers are outlined in the study aims as the patient and treatment characteristics. Their influence will be statistically evaluated using stratified univariate and multivariate analyses.

The study outcomes of VAS pain score and opioid sparing/rescue time will be calculated as a mean using PACU VAS pain scores noted in EMR and time from extubation to when opioid demanded in PACU for pain. Comparison to detect a statistical difference of these outcomes compared to historical control group will be done using student's t test. Furthermore, patient and treatment characteristics will be evaluated using univariate and multivariate analyses with cox proportional hazards regression modeling. Atypical associations or unmet assumptions will be handled by data transformation to meet assumptions or by the use of alternative modeling methods. The source of biostatistical expertise will come from the department biostatistician.

6.2.2 Safety/Pregnancy-related policy

Pregnant patients are excluded from study.

The risks of the MMA include drug hypersensitivity reactions or adverse effects of the medications. In order to minimize these risks a thorough pre-operative history would be conducted and reviewed to screen for any known allergies as well as any health conditions (ie liver or kidney disease) which would lead to higher risk of adverse effects of the MMA medications. Furthermore, since a single dose is use of the medication it limits medication exposure and risk of adverse effects.

6.2.2.1 Adverse Events Definition and Reporting

Adverse events will be defined as any events not considered within the realm of routine post-operative course. Adverse events will be monitored in the post-operative period while in the hospital as well as once seen outpatient in the office. Chart review from all providers will be screened for adverse events until last follow-up to date.

6.2.3 Pharmacokinetics

6.2.4 Biomarkers

6.3 Study Procedures

Administration of pain medication, including those given in this study are considered standard of care. However, the novel use of them in the pre-operative period rather than the post-operative period is the question of interest. Furthermore, the use of them in this particular regimen is evaluated for efficacy. The outcomes will be assessed from chart review in the immediate post-operative period including the PACU and hospital admission course. Furthermore, secondary outcomes will be assessed as chart review from office as part of outpatient follow-up.

6.3.1 Study Schedule

Patient visits in the office will be based on standards of care and routine follow-up practices without affect from this study.

6.3.2 Informed Consent

Informed consent process will be followed per NYU policy.

Informed consent will be received from all patients included in the study. The information obtained will be of vital importance to the progression of the field and future treatment of patients. Informed consent will be obtained by either the PI or the sub investigators listed on the study. Informed consent process will be conducted with a thorough discussion of risks and benefits of the study to the patients followed by permission for participation or declination. The consent will be obtained either in print or electronically (utilizing ipad resource common used for surgical consents). Consent will be obtained either at pre-op visit in the office or at check in to the hospital. Privacy will be protected by keeping all information in a safe and secure platform. Consent will be documented and recorded alongside the remaining patient variables in order to ensure consent is achieved for all participants.

6.3.3 Screening

Patient screening will be conducted by primary researcher at pre-operative visits or on the day of surgery.

6.3.4 Recruitment, Enrollment and Retention

6.3.5 On Study Visits

No specific visits related to study

6.3.6 End of Study and Follow-up

Patient follow-up will be reviewed from outpatient records.

6.3.7 Removal of subjects

Since patients will receive routine care after the single administration of MMA pre-operatively. The outcomes are assessed purely from chart review and patient reported basis.

6.4 Statistical Method

6.4.1 Statistical Design

Measurement reliability is dependent on accuracy of data reported in EMR and by patients in follow up visits. The use of standardized data collection procedures will limit any measurement bias that may be observed. Discretionary data outside the standardized collection criteria will not be collected. Potential confounders and effect modifiers are outlined in the study aims as the patient and treatment characteristics. Their influence will be statistically evaluated using stratified univariate and multivariate analyses.

The study outcomes of VAS pain score and opioid sparing/rescue time will be calculated as a mean using PACU VAS pain scores noted in EMR and time from extubation to when opioid demanded in PACU for pain. Comparison to detect a statistical difference of these outcomes compared to historical control group will be done using student's t test. Furthermore, patient and treatment characteristics will be evaluated using univariate and multivariate analyses with cox proportional hazards regression modeling. Atypical associations or unmet assumptions will be handled by data transformation to meet assumptions or by the use of alternative modeling methods. The source of biostatistical expertise will come from the department biostatistician.

6.4.2 Sample Size Considerations

At a significance level of 5%, in order to achieve 80% power for detecting a 1 point mean difference in VAS pain scores[1], we would need a sample of 31 patients to assess the primary outcome. Adjusting by approximately 5% to account for patients that are found ineligible retrospectively, the total sample size required is 33 patients. Furthermore, additional analyses to fulfill Aims 1-4 would require a larger sample size and would constitute separate studies based on final sample size achieved.

[1] Using the reported control group VAS scores by Garcia et al.[8] of 8.4 and standard deviation of 2

6.4.3 Planned Analyses

6.4.3.1 Primary Analyses

6.4.3.2 Secondary Objectives Analyses

6.4.3.3 Safety/Pregnancy-related policy

6.4.3.4 Analysis of Subject Characteristics

6.4.3.5 Interim Analysis

6.4.3.6 Health economic evaluation

6.4.3.7 Other

6.4.4 Subsets and Covariates

see aims and statistical design.

6.4.5 Handling of Missing Data

Given the acute and short term nature of study's primary outcome. Missing data is expected to be minimal. However, if data is missing then statistically valid analyses under the primary missing-data assumptions would be conducted to account for it.

7 - Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

In addition to IRB approval and guidelines, all patient data will be kept protected under HIPAA guidelines. Informed consent will be obtained from all patients. Patients will be treated in a professional manner consistent with standard of care. All data will be handled in a secure and professional manner. No financial or other incentives will be provided to participants.

7.2 Institutional Review Board (IRB) Review

7.3 Subject Confidentiality

7.4 Deviations/Unanticipated Problems

7.5 Data Collection

Data will be collected using review of EPIC care electronic medical record (EMR) with notation of VAS score in RN documentation in PACU as well as EMR record of time of opioid administration if requested. The pre-op history and physical will be utilized for extracting demographic and clinical data. Finally, long term data will be requested from outpatient office patient records at defined time intervals. Pain medication usage will be reviewed with prescriptions given / noted in state (ISTOP) registries. Complication rates will be assessed using outpatient records as well as readmission/ER documentation in EMR.

7.6 Data Quality Assurance

Measurement reliability is dependent on accuracy of data reported in EMR and by patients in follow up visits. The use of standardized data collection procedures will limit any measurement bias that may be observed. Discretionary data outside the standardized collection criteria will not be collected. Potential confounders and effect modifiers are outlined in the study aims as the patient and treatment characteristics. Their influence will be statistically evaluated using stratified univariate and multivariate analyses.

7.7 Study Records

7.8 Access to Source

7.9 Data or Specimen Storage/Security

Data will be stored in a password-protected Microsoft Excel file stored on NYU network drive.

7.10 Retention of Records

Records will be retained until 1 year from the conclusion of the study.

7.11 Study Monitoring

7.12 Data Safety Monitoring Plan

Primary oversight of the study will be done by the PI to ensure proper evaluation, following, and reporting of AEs from study participants. Secondary monitoring will be done by each sub investigator on the review. Furthermore, systematic periodic review of data and AEs will be done on a monthly basis. The accumulated data will include patient pain variables collected in the hospital, patient clinical information in EMR, and patient follow-up data. Adverse events will be noted and recorded at follow-up visits and include any described (see drug package inserts) or undescribed events noted by patients considered by the clinician to be outside the realm of normal postoperative care and or recovery. These events will be reported to the IRB as soon as possible or at the monthly review. The study will be stopped if any unexpected or adverse events not previously reported for the MMA are noted. A summary of AEs, deviations, and report of the outcomes of these data safety monitoring reviews will be submitted to the IRB annually with the Continuation Submission

7.13 Study Modification

7.14 Study Discontinuation

7.15 Study Completion

7.16 Conflict of Interest Policy

7.17 Funding Source

N/A

7.18 Publication Plan

The PI and lead investigator will hold responsibility for publication of data. Authorship will be given based on significant contributions in the project and writing process.

Appendices

Appendix #	Title	Section	Topic
1	Acetaminophen Package Insert	6 Methods	6.1.5 Packaging/Labelling
2	Gabapentin Package Insert	6 Methods	6.1.5 Packaging/Labelling
3	Oxycodone Package Insert	6 Methods	6.1.5 Packaging/Labelling
4	Celecoxib Package Insert	6 Methods	6.1.5 Packaging/Labelling
5	REFERENCES	7 Trial Administration	7.18 Publication Plan

References