Evaluation of a Spine Surgery Analgesic Pathway:

A Randomized Controlled Trial

The Cleveland Clinic

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Amendments:

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Summary of Changes:

a. Page 8 Paragraph 2 : Lidocaine and ketamine will start before the incision
b. Page 9, under exploratory outcomes: The patient satisfaction Patient satisfaction with pain management at discharge (NRS 1-100) or on day 3 whichever comes earlier
c. Page 10, paragraph 4 : Pain scale changed to NRS.
d. Page 11,paragraph 1: PONV will be measured at 24 hrs
e. Page 11: Under 4.1.1: inclusion criteria clarified as described in the (table 1) added.
f. Page 17: Under exploratory outcomes measurements PDQ(Pain disability questionnaire measured at 3 months with the flexibility of+/-5 days

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1. BACKGROUND

About 51 million inpatient surgeries were performed in United States in 2010, based on National Hospital Discharge Survey.[1] Complications are in fact common, with as many as half of high-risk surgical patients experiencing substantive morbidity.[2,3] Postoperative morbidity results from complications that can be divided into various domains as described in post-operative morbidity scores (POMS).[4-6] Enhanced Recovery After Surgery (ERAS) Program, a standardized care pathway, is gaining widespread acceptance to achieve the goal of reducing post-operative morbidity and improving perioperative outcomes.[7,8] But the evidence of benefit of ERAS program is limited for widespread application in clinical practice.

Pain management is an essential component of ERAS pathway and can have high impact on patient centered outcomes. Pain management is important because it can help reduces complications[9],and improves patient comfort, patient satisfaction and long-term health related quality of life.

Poor acute pain management can result in chronic post-surgical pain**.** Chronic post-surgical pain causes an immense burden of pain and suffering, leading to a substantial reduction in patients' quality of life and serious economic consequences.[10,11] Persistence of pain after surgery or

trauma is poorly understood complex phenomenon involving endogenous pain-modulatory processes and individual's psychological flexibility.[12] Various factors - preoperative, intraoperative and postoperative, surgical, psychosocial, socio-environmental and patient-related- are thought to be involved in transition from acute pain to chronic pain.[13] Due to lack of certainty about mechanism of transition from acute pain to chronic pain, sufficient preventive and therapeutic approaches are lacking.[14] However appropriate management of acute pain with multimodal analgesia is one of the therapeutic approaches recommended by American Society of Regional Anesthesia.[15]

Pain management also influences patient satisfaction metrics. The fact that patient satisfaction is influenced by pain management during hospitalization is well documented, highlighting the importance of the specialized care pathway focused on improving pain managment.[16] Furthermore, health related quality of life,[17-19] pain related disability,[20]and depression.[21] are all relevant patient-centered outcomes which are potentially influenced by effective analgesic strategies. Depression and pain share common neurotransmitters and neural pathway that might explain high incidence of depression in patient suffering from chronic pain.[22,23] Antidepressant medication has been shown to help in treatment of both pain and depression.[24] Also inappropriate treatment of pain can exacerbate depression and other mood disorders.[25]

1.1 Pain management in spine surgery

Spine surgeries can be divided into simple (e.g. laminectomy, discectomy, disc decompression, 1-2 level fusion) and complex (e.g. spine fusion, instrumentation, scoliosis surgery). There is wide variation in anesthetic and analgesic management both during and after the procedure. Patient related factors, including age, sex, and previous opioid use, also contribute to anesthetic and analgesic planning. But opioid are mainstay of therapy for both intraoperative and post-operative pain control.[26] Gabapentin is an excellent drug for neuropathic pain, and can help in perioperative pain management with additional benefits of reducing chronic post-surgical pain.[27-29] However, Gabapentin is not used routinely for postoperative pain management. Similarly lidocaine,[30,31] ketamine,[32-34] acetaminophen,[35] non-steroidal anti-inflammatory drugs (NSAIDs)[36] all improve acute pain management but are not routinely used for spine surgery patients.

1.1.1 Risk factors for uncontrolled postoperative pain

Age, sex, history of chronic pain and opioid use, and anxiety are risk factors for inadequate postoperative analgesia (table 1).[37,38] Identification of high risk patient before surgery and developing an analgesic plan is crucial for optimal pain management. A patient with ≥2 risk factors out of six is at high risk for severe postoperative pain.

Table-1 Risk for uncontrolled post-operative pain

Low risk for severe postoperative pain	**High risk value for severe postoperative pain:**
1. Age > 60 yo	1. Age< 60 yo
2. Male	2. Female
3. No chronic Pain	3. Chronic Pain (> 3 months duration)
4. Preoperative VAS < 6	4. Preoperative VAS >=7
5. Low Anxiety Level (APAIS)	5. High Anxiety Level (APAIS)
6. 1-2 Levels Surgery without instrumentation	6. Complex Multilevel Spine Surgery with instrumentation

1.1.2 Role of the Acute Pain Management Service

The practice guidelines, published by American Society Anesthesiologists for acute pain management in the perioperative setting, recognize the role of Acute Pain Management Service (APMS) in reducing perioperative pain.[15,39] APMS helps to reduce analgesic gaps by providing education and training for healthcare providers. Furthermore, APMS can help in providing consistent evidence based therapies, coordination of care, and help in transition from acute care to home.

In a prospective study involving 23 hospitals, using a standardized approach for pain management by anesthesia-based pain services was evaluated in a total of 5,837 patients.[40] Anesthesia-based pain services reduced pain scores, along with pruritus, sedation, and nausea. In a single center, before-and after design (n=605), using APMS effect on pain satisfaction was

unreliable but it does have positive effect on pain control by reducing pain scores at rest and with movement.[41]

Though APMS are widely used, the economic impact is not well studied. In a systematic review Lee et al concluded that high-quality economic studies are required to support the cost-effectiveness and cost-benefits of APMS.[42] APMS is well developed at the Cleveland Clinic, yet provided to only fraction of spine surgery patients. It thus seems likely that providing APMS to the spine surgery program enhance postoperative analgesia and improve pain outcomes like; better functional recovery, lower pain scores and better patient satisfaction. But whether our pathway actually enhances recovery remains unknown.

1.1.3 Role of the care pathway

A care pathway provides consistent, guideline based care to all patients and can be useful when high practice variation exist for a standard procedure. For example, care pathway for low back pain has been shown to provide consistent care to all patients.[43] Schrijvers et al defined care pathway as "complex intervention for the mutual decision-making and organization of care processes for a well-defined group of patients during a well-defined period." The authors further noted that care pathways have explicit statements of the goals and key elements of care based on evidence, best practice, and patients' expectations and their characteristics.[44]

Care pathway can improve quality of care. For example, proximal femoral fracture care pathway has allowed improvement in the qualitative and quantitative efficiency, in terms of clinical, process, and financial factors.[45] Care pathways cannot be implemented in all clinical areas with comparable ease, and the resultant benefit is also not universal. In the UK, care pathways are used as a tool to modernize healthcare services, promoting quality care, and improving patient safety and cost. Bragato et al noted success with care pathways in orthopedic units, but not in trauma units, and cautioned against universal implementation of care pathways in all clinical areas.[46] Spine surgery is a highly specialized and a small group of healthcare providers usual care for these patients who have relatively similar clinical needs. Implementaing spine surgery care pathways will presumably provide more consistent care, and may improve pain outcomes and functional recovery, reduce pain scores, and enhance patient satisfaction.

1.2 Spine surgery care pathway

The proposed care pathway will consist of following interventions-

Preoperative management
Preoperative oral gabapentin 600 mg oral at the time of check-in
If a patient is on gabapentenoids (gabapentin, pregabalin), please continue in perioperative period
If patient has not taken his morning dose of gabapentenoids (gabapentin, pregablin) than resume home meds after the surgery.
If patient is on muscle relaxant (zanaflex, flexeril) preop, please continue
Preoperative oral acetaminophen 1000 mg at the time of check-in
IV acetaminophen 1 g over 15 min, if preoperative oral dose not given

Intraoperative management
Lidocaine: Lidocaine 1.5 mg/kg/hr start prior to incision and decreased to 1 mg/kg/hr at start of closing and continued to PACU and stop at the first PO intake (200mg /hr maximum dose, 8 hours maximum)
Ketamine: Ketamine 5 mcg/kg/min prior to incision and stop at closing
Intraoperative analgesia regimen: fentanyl or hydromorphone boluses. Opioid infusion as per anesthesia care team
Epidural analgesia or local would infiltration by the surgeon's case by case basis.

Post-operative management
Consider fentanyl or hydromorphone PCA for post op pain management.
Continuing lidocaine until discharge from PACU
Continue acetaminophen (IV if not tolerating oral acetaminophen).
Continue gabapentin (200-400) mg TID, and escalate dose (by 100mg per dose per day) as tolerated for at least one week after surgery.
Consider diazepam for post op muscle spasm - 2.5-5 mg IV every 6 hours as needed for muscle spasms
Use NSAID if OK with surgical service

APMS as needed for uncontrolled pain– Call APMS pager : 28270

1.2 Summary

Multiple strategies has been proven to help in pain control after spine surgery but are not consistently used at the Cleveland Clinic. It also remains unclear whether care pathways actually improve functional and pain outcomes after spine surgery. We therefore propose to study the role of the spine surgery analgesic pathway in patients having spine surgery.

2. HYPOTHESIS

2.1 Primary

1. Patients receiving care under Spine Surgery Analgesic Pathway will have *superior* quality of recovery (QOR) at three days compared to usual care.

2.2 Secondary

1. Patient receiving care under Spine Surgery Analgesic Pathway will have *lower* opioid consumption and lower pain scores compared to usual care (joint hypothesis test) at 48 hours after surgery**.**
2. Patient receiving care under Spine Surgery Analgesic Pathway will have *lower* opioid related side effects as measured by opioid related side-effect score at POD 1 and POD 2 compared to usual care

3. OUTCOMES

3.1 Primary outcomes

1. Quality of recovery (QOR) at 3 days

3.2 Secondary outcomes

1. Pain scores and opioid utilization (Joint, at 48 hours)
2. Opioid related side effects (ORSDS score) POD 1 and POD2

3.3 Exploratory outcomes

1. Quality of recovery (QoR) at 1 month
2. Patient satisfaction with pain management at discharge (NRS 1-100) or on day 3 whichever comes earlier.

3. Cost effectiveness analysis (EuroQol EQ-5D baseline and 3 months)
4. Chronic post-surgical pain at 3 months.[10,47]
5. Pain disability questionnaire (PDQ) at 3 months
6. PACU length of stay
7. PONV 24 hours after surgery.
8. Hospital length of stay.
9. Need for Acute Pain Consultation, as determined by clinical need.

Quality of recovery (QoR)- Assessment of postoperative recovery should be multidimensional including physiological parameters, functional recovery parameters and patient reported outcomes.[48] Quality of recovery is a valid, reliable and responsive measure of quality of recovery after anesthesia and surgery and it encapsulates all dimensions.[48,49]

EQ-5D - It is one of several instruments used to verify the quality-adjusted life years associated with a health state. It is defined as a survey instrument for measuring economic preferences for health states based on the assessment of: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[50] Each dimension has 3 levels: no problems, some problems, extreme problems.[51] This system was originally developed by the EuroQol Research foundation.

Pain Disability Questionnaire (PDQ) - The Pain Disability Index is a tool designed to help patients measure the degree their daily lives are disrupted by chronic pain. It was initially designed by Pollard and it was revalidated by many. It is a seven item, self-report inventory designed to measure domain-specific and general disability related to chronic pain.[52]

Pain scale (1-10 back and limb) – The NRS (Numeric Rating Scale) is a validated, simple-to-use, reproducible method of determining pain intensity.[53] It is considered to be superior to the Visual Analogue Scale (VAS) and to the Verbal Response Scale (VRS) in terms of accuracy in determining changes in pain intensity [Gillian 2011] and having better compliance rates and ease of use, especially in telephone follow-up or with the illiterate.[54,55] NRS is a one-dimensional measure of pain intensity, comprised of "no pain" (score of 0) up to "pain as bad as it could be" (score of 10). The 2 point reduction in time weighted pain scores(0-10) at 48 hours as a clinically significant measure of pain control.[56]

Opioid related side effects - we will use Opioid related symptom distress scale (ORSDS), a valid tool, on first and second post op day.[57,58]

Postoperative nausea vomiting (PONV)at 24 hrs : Postoperative Nursing Progress Record (NPR) - Records nausea vomiting severity as: 0=none, 1= mild, 2=moderate, 3= severe; analysis will compare nausea vomiting (1, 2, 3) to no nausea vomiting (0).

4. METHODS

4.1 Subject selection

Following written informed consent, a maximum of 440 patients scheduled for spine surgery will be enrolled. The spine surgery departments approve of the study and are aware that their patients will be approached about participation.

4.1.1 *Inclusion Criteria*

Patients to be included in this protocol will be adult patients meeting the following criteria:

- 18 to 80 years old at time of surgery – adult patients differ from pediatric patients in that adult spines are stiffer than pediatric patient.
- Posterior spine surgery
- Surgery performed at Cleveland Clinic main campus
- High risk for postoperative pain as mentioned in (Table 1) **(patients with 2 or more risk factors for severe post-operative pain)**
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4.1.2 *Exclusion Criteria*

- Allergy or hypersensitivity to lidocaine, ketamine, acetaminophen, gabapentin
- Current or recent drug abuse (within past 6 months) – alters post-operative complications
- Pregnancy
- Immune system disease such as HIV, AIDS – alters measurement of inflammatory markers and possible post-operative complications
- Undergoing immunosuppressive treatment – alters measurement of inflammatory markers
- Recent history of sepsis – alters measurement of inflammatory markers
- Contraindications to lidocaine such as heart block and hepatic insufficiency
- Heart failure with ejection fraction less than 30%

- Liver dysfunction manifested with increased liver enzymes to double the normal and INR of 2 or higher

4.2 Informed consent

Written informed consent will be obtained during a Clinic visit at least one day before surgery. The study protocol will be explained to patients verbally and in writing. Risks, benefits, and alternatives will be discussed with eligible patients. We will explain to patients that they may withdraw from study at any time.

4.3 Randomization and allocation

After applying inclusion and exclusion criteria, eligible spine surgery patients (high risk patient for severe postoperative pain) will be randomized 1:1 (see section Risk factors for uncontrolled postoperative pain on the day of the surgery.

Randomization will be computer-based and allocation will be concealed until just before surgery by a web-based system. Randomization will be initiated after the pre-surgical assessment at the day of the surgery just before the surgery to minimize/eliminate drop-outs due to cancelled surgeries, withdrawn consent, and other unexpected events.

4.4 Withdrawal Criteria

Patients will be free to withdraw from study at any time. Patients will also be removed from study at any time for adverse events, or as deemed necessary for patient safety.

4.5 Protocol

This is a randomized controlled trial comparing "spine surgery analgesic pathway" with usual care in improving quality of recovery after surgery and pain management. At the time of surgery office visit or at the time of preoperative assessment by anesthesia care team risk factors for suboptimal pain management will be identified and documented. Patients will be assessed at the time for surgical office visit for their risk for severe post-operative pain. Patients with 2 or more risk factors will be classified as high-risk for severe postoperative pain and the patients with less than 2 factors as low risk. After obtaining informed consent spine surgery patients will be randomized in one of the 2 study groups. (Table-2)

1. "Usual care" group A
2. "Care pathway" group B

Table 2 - Group specific intervention.

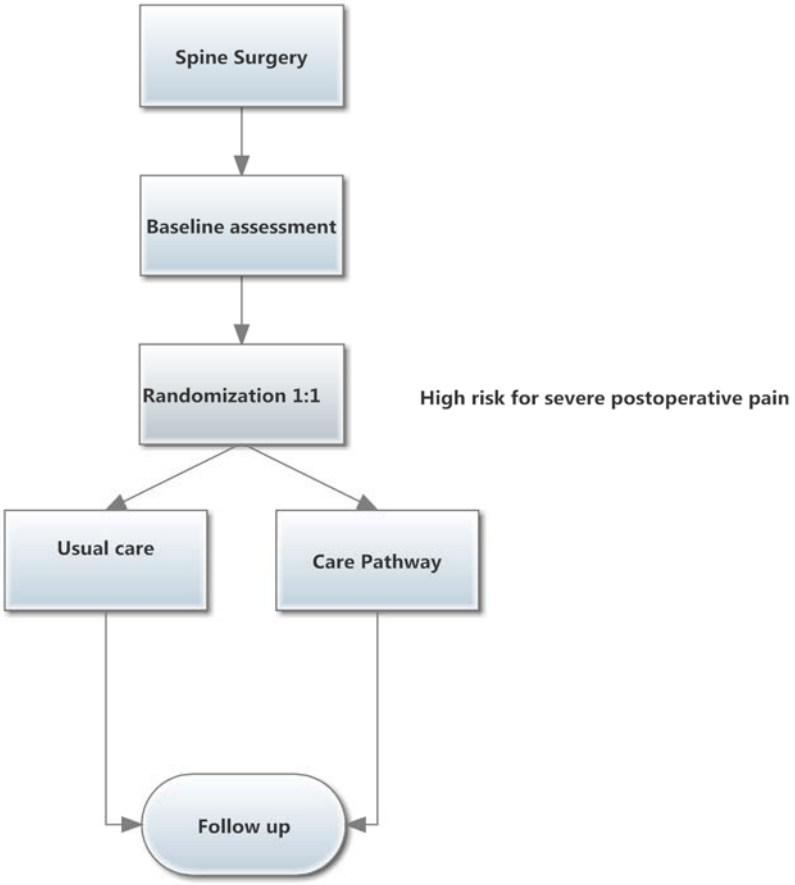
	Group A	**Group B**
Pre-operative	-	Gabapentin Acetaminophen
Intraoperative	-	Lidocaine infusion Ketamine infusion

1. Group A – Patient will receive preoperative (placebo) oral acetaminophen 1 gram and preoperative oral gabapentin 600 mg. Patients will receive intraoperative (placebo) infusion of ketamine and lidocaine.
   Lidocaine (placebo) : Lidocaine 1.5 mg/kg/hr start at incision and decreased to 1 mg/kg/hr at start of closing and continued to PACU and stop at the first PO intake (200mg /hr maximum dose, 8 hours maximum)

   Ketamine (placebo): Ketamine 5 mcg/kg/min starts at incision and stop at closing

2. Group B - Patient will receive preoperative oral acetaminophen 1 gram and preoperative oral gabapentin 600 mg. Patients will receive intraoperative infusion of ketamine and lidocaine.
   Lidocaine(active): Lidocaine 1.5 mg/kg/hr start at incision and decreased to 1 mg/kg/hr at start of closing and continued to PACU and stop at the first PO intake (200mg /hr maximum dose, 8 hours maximum)

   Ketamine(active): Ketamine 5 mcg/kg/min starts at incision and stop at closing



Acute pain team consult will be available to all patients (both groups) _ with poor pain control as assessed by the primary team.

Anesthetic Management

Patients will be pre-medicated with oral or intravenous midazolam as clinically indicated. On arrival to the operating room patients will be monitored according to American Society of Anesthesiogists standards (ECG, noninvasive blood pressure, oxygen saturation, temperature). An arterial catheter will be inserted if clinically indicated, as will a central venous catheter. Colloids and blood products will be used at the discretion of anesthesia care team.

Anesthetic management (Figure- 1) will be standardized. Etomidate (0.2-0.3 mg/kg) or propofol (1-2 mg/kg), lidocaine 1.5mg/kg, vecuronium (0.1 mg/kg) or rocuronium (0.6 mg/kg), and fentanyl (1-2 μg/kg) will be used for induction. Anesthesia subsequently will be maintained with sevoflurane (up to 1.5 MAC) in a carrier gas of 50-80% inspired oxygen and air.

Opioid medications will be administered according to patient's requirements. Fentanyl and hydromorphone boluses will be used as guided by anesthesia care team. Opioid infusion can be used if neurophysiologic monitoring is required. Additional muscle relaxant will be given as necessary to maintain 1-2 mechanical twitches in response to supra-maximal stimulation (Train-of-four stimulation) of the ulnar nerve at the wrist. Ventilation will be mechanically controlled to maintain end-tidal carbon dioxide tension near 35 mmHg. Tidal volume will be set between 8 and 10 ml per kilogram lean body weight to keep the peak inspiratory pressure below 30 mmHg and a positive end expiratory pressure of 5 mmHg or higher according to patient's requirements will be administered. Clinically necessary modifications to the general management and monitoring plan will be allowed. Temperature will be monitored, and normothermia (core temperature > 36 degrees Celsius) will be maintained with forced-air warming.

If an epidural catheter is inserted by the surgeon for postoperative analgesia, it will not be activated until shortly before the end of surgery or in postoperative care unit. Only small fraction of patient receives epidural catheter or local anesthetic infiltration. The decision of placing the epidural catheter is made during the surgery based on the surgical exposure and it is difficult to know which patient will get this intervention before randomization.

4.6 Blinding

Patients will not be specifically told to which group they were assigned, and will only be told that they will receive baseline standard care per anesthesia and surgical team irrespective of group assignment

Pre-operative intervention (acetaminophen and gabapentin) will be placebo controlled. The pharmacy will provide the study drug as per individual group assignments. Placebo oral drugs will either be identical looking capsules provided by the manufacturers or encapsulated versions provided by the CCF Research Pharmacy. IV infusions will be placebo control and will

be prepared by pharmacy as per institutional guidelines. The infusion medications will then be provided to the anesthesia team at the start of the case by the research fellow.

All post-discharge evaluations will be performed by investigators who are fully blinded to randomization and actual treatment received. Also pain scores are assessed by the nurses — who will be blinded to the treatment arm — and recorded in the electronic health record. Contact with study patients will be highly scripted by our research coordinator and avoid questions that might unblind the studies. In the event that one follow-up investigator is inadvertently unblinded to a particular patient's treatment, another blinded investigator will be substituted.

5. MEASUREMENTS

VAS pain and anxiety level (APAIS scale) will be recorded by preoperative nurse /or anesthesia team. A baseline Euroqol-5d (EQ-5D), pain score (numeric rating scale) at rest and movement will be documented.

Primary and Secondary

	Outcomes	**Measurements**	**Data source**
Primary	Quality of recovery-15	POD 3 POD 30	Questionnaire
Secondary	Opioid related side effects score (ORSDS)	POD 1 POD 2	Questionnaire
Secondary	Pain scores and opioid utilization at 48 hours (Joint)	48 hours after surgery	Database (EPIC)

Exploratory

	Outcomes	**Measurements**	**Data source**
Exploratory	Patient satisfaction with pain management NRS 1-100	At discharge	Questionnaire
Exploratory	EQ-5D	Baseline 3 months +/-5 days	Questionnaire
Exploratory	Chronic post-surgical	3 months	Questionnaire

	pain (CPSP) NRS 0-10		
Exploratory	PACU length of stay		Database (EPIC)
Exploratory	PONV in 24 hrs.	Nothing (0) Mild (1)/moderate(2)/severe(3)	Database (EPIC)
Exploratory	Pain disability questionnaire (PDQ)	3 months +/- 5days	Questionnaire
Exploratory	Hospital length of stay		Database (PHDS)
Exploratory	Acute Pain consult	Clinician request, in hospital	Electronic records

6. DATA ANALYSIS

First, randomized groups will be compared for balance on potentially confounding baseline variables (see the list below) using descriptive statistics and the standardized difference, i.e., the difference in means or proportions divided by the pooled standard deviation. The potential confounding and risk variables include the following: age, body mass index (BMI), gender, chronic pain status (> 3 months duration) (Y/N), preoperative pain score in NRS scale, anxiety level (high vs. low level by APAIS) type of surgery (1-2 Levels Surgery without instrumentation vs. Complex Multilevel Spine Surgery with instrumentation vs.)

Potential Confounders

- Age
- Gender
- Race
- BMI
- ASA status
- Type of surgery
- Duration of surgery
- Smoking status (yes/no)
- History of chronic opioid use
- Type of insurance
- Diabetes mellitus

All analyses will adjust for any imbalanced baseline variables, with imbalance defined as an absolute value of the standardized difference > 0.20.

Primary hypothesis

To assess the relationship between two pain management approaches and quality of recovery (QOR) score on third post-operative day we will build the linear regression model with the study group as a predictor and QOR score as an outcome with adjustment for potentially imbalanced risk factors and potential confounding variables listed above. The original paper on quality of recovery (QOR) score[59] indicates that it is normally distributed measure; therefore, use of the linear regression model is justifiable. To compare patients from two study groups the model based differences in means QOR score of two groups (Group A vs. Group B) along with 95% confidence intervals will be reported. The hypothesis will be tested with Wald-test with 0.05 level of significance.

Secondary hypotheses

Secondarily, we will assess the effectiveness of spine surgery care pathway comparing to usual care (Group A vs. Group B) measured by cumulative opioid consumption and pain intensity scores within the first 48 hours after surgery, using a joint hypothesis testing framework described by Mascha and Turan.[60] We will consider Group B to be superior to Group A on postoperative pain management if both outcomes are noninferior (i.e., not worse) and at least one of the outcome will be superior for Group B patients. We define the a-priori noninferiority pain score delta as 1 point (on a scale of 0-10) and the opioid delta as 1.2 for the ratio in geometric means IV morphine equivalent doses.

We will first estimate confidence intervals for the treatment effect for both pain score and opioid consumption. Assuming log-normal distribution of opioid consumption, we will evaluate the percent difference in geometric mean IV morphine equivalent dose between the two groups using a log-linear regression model. To evaluate the difference in mean pain scores (in VAS scale) we will first summarize the pain scores (in VAS scale) by computing time weighted average (TWA) pain score for each patient. Then we will use a linear regression model to assess the exposure effect on the TWA pain scores.

Joint hypothesis testing of pain score and opioid consumption will be conducted at the overall 0.025 significance level (Bonferroni corrected for two secondary hypotheses), and all tests were 1-tailed in the direction favoring a novel pain management approach. Noninferiority of Group B

to Group A will be assessed for each outcome at the 0.025 level (no Bonferroni correction) since noninferiority will be required on both outcomes. Therefore, noninferiority (being "not worse") will be concluded for both outcomes at the significance level of 0.025 if the upper limit of 95% confidence interval is below the corresponding noninferiority delta. If noninferiority on both outcomes is found, superiority will be assessed on each. We will adjust for two outcomes for the superiority testing only, using a significance criterion of 0.0125 for each outcome (i.e., 0.025/2, Bonferroni correction), since superiority on either outcome would suffice. Superiority will thus be claimed for a particular outcome if the 97.5% interval limit is below zero for pain score and below 1 for opioid consumption. No multiple testing adjustment will be required for assessing both noninferiority and superiority since significance for both will be required to reject the null hypothesis, and also because superiority falls in the noninferiority rejection region.

The exploratory outcomes will be summarized for each study group with appropriate descriptive statistics.

7. SAMPLE SIZE AND POWER CONSIDERATION

Sample size estimation is based on the analysis of superiority of the primary QOR score on third post-operative day. Assuming the coefficient of variation (SD/mean before log-transformation) of 0.43 for both groups, sample size of **184 patients in each group** (total 368 patients) would provide about 90% power at the 0.05 significance level to detect the ratio in geometric means of 1.15 or higher (i.e., a mean QOR score at least 15% increased) comparing Group B to Group A. For the planning purposes, the assumption on variability of the QOR scores (coefficient of variation of 0.43) was fairly conservative comparing to the original paper on quality of recovery (QOR-15) score.[59] Assuming the drop-out rate of about 10% (due to surgery cancellation, withdraws and other unexpected events) we plan to enroll 203 patients in each group, total of 406 patients.

We also plan for two interim analyses at 33% and 67% of the planned enrollment, therefore, adjusted sample size is N=220 patients per group, or N=440 total. We will use the gamma spending function with parameters -4 and -1 for alpha (efficacy) and beta (futility), respectively. If the alternative hypothesis is true (if the effect is there) there will be a cumulative probability of 17%, 64% and 100% of crossing either an efficacy or futility boundary at the 1st, 2d and final analyses, respectively (Figure 2 and Table 3 below contains boundary Information). Planned

first and second interim analyses will be performed upon accrual of 148 and 294 patients respectively. In addition, we plan for 4 pilot patients (2 per group) in the beginning of the study. **Therefore, planned enrollment is a maximum** of N=**222** patients per group, or N=**444** total.

Figure 2. Boundary plot

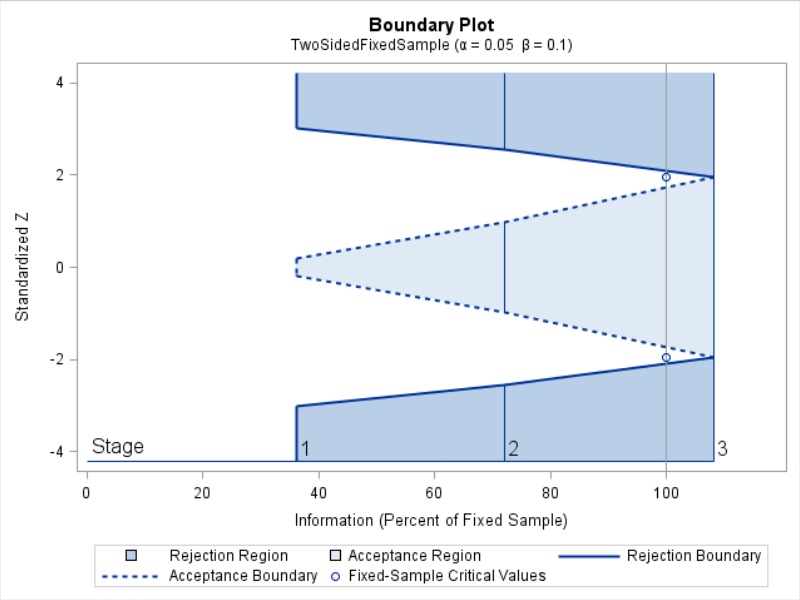


Table 3 Boundary Information for interim analysis (3 analyses = 3 stages):

Boundary Information (Standardized Z Scale)
Null Reference = 0

Stage	Information Level	Alternative Reference		Boundary Values Lower		Upper	
	Proportion	Lower	Upper	Alpha	Beta	Beta	Alpha
1	0.3333	-1.94613	1.94613	-3.01074	-0.18862	0.18862	3.01074
2	0.6667	-2.75225	2.75225	-2.54483	-0.98712	0.98712	2.54483
3	1.0000	-3.37080	3.37080	-1.94481	-1.94481	1.94481	1.94481

Cleveland Clinic leadership is initiating a cost transformation process, looking at pain management plans for surgical services, across Cleveland Clinic Foundation. Our quality improvement program, “Spine surgery analgesic pathway”, aligns with institutional priorities of improving patient care, better perioperative pain control and to decrease the length of stay of surgical patients.

Propose Proposed Timetable

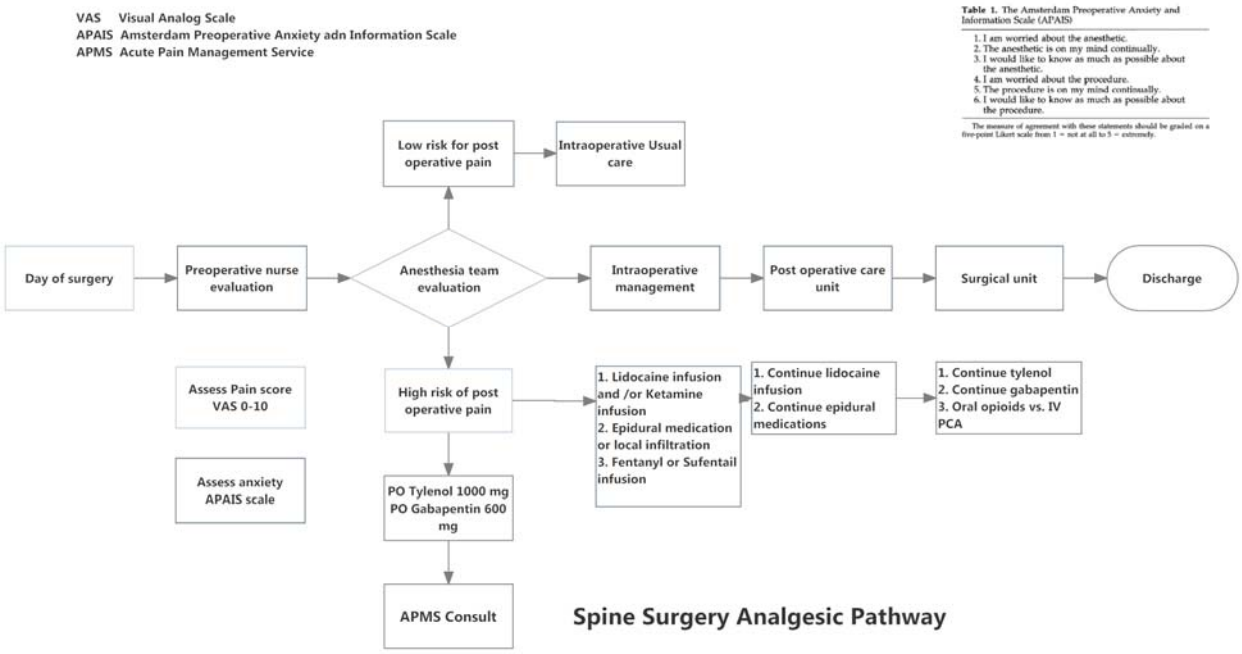
- Preparation of Case Report Forms (CRF) and databases: 2-4 weeks
- Patient enrollment and data collection: 1-1.5 years
    - At Cleveland Clinic main campus we perform 100-120 spine surgery per month. We expect an average of 5-8 patients per week considering all inclusion and exclusion criteria as well as the success rate of obtaining research informed consent in our department.)
- Statistical Analysis: 4 weeks
- Manuscript drafting: 4-8 weeks
- Total: Minimum 1 year , Maximum 2 years

8. SUMMARY

This randomized controlled trial will assess the efficacy of patient centered approach to implement analgesic care pathway for spine surgery to improve meaningful patient centered outcomes.

9. FIGURE LEGENDS

Figure 1



10. APPENDIX

1. Amsterdam preoperative anxiety and information scale

Table 1. The Amsterdam Preoperative Anxiety and Information Scale (APAIS)

1. I am worried about the anesthetic.
2. The anesthetic is on my mind continually.
3. I would like to know as much as possible about the anesthetic.
4. I am worried about the procedure.
5. The procedure is on my mind continually.
6. I would like to know as much as possible about the procedure.

The measure of agreement with these statements should be graded on a five-point Likert scale from 1 = not at all to 5 = extremely.

2. EQ-5D (Dolan P: Modeling valuations for EuroQol health states. Med Care 1997; 35: 1095-108)

Is patient able to give answers to EQ5D? YES / NO
First I'd like to ask you about mobility. Would you say you have…
1. No problems in walking about?
2. Some problems in walking about?
3. Are you confined to bed?

Question 2: Self-Care
Next I'd like to ask you about self-care. Would you say you have…
1. No problems with self-care?
2. Some problems washing or dressing yourself?
3. Are you unable to wash or dress yourself?

Question 3. Usual activities
Next I'd like to ask you about usual activities, for example work, study, housework, family or leisure activities.
Would you say you have…
1. No problems with performing your usual activities?
2. Some problems with performing your usual activities?
3. Are you unable to perform your usual activities?

Question 4: Pain/Discomfort

Next I'd like to ask you about pain or discomfort. Would you say you have.

1. No pain or discomfort?
2. Moderate pain or discomfort?
3. Extreme pain or discomfort?

Question 5: Anxiety/Depression

Finally I'd like to ask you about anxiety or depression. Would you say you are…

1. Not anxious or depressed?
2. Moderately anxious or depressed?
3. Extremely anxious or depressed?

PLEASE REMEMBER IT IS IMPORTANT TO HAVE ONE AND ONLY ONE RESPONSE TO EACH GROUP OF THREE RESPONSES

3. Pain Disability Questionnaire (PDQ)

4. ORSDS score - Yadeau JT, Liu SS, Rade MC, Marcello D, Liguori GA: Performance characteristics and validation of the Opioid-Related Symptom Distress Scale for evaluation of analgesic side effects after orthopedic surgery. Anesth Analg 2011; 113: 369-77

ORSDS Questionnaire[3]

In the last 24 h, have you experience any of the following?	Did not experience	If yes, how frequently did it occur?				If yes, how severe?				And how bothersome was the experience?				
		Rarely	Occasionally	Frequently	Almost constantly	Slightly	Moderately	Severe	Very	Not at all	A little bit	Some what	Quite a bit	Very much
Nausea		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Vomiting		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Constipation		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Difficulty passing urine		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Difficulty concentrating		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Drowsiness/ difficulty staying awake		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Feeling lightheaded or dizzy		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Feeling confused		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Feelings of general fatigue or weakness		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Itchiness		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Dry mouth		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0
Headache		1	2	3	4	1	2	3	4	0.8	1.6	2.4	3.2	4.0

ORSDS = Opioid-Related Symptom Distress Scale.

6. QoR-15 . Development and Psychometric Evaluation of a Postoperative Quality of Recovery Score: The QoR-15 .Anesthesiology. 2013; 118 (6):1332-1340. doi:10.1097/ALN.0b013e318289b84b

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time

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