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A Introduction

A1 Primary Hypothesis

We hypothesize the systemic infusion of lidocaine will improve pain control in patients undergoing posterior spinal fusion for adolescent idiopathic scoliosis, decreasing opiate consumption in the acute perioperative period. We further hypothesize that lidocaine infusion will attenuate the inflammatory response to injury and surgery, and that taken together decreased perioperative opiate consumption and decreased inflammation will lead to improved longer-term outcomes including decreased chronic opiate use and improved physical function.

A2 Purpose of the Study Protocol

To evaluate the efficacy of intravenous lidocaine to reduce opioid consumption, improve recovery, and reduce the systemic inflammatory response to surgery posterior spinal fusion for AIS (Adolescent Idiopathic Scoliosis).

B Background

B1 Rationale for this Study

Opiate dependence is a serious complication of surgery. Systemic opioids are one of the most effective analgesics to treat severe pain after spine surgery. Despite their effectiveness for treating severe pain, administration of systemic opioids is associated with adverse effects including long-term dependency and overdose.1-3 In the last 20 years, opiate addiction the associated risk of drug overdose has become a crisis of public-health proportions, with overdose deaths exceeding those from both motor-vehicle collisions and firearms (Figure 1). Amongst the current epidemic of opioid use disorders (by prescription opioids and heroin), there is also an alarming growing public health problems in adolescents opioid dependency, which comes with devastating consequences. Early age onset of prescription opioid and heroin use has been associated with higher prevalence of dependency and increasing clinical severity.4 Opioid dependency following trauma relates to issues beyond pain severity, such as depression and anxiety.5

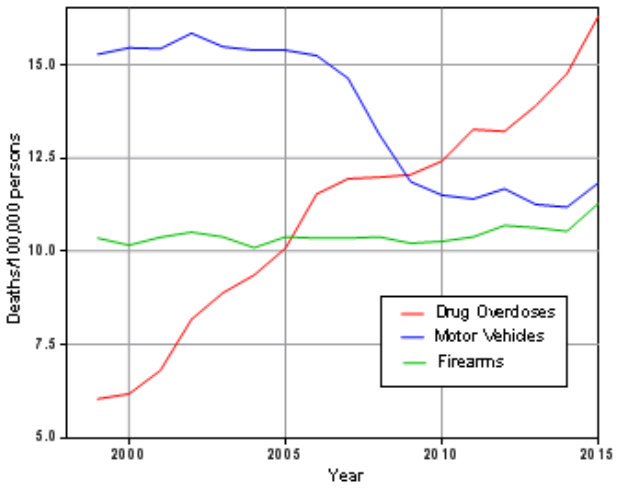

Figure 1: Crude US death Rate 1999-2015. Data Source: NCHS Vital Statistics System for numbers of deaths. Bureau of Census for population estimates. US Firearms, MVC and Drug Overdose Death Rates (all ages), 1999-2015.

Preliminary data obtained in our institution has followed adult spinal deformity patients after complex reconstructions. 27% of opioid-naïve patients undergoing adult spinal deformity surgery required opioid medications at one-year followup and the majority (62%) of patients using opioids before surgery continued their use at one-year after surgery. These data demonstrate that a subset of spine surgery patients are introduced to opioids and become dependent, while also emphasizing the difficulty of cessation of chronic opioid use. Furthermore, we have collected health-related quality of life (HRQOL) data, a necessary component of value-driven healthcare. Our preliminary data shows that opioid dependent patients, on average, complain of worse pain function versus the opioid naïve at baseline and after surgical treatment. (Figure 2) These data support the need for non-opioid pain control methods to minimize long-term opioid use in trauma patients, as up to 30% of patients may become opioid dependent and incur the risks associated with this condition, including chronic pain complaints refractory to treatment.

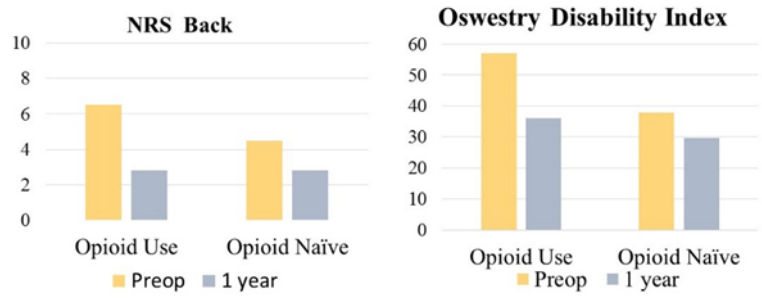

Figure 2. **Opioid use for chronic pain is associated with worse complaints and less improvement.** Preoperative and 1-year followup patient reported outcomes (NRS-Back, ODI) for patients undergoing complex thoracolumbar reconstructions.

Exposure to opioids in the perioperative period may affect recovery beyond the psychological effects of dependency. Opioids are immunosuppressive, both in-vitro and in-vivo, to the innate and native immune system and can further exacerbate the immune dysfunction induced by trauma and surgery.6 Tissue damage, either from traumatic injury or surgery causes release of damage-associated molecular patterns (DAMPS) that serve as danger signals to the immune system, signaling the need for an inflammatory response 7. When the acute inflammatory response is limited to injured tissue, inflammation can contribute to hemostasis, help to prevent infection, and facilitate tissue repair 8,9. In the setting of major invasive surgery, the inflammatory response can become dysregulated and extend systemically, manifest as a massive activation of the innate immune system with an almost concomitant inhibition of adaptive immunity. These pathophysiologic responses frequently complicate the care of complex-spine patients. By example, surgery for acute spinal injuries in polytrauma patients causes an increase in circulating levels of the inflammatory cytokines IL-8 and IL-6 at 7 and 24 hours after injury respectively 10-12. Further, the dysregulation of immune response in these patients is frequently exacerbated by the fact that these patients often need ongoing critical care, which is itself associated with immune dysfunction 13.

IV lidocaine is an effective adjunct for perioperative analgesia. Intravenous lidocaine is a nonopioid method of perioperative analgesia.14-16 It is an amide local anesthetic that works primarily through inhibition of nociceptive stimuli via sodium channel blockade. This is not the primary mode of action when given intravenously. This is because the concentrations achieved with low-dose intravenous administration are similar to systemic absorption with epidural delivery, approximately 1μM. These low concentrations would not be sufficient to block any substantial number of sodium channels throughout the body. Intravenous lidocaine likely has local and central actions, including inhibition of noxious stimuli and encouraging the release of endogenous opioids.17 As a non-opioid analgesic, intravenous lidocaine is effective in reducing pain, opioid consumption, ileus, and hospital length of stay.18-20

Intravenous lidocaine has been studied most extensively in abdominal surgeries.18,20-23 Koppert et al found a 35% reduction in morphine equivalent opioid consumption after major abdominal surgery.20 These authors also reported reduced pain complaints with activity, which supports our hypothesis that systemic lidocaine will improve recovery with faster rehabilitation. Similarly, Kuo et al found a 33% reduction in opioid requirements after major abdominal surgery with reduced ileus and a reduced mean length of stay.22 There has been only limited investigation into systemic lidocaine in orthopedic surgery.. Farag et al performed a randomized trial of intravenous lidocaine versus placebo in elective spine surgeries.19 Subjective pain complaints were less in the lidocaine cohort. It is important to note that nearly 50% of the patients in this study underwent cervical surgeries, distinctly less invasive than thoracolumbar surgery.. Thus, the efficacy of intravenous lidocaine in a population at highest risk for large opioid requirements has not been investigated.

Systemic lidocaine has been safe in the studies performed21,24. Serum concentrations of lidocaine at commonly prescribed doses (2mg/kg bolus, 2mg/kg/hr infusion) remain lower than toxic levels.25 Adverse events may include cardiac abnormalities, such as arrhythmias. Studies investigating lidocaine in cardiothoracic surgery, however, have not found evidence of an increased risk of arrhythmia in this high risk population.26-28 A systematic

review of studies involving intravenous lidocaine failed to find relevant adverse events attributed to the study drug.24

Injury-induced Inflammation drives perioperative pain. Nociception is the neurologic response to tissue injury or damage and is mediated by specialized sensory neurons which convey the signal of tissue damage from the periphery through the spinal dorsal root ganglion to ascending fibers of the spinal cord that transmit these signals to the brain. At each level (periphery, spinal cord and brain) the immune systems modulates the pain signal through both pro-nociceptive and anti-nociceptive mediators. These mediators influence both the sensation of pain and the threshold for a pain response to stimulation.

Peripheral nociceptors respond to injury both directly and indirectly. Outside of a normally tolerated thresholds, specialized sensory neurons response to thermal and mechanical stress to transduce a pain signal. In addition to a direct response to thermal or mechanical stimulation, nociceptors respond to neuroactive signalling molecules and inflammatory mediators produced by non-neural cells such as glia and leukocyte. These signals can both amplify (pro-nociceptive) or attenuate (anti-nociceptive) the response of sensory neurons 29. Pro-nociceptive mediators include the canonical inflammatory cytokines TNF-alpha 30, IL-6 31 and IL-1-beta32, produced in response to inflammation by innate immune cells such as monocytes and macrophages. Nociceptors express cell surface receptors that can respond directly to these mediators, decreasing the threshold for activation resulting in a pro-nociceptive effect 33. Conversely, antiinflammatory mediators such as IL-10 can decrease sensory neuron activation, having an anti-nociceptive effect 29. The effect of these mediators can be to both increase the intensity of an otherwise low-amplitude pain signal or to decrease the threshold for a response. In addition, there are cohorts of neurons that are normally that are insensitive to mechanical or heat stimulation, but in response to inflammatory mediators these neurons become sensitized to noxious mechanical or thermal stimulation, and are thereby recruited as nociceptors 6,34. Thus inflammation both facilitates the activation of the normal complement of peripheral nociceptors, but also recruits novel nociceptors, further amplifying the pain signal.

In patients undergoing major spine surgery, the dynamics of inflammation and pain are particularly complex. Major surgery can cause dysregulated immune response resulting in a systemic inflammatory response, characterized in part by elevated levels of circulating inflammatory mediators 35. These circulating inflammatory mediators can interact with pain neural pathways across the anatomic spectrum from the peripheral nociceptors to ascending spinal tracts, broadly decreasing the threshold for activation of pain pathways, resulting in the syndrome of hyperalgesia whereby normally innocuous stimuli cause a pain response. In the setting of recovery from major spine surgery, hyperalgesia may exaggerate the pain response from minor injuries, exacerbating the challenge of pain control.

Injury and surgery induce a strong immuno-inflammatory response. The dysregulated immune response to major surgery and the associated exaggerated systemic inflammatory response contribute to the challenge of pain control. At the biochemical level, surgery increases pain signaling at the local, regional and central levels signal transduction exacerbating the challenge of pain control. In addition, systemic inflammation contributes to hemodynamic instability, driving hypotension and compromising spinal cord perfusion. Unchecked, this immune dysfunction can lead to the persistent inflammation,

immunosuppression and catabolism syndrome (PICS) that underlies chronic pain and critical illness 13. Prior studies have demonstrated that immunophenotype correlates with clinical recovery from surgery, with immune metrics measured in the first 24 hours correlating with metrics of clinical function measured out to more than 30 days 36.

To better understand the effect of spine surgery immunophenotype, we first sought to develop a practical, high resolution clinical immunophenotyping protocol. High-resolution clinical immunophenotyping has been limited by the logistics of performing flow-cytometric analysis. Conventional tissue processing protocols require real-time sample processing, as both prolonged storage or cryopreservation can result in changes in cell number, cell morphology and cell-surface marker expression 37,38. In the setting of a clinical trial were samples be acquired during evening or weekend hours, 24/7 laboratory staffing by research personnel is logistically prohibitive. To address this issue, we have developed and validated a protocol for cell preservation using a novel buffer/fixation system (Proteomic Stabilizer, Smart Tube Inc, San Carlos, CA) which allows for stable cryopreservation of peripheral blood samples, with reproducible flow-cytometric immunophenotyping at least up to 72 hours after freezing. We find that Smart Tube proteomic stabilizer provides excellent reproducible results as compared to gold-standard immediate processing of samples (see Figure 3).

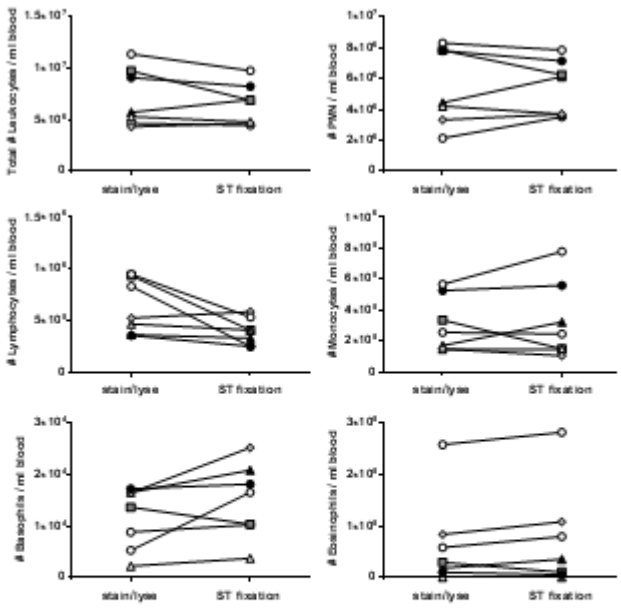

Figure 3: Proteomic Stabilization and Freezing Preserves Epitopes for FACS Based Immunophenotyping. Blood was collected from critically ill trauma patients (n=6). Cells were stained and analyzed immediately after collection or fixed and stored at -80 degrees C for 72 hours, then analyzed. Peripheral blood immunophenotype was determined by flow cytometry. There was no significant difference in cell numbers measured immediately vs. after storage.

We have successfully applied this technology to more than 500 clinical samples as part of a Phase-2 randomized, controlled trial (Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury, ClinicalTrials.gov #NCT02545949), done in collaboration with the United States Department of Defense.

We then determined the effect of traumatic thoracic spine injury on immunophenotype. Using our established protocol our immunophenotyping protocol to measure cell surface marker expression on circulating leukocytes from n=4 patients suffering traumatic spine injuries (Figure 4). The initial blood sample was collected within 2 hours of injury, on presentation to the emergency department; subsequent blood samples were taken at 6 hours, 24 hours and 72 hours. In these preliminary data, we find that trauma patients with a thoracic spine fracture have reproducible changes in the circulating leukocyte cohort within 6 hours of presentation, with a dramatic decrease in the number of circulating Natural Killer (NK cells) and a trend towards increased numbers of dendritic cells (DC). We also detected an increase in monocyte CD14 expression and a decrease in monocytes HLA-DR expression. These preliminary data demonstrate that technical and logistical feasibility of our immunophenotyping approach.

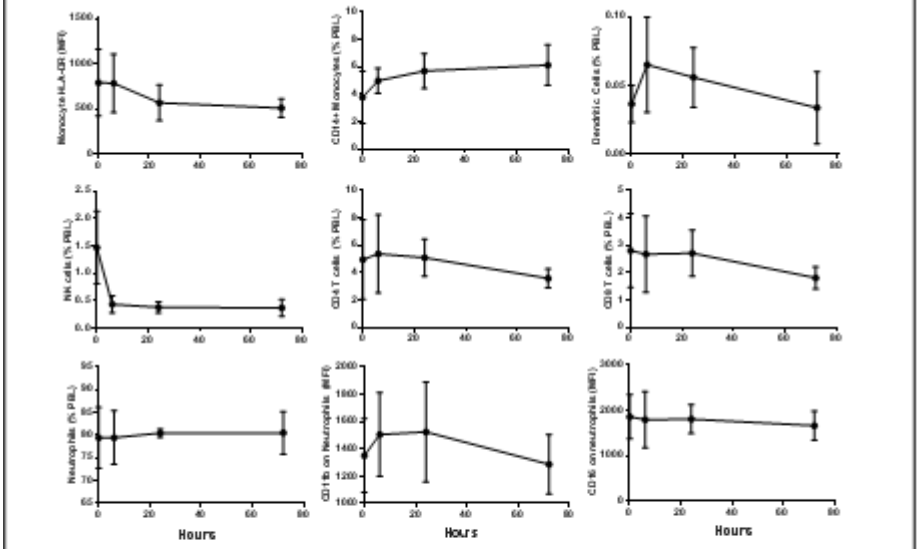

Figure 4: Changes in Circulating Leukocyte Immunophenotype Induced by Spine Trauma. Blood from N=4 spine trauma patients was subjected to flow-cytometric analysis at hospital admission and then at 6 hours, 24 hours and 72 hours after admission. Samples were fixed and stored at -80 degrees C, then thawed, immunostained and analyzed by flow cytometry. Data are shown as either mean-florescence intensity (MFI) or % of peripheral blood leukocytes (PBL) as appropriate.

Lidocaine is a potent immunomodulator. In addition to its well-described functions as a local anesthetic, lidocaine directly modulates the function innate immune cells including macrophages, monocytes and polymorph neutrophils (PMN). In a rabbit model of acid-induced acute lung injury, pretreatment with systemic lidocaine at clinically significant levels (2 mg/kg bolus +2 mg/kg/hr continuous infusion) resulted in decreased PMN accumulation in the lung after injury39; ex-vivo analysis of PMN isolated from the lungs of injured animals found that treatment with lidocaine reduced reactive oxygen species production,

which would correlate with decreased free-radical production with an associated decreased injury to the pulmonary vasculature. Similar results were reported by Takao et al, who reported that lidocaine infusion was associated attenuated the levels of the inflammatory cytokines TNF-alpha and IL-1beta in the BAL of rabbits with a hyperoxic lung injury16. Critically, study of PMN isolated from septic human patients demonstrate that lidocaine treatment can reduce PMN recruitment. These authors also demonstrate that lidocaine can interact directly with PMN, modulating integrin-mediated activation of protein-kinase C (PKC)-theta.15 These data support those from Hollmann et al which demonstrate that lidocaine can attenuate PMN superoxide production, which is mediated in part by outside-in integrin signalling.40 Lidocaine modulates the systemic inflammatory response. Pretreatment with systemic lidocaine prior to endotoxin-induced acute lung injury (ALI) in rabbits resulted in decreased levels of inflammatory cytokines TNF-alpha and IL-1-beta in the broncheoalveolar lavage fluid.39 Similar results were reported for both hyperoxic and hydrochloric acid induced ALI.16,39 Similarly, systemic infusion of lidocaine was found to ameliorate shock in a rabbit model of endotoxemia, and this was associated with a significant decrease in the circulating levels of TNF-alpha, IL-6 and IL-8.41 Analogous results were seen in both rodent and equine models of endotoxemia.41-44

To demonstrate the effect of lidocaine on the immuno-inflammatory response, we measured cytokine production by human peripheral blood mononuclear cells in response to either LPS or T-cell receptor ligation with anti-CD3/anti-CD28 antibody in the presence of increasing doses of lidocaine (Figure 5). We found that lidocaine strongly inhibits cytokine production in response to both stimuli, demonstrating that lidocaine can attenuate both the innate and adaptive immune response at physiologically relevant doses. These preliminary data directly demonstrate the immunomodulatory effects of lidocaine on human leukocytes.

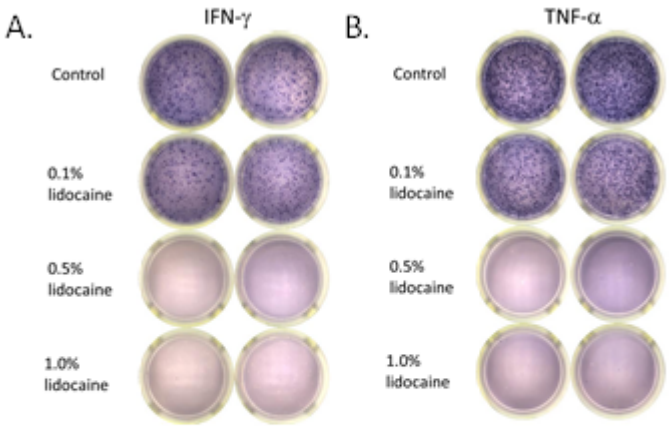

Figure 5. Lidocaine attenuates the innate and adaptive immune response. Human peripheral blood mononuclear cells were isolated by centrifugation over a Ficol gradient; equal number of cells were incubated in the presence of either anti-CD3/anti-CD28 antibody (A, left panel) or LPS (B, right panel) in the presence of increasing doses of lidocaine as indicated. TNF-alpha or IFN-gamma production was measured by ELISPOT assay; cells producing cytokine stain purple. Lidocaine strongly inhibited production of both cytokines in a dose-dependent fashion

C Study Objectives

C1 Primary Aims

Specific Aim 1:

a. To determine the effect of systemic lidocaine on postoperative opioid consumption following posterior spinal fusion surgery for AIS.

Specific Aim 2: Determine the effect of lidocaine infusion on the immuno-inflammatory response following posterior spinal fusion for AIS.

a. Determine changes in leukocyte frequencies and phenotype during and following surgery by flow cytometric immunophenotyping.
b. Assess systemic cytokine responses during and following surgery with and without IV lidocaine treatment.
c. Define surgery- and lidocaine-induced functional changes in immune cell populations by mass cytometry.

C2 Secondary Aims

To determine the effectiveness of systemic lidocaine to improve recovery after posterior spinal fusion for AIS. We hypothesize that patients receiving intravenous lidocaine will experience faster recovery from surgery. To test this hypothesis PROMIS-Computer Adaptive Tests (CAT) for Mobility (M) and Pain Interference (PI) will be compared between groups at enrollment, 6 weeks, 3 months, 6 months, and 12 months after surgery. The Scoliosis Research Society 22 (SRS-22) will also be completed at these time points.

D Investigational Agent

D1 Clinical Data to Date

Lidocaine hydrochloride (2-Diethylamino-2', 6'-acetoxylidide monohydrochloride) is an amide-type, short-acting local anesthetic and delivered as an aqueous solution for intravenous administration. It has a half-life of 1.5-2 hours. A traditional method of administration is via epidural delivery. Epidural lidocaine is effective and this effect is due, in part, to systemic absorption. Systemic (intravenous) administration of lidocaine is a Food and Drug Administration approved method of delivery. Low plasma levels are needed for effective use, 0.5µg/mL to 5.0µg/mL. Given this low concentration required and the short half-life, continuous infusion of lidocaine is thought to be generally safe with low risk of complication.

The low plasma levels have not been associated with hemodynamic instability nor have they been associated with changes in cardiac contractility. No interactions with the autonomic nervous system have been reported and there are no known effects on sinoatrial conduction. Lidocaine is metabolized by the liver, with less than 10% excreted in urine. Complications are rare. Despite concerns for arrhythmias, intravenous lidocaine has been used in cardiothoracic

surgery without increased rates of cardiac complications. Give this volume of evidence, we feel that intravenous lidocaine in the setting of AIS surgery is safe.

D2 Dose Rationale and Risk/Benefits

There are no prior studies investigating the use of intravenous lidocaine for the management of pain associated with adolescent idiopathic scoliosis surgery. As such, the dosage chosen comes from prior work in abdominal surgery and elective spine surgery18,19,22. These studies have shown lidocaine to be effective in improving pain scores, reducing opioid consumption, and improving patient reported outcomes measures. Lidocaine will be given at the induction of anesthesia until 24 hours after arrival to the Post-Anesthesia Care Unit (PACU) or Pediatric Intensive Care Unit (PICU).

A research pharmacist not involved in the care of the patient will deliver lidocaine, 8mg/mL, in D5W (Baxter International, Deerfield, IL, USA), or D5W (Baxter International) to the operating room for continuous infusion. A separate bag containing 1mg/kg of lidocaine in D5W, or an identical volume of plain D5W, will be delivered for bolus delivery. All solutions will be packaged identically, to avoid accidental unblinding. The study pharmacy will report both loading bolus volume and volume/hr rate for the infusion in the electronic medical record. The total volume of study drug/placebo administered will be recorded.

E Study Design

E1 Overview or Design Summary

Anesthesia, other than the lidocaine, will be given as standard of care per physician discretion

Study Drug: After a 1 mg/kg lidocaine bolus with induction, a lidocaine 1 mg/kg (IBW)/hr IV infusion with maximum dose of 200 mg/hr or D5W (placebo) at equal volume rate of administration will begin prior to skin incision and continue intraoperatively for duration of the case. Study drug will be discontinued upon 24 hours of stay in PICU or PACU postoperatively. Study drug will be dosed according to ideal body weight (IBW). Patient height, weight, age, and gender will be delivered to the study pharmacy prior to the day of surgery for calculation of IBW and dosing parameters.

E2 Subject Selection and Withdrawal

Study participants will be AIS patients recruited from Orthopaedic Spine clinics at Center of Advance Medicine Barnes Jewish and St. Louis Children's hospitals. Given the single disease investigated, AIS, we anticipate that our results will be generalizable to AIS patients at other institutions. We will enroll 50 patients, 25 per group, over two years. Approximately 60 AIS surgeries are performed per year at our institution.

2.a Inclusion Criteria

1. Adolescent idiopathic scoliosis indicated for posterior spinal fusion.
2. Ages between 12 and <18 years of age.
3. Parent/Guardian capable of providing informed consent for study participation.

2.a Exclusion Criteria

1. Age < 12 or > 17.9 years old.

2. Unable to obtain consent for the surgical intervention or study, or if mental capacity prohibits the ability to provide consent and complete patient-reported outcomes tools.
3. Diagnosis of sepsis or infection
4. Diagnosis of primary or metastatic malignancy.
5. Participation in another clinical trial.
6. Past or current diagnoses of a cardiac arrhythmia or first/second degree heart block.
7. Past or current seizure disorders.
8. Known allergy to bupivacaine.
9. Significant liver disease
10. Significant kidney disease
11. Known pregnancy
12. Known allergy to lidocaine and/or benzocaine
13. Planned anterior approaches for treatment of scoliosis deformity.
14. Limited English proficiency (e.g. unable to obtain informed consent for surgery without a translator)
15. Ward of the State children

2.b Subject Recruitment Plans and Consent Process

Description of Recruitment Process

1. Subject selection will be equitable. No patient will be included or excluded on the basis of gender, race, religion, national origin, or sexual orientation. Refusal to participate in the study will not affect the patient's access to care or surgical priority.
2. The research coordinator will identify all patients with AIS in the orthopedic clinics. An interview will determine study eligibility.
3. Subjects will not be compensated for their participation. There will be no advertisement material. All follow-up care is according to standard of care, with no non-standard tests, imaging, or follow-up appointments.

2.c Randomization Method and Blinding

Patients consenting to randomization will be randomized 1:1 to the control or study group. A permuted randomized block approach1 with blocks of size 4, 6 and 8. Given the relatively large number of patients to be enrolled, no stratification will be performed. After 30 patients are enrolled, an interim analysis, without unblinding, of baseline covariates will be performed to ensure equal distribution between groups. If distribution is uneven for covariates concerning for confounding, then stratification by these covariates will be employed to ensure equal distribution with randomization.

Patient loss to follow-up can affect the randomization balance and quality. Aims 1a and 2 are in-hospital studies and outcome data will be collected during the hospital stay. Loss-to-followup is not expected during the hospital stay. Aims 1b and 3 may be affected by loss-to-followup. All efforts will be made to collect follow-up data. A scheduled spine clinic visit is the preferred method of data collection. If the patient will not attend clinic, then they will be contacted by mail, email, and/or phone. Surveys may be sent electronically for completion. At enrollment, the contact information for two family members not living with the patient will be obtained. These people will be contacted should contact with the patient be lost. Registered mail will be sent to the last known address, with a self-addressed, stamped return envelope to collect outcomes data. Administration of PROMIS-CAT and SRS are valid by telephone and email.47

2.d Risks and Benefits

E3 Study Drug

3.a Description

Lidocaine hydrochloride (2-Diethylamino-2', 6'-acetoxylidide monohydrochloride) is an amide-type, short-acting local anesthetic and delivered as an aqueous solution for intravenous administration. It has a half-life of 1.5-2 hours. A traditional method of administration is via epidural delivery. Epidural lidocaine is effective and this effect is due, in part, to systemic absorption. Systemic (intravenous) administration of lidocaine is a Food and Drug Administration approved method of delivery. Low plasma levels are needed for effective use, 0.5μg/mL to 5.0μg/mL. Given this low concentration required and the short half-life, continuous infusion of lidocaine is thought to be generally safe with low risk of complication.

The low plasma levels have not been associated with hemodynamic instability nor have they been associated with changes in cardiac contractility. No interactions with the autonomic nervous system have been reported and there are no known effects on sinoatrial conduction. Lidocaine is metabolized by the liver, with less than 10% excreted in urine. Complications are rare. Despite concerns for arrhythmias, intravenous lidocaine has been used in cardiothoracic surgery without increased rates of cardiac complications. Give this volume of evidence, we feel that intravenous lidocaine in the setting of AIS surgery is safe.

3.b Treatment Regimen

After a 1mg/kg IBW lidocaine bolus with induction, a lidocaine 1 mg/kg/hr (IBW) IV infusion with maximum dose of 200 mg/hr or D5W (placebo) at equal volume rate of administration will begin prior to skin incision and continue intraoperatively for duration of the case. Study drug will be discontinued upon 24 hours of stay in either PACU or PICU postoperatively.

Method for Assigning Subjects to Treatment Groups

Patients consenting to randomization will be randomized 1:1 to the control vs study groups. A permuted randomized block approach1 with blocks of size 4, 6 and 8. Given the relatively large number of patients to be enrolled, no stratification will be performed. After 30 patients are enrolled, an interim analysis, without unblinding, of baseline covariates will be performed to ensure equal distribution between groups. If distribution is uneven for covariates concerning for confounding, then stratification by these covariates will be employed to ensure equal distribution with randomization.

3.c Blinding of Study Drug

This is a Phase IV, randomized, triple-blind, placebo-controlled trial with two study groups: postoperative standard of care with opioid patient controlled analgesia (PCA) and IV lidocaine infusion versus postoperative standard of care plus normal saline placebo. Block randomization into one of the two groups will be based on a random table generated using an R-program. Group 1 (Study) will receive intravenous lidocaine during and after posterior spinal fusion for AIS. Group 2 (Control) will receive saline placebo during and after surgery.

F Study Procedures

F1 Screening for Eligibility

The research coordinator will screen all new patients for enrollment qualifications according to inclusion and exclusion criteria. Eligible patients will be approached by the study coordinator to introduce the study and obtain consent prior to surgery.
We will screen that the following tests to confirm study eligibility:

1. Negative result of pregnancy test by urine hCG
2. Normal CMP tests to assess liver and kidney function

F2 Schedule of Measurements

The research coordinator will screen all new patients with Adolescnet Idiopathic Scoliosis (AIS) for enrollment qualifications according to inclusion and exclusion criteria. Eligible patients will be approached by the study coordinator to introduce the study and obtain consent prior to surgery.

Patients consenting to randomization will be randomized 1:1 to the standard of care or study intervention arms. A permuted randomized block approach1 with blocks of size 4, 6 and 8. Group 1 (Study) will receive intravenous lidocaine during and after posterior spinal fusion for AIS. Group 2 (Control) will receive saline placebo during and after surgery.

After a 1mg/kg lidocaine bolus with induction, a lidocaine 1 mg/kg (IBW)/hr IV infusion with maximum dose of 200 mg/hr or D5W (placebo) at equal volume rate of administration will begin prior to skin incision and continue intraoperatively for duration of the case. Study drug will be discontinued upon 24 hours of stay in either PACU or PICU postoperatively.

Both the leukocyte frequencies and leukocyte cell surface phenotype will be measured by flow cytometry. This approach will allow hypothesis-based assessment of pathways demonstrated to contribute to the postoperative immune phenotype, while also providing data for a discovery-driven analysis to define novel mechanisms. Patients will be identified based on inclusion/exclusion criteria as described above. Blood samples with following time points: immediately preoperatively, 4 hours and 8 hours post incision, day 1 post surgery, and day 2-3 post surgery. All blood samples will be collected into 6 ml EDTA-containing vacutainers and three aliquots prepared for fixation by mixing 1.25 ml blood with 1.75 ml Proteomic Stabilizer (Smart Tube, Inc, San Carlos, CA). Following fixation, samples will be stored at -80 °C until flow cytometric analysis. For each patient and time point, one aliquot of the fixed and frozen blood will be used for immunophenotyping. The remaining aliquots will be used for mass cytometry as described and preserved as a "biobank" for potential future studies.

We will analyze signaling events in all major leukocyte subsets and compare phospho-signal median intensities between the different time points and treatment groups to define any immune modulatory effects of lidocaine during surgery.

The primary outcome measure is total, in-hospital opioid consumption following surgery for AIS Opioid consumption will be measured in morphine-equivalent dosage (MED), to allow for the use of different opioid medications (e.g. fentanyl, hydromorphone, oxycodone) over the course of care.

Secondary outcome measures to assess recovery are the Patient Reported Outcomes Measurement Information System (PROMIS) Mobility (M) and Pain Interference (PI) domains. PROMIS is a general measure of health administered over particular health domains. The SRS-22 will be used in assessing the quality of life in AIS patients. The SRS-22r includes 22 items distributed among five different factors (pain, self-

image/appearance, function/activity, mental health, and satisfaction with management). Each component includes five items, except for the "satisfaction with management", which only contains two items. Secondary measures to assess the anti-inflammatory effect of lidocaine will be serum levels of IL-10, IL-4 and IL-12.

The anticipated outcome is decreased in-hospital opioid consumption for those patients treated with intravenous lidocaine. Other anticipated outcomes are improved recovery as measured by PROMIS-M and PROMIS-PI measures at 6 weeks, 3 months, 6 months, and 12 months after surgery. We anticipate that the anti-inflammatory effect of lidocaine will reflect a smaller postoperative inflammatory response as measured by IL-10, IL-4, and IL-12.

F3 Safety and Adverse Events

Serum lidocaine levels will be drawn at 12 hours after incision and reviewed by an individual independent from the study team. Lidocaine toxicity will result in immediate cessation of study drug, unblinding, and reporting to the Medical Monitor and IRB. If intraoperative surgical, medical, or anesthetic complications occur, including cardiac arrhythmia, the study medication will be stopped and the patient withdrawn from the study. The patient will be analyzed in an intent-to-treat analysis, though they will be excluded from as-treated analyses. After surgery, patients will be seen and examined twice daily with attention to postoperative complications. As the study-drug will have completed infusion, all complications will be recorded though patients will remain enrolled in the study and analyzed per-protocol. All adverse events will be recorded up to 12 weeks after surgery. These will be captured via interview at the visit or via telephone if a clinic visit is not possible. Readmission for any reason will be recoded and details of this hospitalization will be recorded. Any reason reasonably related to the research protocol will be reported to the Medical Monitor and the IRB.

We believe there are minimal risks associated with participation in this clinical trial and with the study intervention (intravenous lidocaine). The most concerning serious adverse event that might be attributed to systemic lidocaine administration is cardiac arrhythmia/arrest. Therapeutic serum concentrations are far lower than toxic levels and we believe the risk of serious adverse events to be low. The intervention will not add time to the surgical intervention and, thus, does not pose additional risk from this perspective. All patients will receive standard of care treatment before, during, and after surgery and the study intervention will pose no risk to this.

Safety measures to minimize/eliminate risks to human subjects and study personnel include the use of the Medical Monitor and immediate reporting of any adverse (expected or unexpected) to the project PI and project manager. If any intraoperative complications occur, such as but not limited to cardiac arrest or seizure, the study medication will not be administered and the patient will be excluded from the study. However, if one of these problems occurs after the application of the study medication the patient will be unblinded. The patient will be followed for the occurrence of further adverse events or complications.

For any serious adverse event, the Medical Monitor at the enrollment site will perform a root cause analysis and will notify the project PI in the study medication is believed to be a potential cause of the adverse event. The Monitor may recommend stopping the study. Any serious adverse event will be reported to the PI and the IRB within 10 working days.

F4 Study Outcome Measurements and Ascertainment

The primary outcome measure is total, in-hospital opioid consumption following surgery for thoracolumbar trauma. Opioid consumption will be measured in morphine-equivalent dosage (MED), to allow for the use of different opioid medications (e.g. fentanyl, hydromorphone, oxycodone) over the course of care.

Secondary outcome measures to assess recovery are the Patient Reported Outcomes Measurement Information System (PROMIS) Mobility (M) and Pain Interference (PI) domains. PROMIS is a general measure of health administered over particular health domains. This instrument has been tested extensively and is reliable and precise.45 Scores range from 0-100 and are normalized so that a score of 50 is the population mean, with 10 points representing a standard deviation is 10 points. For the Mobility domain larger scores represent more function; for the PI domain larger scores represent more pain. The instrument administered via computer-adaptive testing (CAT) to minimize question burden. The Scoliosis Research Society 22 (SRS-22) will be used in assessing the quality of life in AIS patients. The SRS-22r includes 22 items distributed among five different factors (pain, self-image/appearance, function/activity, mental health, and satisfaction with management). Each component includes five items, except for the “satisfaction with management”, which only contains two items. Secondary measures to assess the anti-inflammatory effect of lidocaine will be serum levels of IL-10, IL-4 and IL-12.

The anticipated outcome is decreased in-hospital opioid consumption for those patients treated with intravenous lidocaine. Other anticipated outcomes are decreased opioid consumption at three-months after surgery, with improved recovery as measured by PROMIS-M and PROMIS-PI measures at 6 weeks, 3 months, 6 months, and 12 months after surgery. We anticipate that the anti-inflammatory effect of lidocaine will reflect a smaller postoperative inflammatory response as measured by IL-10, IL-4, and IL-12.

G Statistical Plan

G1 Sample Size Determination and Power

The target sample size of 50 patients, 25 per group, is based upon a two-tail test at the 0.05 level of significance, with 80% power to detect an effect size of d=0.8. Prior data from our institution has shown an average postoperative morphine-equivalent consumption of 149 mg with a standard deviation of 37 mg. The proposed effect size is equivalent to approximately a 20% reduction in postoperative morphine-equivalent opioid consumption. The primary outcome measure is the inpatient measure of postoperative opioid consumption. As such, loss-to-followup is not possible, though 25 per group accounts for 10% loss due to treatment noncompliance which is unlikely.

G2 Analysis Plan

General Analysis Strategy: Our approach to data analysis includes three consecutive stages. Most analyses will be performed using SAS software, which

has a wide range of statistical routines and offers great flexibility in data manipulation.

Descriptive Analysis and Data Reduction:

Quality control will be ongoing throughout the project, as part of data management procedures that monitor data quality at each site and overall. However, prior to analysis, the data will be fully examined to confirm data quality and make final corrections. After addressing data quality, each variable will be summarized via marginal distributions as well as by relevant separate and combined study factors [(e.g., treatment, crossover status, patient demographics (age, gender, race)], and clinical factors (e.g., curve type, curve magnitude, etc.)]. Distribution summaries for continuous variables will include means, medians, interquartile ranges, minima and maxima and standard deviations; those for categorical variables will include proportions and 95% confidence intervals. The amount and patterns of missing data will be examined early and regularly during data collection to detect possible problems with instrument completion. Prior to analysis the amount and patterns of missing data are also important to see whether adjustments will be needed at the Inferential Analysis Stage. Those who complete data collection will be compared with those who drop out before the end of follow-up to identify potential selection biases, causing the study pool to differ from the target population. Transformations will be employed as needed to produce variables that conform to the distributional assumptions underlying the regression models that will be used.

After 10 patients have completed the study, immunophenotyping with flow and mass cytometry will be performed to confirm appropriate data are collected with the chosen panels.

H Data Handling and Record Keeping

H1 Confidentiality and Security

The primary data will come from the information contained in the patient's medical records related to their illness. In order to extract the relevant information, study staff will review the data from their records and record it into a secure database. Only the minimum necessary data will be looked at and recorded for the study. Records will be stored behind secured firewalls maintained by Washington University and is compliant with FDA Code of Federal Regulations Title 2, Volume 1, CITE: 21CFR11 and include the use of: (1) uniqueness of individual log in with restricted access via a strong username and password policy, (2) ability for users to periodically modify identification codes or passwords, (3) secure, computer-generated time-stamped audit trails, (4) 128-bit Secure Socket Layer (SSL) encryption for transactional safeguarding (5) electronic de-authorization of lost, stolen, or missing user authorization codes. Only study staff will have password access. There will be no patient identifiers or information that could link the patient to any published material.

Any paper records will be maintained in locked file cabinets in code-accessed suites.

H2 Case Report Forms and Source Documents

Using the assigned patient ID code, the WU coordinator will enter all eCRF patient data into the study REDCap secure database. The eCRF will be completed by the principal investigator or his designee. If any entry on a source document requires a change, a single line will be drawn throughout the incorrect entry, and the correction will be entered in ink, initialed and dated. Whiteout, erasures, or obliteration on source data are not permitted. The primary data will come from the information contained in the patient's medical records related to their illness. In order to extract the relevant information, study staff will review the data from their records and record it into a secure database. Only the minimum necessary data will be looked at and recorded for the study.

H3 Records Retention

We will retain identifiers indefinitely on patients who consent to participate in this study. This will be done to protect the integrity of our study and for potential use in future, IRB-approved research.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

After the first 15 patients are enrolled, a group consisting of the Principal Investigator and an unengaged physician will review the AE/SAE data. The data will be reviewed blinded. If intraoperative surgical, medical, or anesthetic complications occur, including cardiac arrhythmia, the study medication will be stopped and the patient withdrawn from the study. The patient will be analyzed in an intent-to-treat analysis, though they will be excluded from as-treated analyses. After surgery, patients will be seen and examined twice daily with attention to postoperative complications. As the study-drug will have completed infusion, all complications will be recorded though patients will remain enrolled in the study and analyzed per-protocol.

Special attention will be given if adverse events occur in a higher frequency than expected given patient age and health condition. Serious adverse events, or those that are life threatening, result in death, prolonged hospitalization, readmission, cause persistent disability or require urgent intervention to prevent permanent morbidity will be monitored for up to 30 days after the drug is administered. If there appears to be an imbalance in AE/SAE, unblinding and analysis will ensue to determine if the study should continue. Early termination will occur if SAEs are linked to the treatment arm.

After 10 patients have completed the hospital phase of the study, flow and mass cytometry will be performed to ensure we are capturing cell types and signaling proteins as anticipated.

All protocol violations and SAE's will be reported to HRPO within the WU HRPO policies and procedures reporting guidelines

SAEs will be tracked through resolution.

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