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Lidocaine Infusion for the Management of Postoperative Pain and Delirium (LIMPP): protocol for a randomised control trial

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ABSTRACT

Introduction Postoperative delirium is a frequent adverse event following elective non-cardiac surgery. The occurrence of delirium increases the risk of functional impairment, placement to facilities other than home after discharge, cognitive impairment at discharge, as well as in-hospital and possibly long-term mortality. Unfortunately, there is a dearth of effective strategies to minimise the risk from modifiable risk factors, including postoperative pain control and the analgesic regimen. Use of potent opioids, currently the backbone of postoperative pain control, alters cognition and has been associated with an increased risk of postoperative delirium. Literature supports the intraoperative use of lidocaine infusions to decrease postoperative opioid requirements, however, whether the use of postoperative lidocaine infusions is associated with lower opioid requirements and subsequently a reduction in postoperative delirium has not been investigated.

Methods and analysis The Lidocaine Infusion for the Management of Postoperative Pain and Delirium trial is a randomised, double-blinded study of a postoperative 48-hour infusion of lidocaine at 1.33 mg/kg/hour versus placebo in older patients undergoing major reconstructive spinal surgery at the University of California, San Francisco. Our primary outcome is incident delirium measured daily by the Confusion Assessment Method in the first three postoperative days. Secondary outcomes include delirium severity, changes in cognition, pain scores, opioid use, incidence of opioid related side effects and functional benefits including time to discharge and improved recovery from surgery. Lidocaine safety will be assessed with daily screening questionnaires and lidocaine plasma levels.

Ethics and dissemination This study protocol has been approved by the ethics board at the University of California, San Francisco. The results of this study will be published in a peer-review journal and presented at national conferences as poster or oral presentations. Participants wishing to know the results of this study will be contacted directly on data publication.

Trial registration number NCT05010148.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We have identified a relatively homogenous population at high risk of postoperative delirium, which provides maximum opportunity to identify a meaningful intervention.
⇒ Performing a randomised clinical trial should provide the highest quality evidence for causality of a postoperative infusion of lidocaine to decrease the incidence of postoperative delirium.
⇒ A limitation is that we have not performed a dose finding study to identify the threshold at which lidocaine acts as an opioid sparing adjunct but yields minimal side effects, however, based on analgesic dosing in the literature, multiple pharmacokinetic studies and our significant institutional experience using lidocaine for postoperative pain control, we feel confident that the chosen dose is both safe and clinically effective.
⇒ An additional limitation is that we will only recruit patients who are fluent in English due to the need to conduct all cognitive and delirium measurements in English which may limit the generalisability of our results to English speaking patients.

INTRODUCTION

Postoperative delirium as a problem/pain as a contributor to delirium

Postoperative delirium is one of the most frequent adverse events following elective non-cardiac surgery in older adults and occurs in 20%–80% of postsurgical patients.[1] Delirium is considered a geriatric syndrome, presenting as acute confusion with alterations in attention and consciousness, and the occurrence of delirium increases the risk of functional and cognitive impairments requiring discharge to skilled nursing facilities, as well as increased in-hospital and possibly long-term mortality.[2 3] The pathophysiology of delirium is poorly characterised, but perioperative contributors can be divided into preoperative, intraoperative and postoperative factors. Preoperative factors include preoperative cognitive status, functional and sensory impairments, preoperative psychotropic drug use, psychopathological symptoms, institutional residence, greater comorbidity and the type of surgery.[4–6]

Intraoperative factors include significant blood transfusions, amount of blood loss and length of surgery.[7 8] Postoperative factors include higher pain scores and the analgesic regimen.[9] While non-modifiable risk factors can be minimised by careful presurgical patient selection, there is a dearth of effective strategies to minimise the risk from modifiable risk factors, which entail postoperative pain control and the analgesic regimen. Use of potent opioids, currently the backbone of postoperative pain control, alters cognition and contributes to an increased risk of postoperative delirium. Whether or not multimodal opioid sparing analgesic regimens provide protection against postoperative delirium is incompletely studied.

Lidocaine as a validated pain agent: lack of postoperative data for lidocaine

Lidocaine, an amide local anaesthetic and class-1 antiarrhythmic with sedative and anti-inflammatory properties, is increasingly used as part of a multimodal intraoperative anaesthetic adjunct in a variety of surgical procedures.[10–13] Infusions decrease postoperative opioid requirements, speed return of bowel function and may decrease the risk of chronic postsurgical pain. While there is literature that supports the use of postoperative infusions of lidocaine to decrease opioid requirements, decrease hospital length of stay and hasten return of bowel function, the data are limited in scope and quality.[14–16] Importantly, most prior studies focused on examining lidocaine's effects on opioid consumption or a limited evaluation of functional recovery, and none measure whether postoperative delirium was reduced.[15–17]

The data on postoperative lidocaine infusions and cognition are even more limited. One small study reported that the mean postoperative Mini-Mental State Examination (MMSE) scores were higher in patients who received intraoperative lidocaine infusions, however, the clinical implications for delirium are unclear since MMSE scores have practice and ceiling effects when used repeatedly during a short time frame.[18] Another study noted that patients' cognitive status was unchanged 1 year after undergoing cardiac surgery for patients that received intraoperative and postoperative lidocaine infusions. However, the effects on postoperative delirium were not investigated.[19]

Mechanism for lidocaine effect on cognition

Reduction of opioid doses may explain the potential for postoperative lidocaine infusions to improve postoperative cognitive function and/or limit the incidence and severity of delirium, however, there are other putative mechanisms whereby lidocaine may offer protection. While postoperative cognitive dysfunction and postoperative delirium may coexist, the pathophysiology for either condition is not completely understood. However, both conditions share similar risk factors, many patients with postoperative delirium develop postoperative cognitive dysfunction, and there are animal studies demonstrating possible common pathophysiologic processes, which suggests that there could be an overlap between their respective underlying physiology and/or potential therapeutic interventions.[20–23] Proposed mechanisms of postoperative cognitive dysfunction include systemic inflammation, endothelial dysfunction, cerebral hypoperfusion and microembolism.[24–26] In vitro and animal studies demonstrate that lidocaine decreases cerebral oxygen requirements and protects against hypoxemia and glucose deprivation, while others have shown that lidocaine can protect against isoflurane-induced mitochondrial dysfunction.[27–29] Multiple studies have also documented the anti-inflammatory properties of lidocaine including inhibition of neutrophil priming, inhibition of polymorphonuclear cell accumulation at sites of inflammation, decreased microvascular permeability and decreased release of inflammatory modulators (ie, leukotrienes and interleukin-1alpha).[30–32] Surgery generates a profound local inflammatory state with systemic release of diverse cytokines. Together, these data suggest that lidocaine may decrease inflammatory-induced cognitive dysfunction, and possibly the development of postoperative delirium, and protect against adverse effects from hypoxemia or hypotension.

Aim of the study/objectives

The primary outcome of this trial is to assess the effect of a postoperative intravenous infusion of lidocaine on the incidence and severity of postoperative delirium following major spinal surgery. Additionally, the effects on pain, opioid usage, opioid-related side effects and functional recovery will be investigated.

METHODS/DESIGN

This study was planned according to the updated Consolidated Standards of Reporting Trials statement, the Declaration of Helsinki and the Guideline for Good Clinical Practice issued by the International Conference on Harmonisation and the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[33 34] The study has received institutional review board approval (IRB# 20-32383).

Trial design/setting

We will perform a single-centre prospective randomised double-blinded trial of a postoperative intravenous infusion of lidocaine versus placebo on the incidence of postoperative delirium in patients undergoing major reconstructive spinal surgery at the University of California, San Francisco.

Study flow diagram

See figure 1 for a study flow diagram.

Patient recruitment

Annually, approximately 1000 patients ≥60 years of age present for elective major spinal surgery at our hospital. As described in detail previously, all surgeons will be
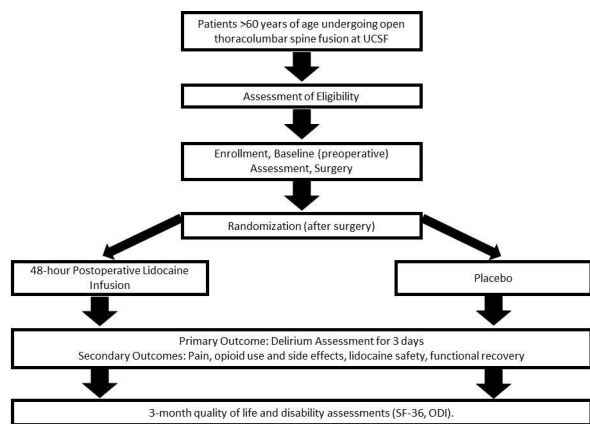
Figure 1 Study flow diagram: a flow diagram of the study procedures is shown, including screening, enrollment, randomisation, intervention and follow-up assessments. ODI, Oswestry Disability Index; SF-36, Short Form 36 Health Survey Questionnaire; UCSF, University of California San Francisco.

contacted before the start of the study to obtain their consent to allow their patients to be studied. Eligible patients will be screened from the operating room roster to determine their eligibility and patients will be contacted by phone or in person when they come for preoperative evaluation.[35 36] The recruitment will be consecutive patients meeting inclusion criteria. We began recruitment in September 2021 and anticipated its conclusion in September 2024.

Eligibility criteria for participants

The inclusion criteria will be English speaking patients aged ≥60 years staying in the hospital for a minimum of 3 days after major elective spinal surgery. Major spine surgery is defined as open posterior thoracolumbar spine fusions >2 levels of instrumentation and fusion, which allows standardisation of the level of surgical insult and postoperative analgesic requirements.

Exclusion criteria include allergy or intolerance of lidocaine, significant heart disease (second or third degree heart block without a pacemaker, left ventricular ejection fraction <30%, significant arrhythmia (Adams-stokes, Wolff-Parkinson-white syndrome), concurrent treatment with a class 1 antiarrhythmic or amiodarone), significant hepatic disease (diagnosis of cirrhosis, elevated liver function tests (aspartate aminotransferase/alanine aminotransferase/bilirubin/albumin)) or renal dysfunction (glomerular filtration rate <30 m)/min×1.73 m^2), history of uncontrolled seizures and acute porphyria. Exclusion criteria will include patients with significant preoperative opioid requirements, defined as the use of long-acting opioids (ms-contin, oxycontin, buprenorphine, fentanyl transdermal patches or methadone) or the use of greater than 60 mg of oral morphine equivalents a day (to be assessed during phone interview). Exclusion criteria will also include severe cognitive impairment (reported by proxy or a score of >5 on the Short Portable Mental Status Questionnaire), or self-reported, or proxy-reported

physical impairment preventing the subject from consenting or answering questions, and evidence of preoperative delirium (Confusion Assessment Method (CAM) assessment).

Randomisation

Patients will be randomised using block randomisation by a random number generator into either placebo or treatment groups by the research pharmacist. The randomisation scheme will be blinded to the researchers and patients.

Blinding

Study medication and placebo will be prepared by the hospital pharmacy. Both lidocaine (formulated as 0.8% lidocaine in 5% dextrose in water) and placebo (5% dextrose in water) are available in pre-made bags that are identical except for the manufacturers labelling. Blinding of the medications will be done by the research pharmacist and accomplished by wrapping the bags in an opaque sticker. The patients, all personnel involved in patient care or treatment, the data collectors, statisticians, and investigators involved in the data analysis will be blind to the treatment allocation.

Perioperative management

The preoperative and intraoperative anaesthetic regimen will be standardised. Preoperative medications will include acetaminophen 1000 mg orally and gabapentin 600 mg orally in the preoperative area.

All patients will receive a general anaesthetic consisting of 50% oxygen and a mostly intravenous anaesthetic to facilitate intraoperative neuromonitoring. The induction regimen will be at the anaesthesiologist's preference, although typically it will consist of a bolus of intravenous propofol. The intraoperative anaesthetic will consist of infusions of propofol (60–150 mcg/kg/min), lidocaine (1 mg/kg bolus, then 1.5 mg/kg/hour infusion), magnesium (30 mg/kg bolus, then 6 mg/kg/hour infusion), fentanyl (1 mcg/kg bolus, then 1 mcg/kg/hour infusion, prn boluses) and 0.3 minimum alveolar concentration of sevoflurane. Anaesthesiologists will be requested to maintain the patient's arterial blood pressure to within 20% of their preoperative baseline using vasoactive agents. Patients will receive mechanical ventilation to maintain normocarbia. Intraoperative warming devices will be used to keep body temperature between 36°C and 37°C. Oxygen saturation will be maintained >95%. Muscle relaxants will be used during tracheal intubation and only as clinically indicated at other time periods. All patients will be continuously monitored before the induction of anaesthesia and during surgery with SEDline Brain Function Monitor (Masimo, Irvine, California, USA), a standard monitor at our institution. Anaesthesiologists will be asked to minimise electroencephalogram (EEG) burst suppression by adjusting the doses of anaesthetic drugs since prior studies have suggested a relationship between burst suppression and postoperative delirium.[37 38] Depth

of anaesthesia will be assessed using a SedLine (Massimo Irvine, California, USA) processed EEG monitor. This generates a number of different outputs including the raw EEG waveform, a Patients State Index, and a density spectral array that displays spectrograms of the EEG. Anaesthesiologists will use the combined information from these outputs to adjust the anaesthetic and minimise burst suppression.

Postoperative analgesic regimen

The postoperative analgesic regimen will be standardised and overseen by the institution's acute pain service. Scheduled medications will include acetaminophen 1000 mg PO every 8 hours, and gabapentin 300 mg PO every 8 hours Patients' preoperative non-opioid analgesic regimen will also be continued including antidepressants and muscle relaxants and so on. As needed medications will include oxycodone 5–15 mg orally every 3 hours as needed for moderate pain and hydromorphone 0.4–1 mg intravenously every 3 hours as needed for severe pain. Other opioid sparing adjuncts, such as a ketamine infusion, will not be used unless patients are in uncontrolled pain and the clinical situation warrants an escalation of care.

Intervention and control

Postoperatively, on arrival to either the post anaesthetic care unit or the intensive care unit, patients will be randomised to receive either placebo or the lidocaine infusion. The lidocaine infusion will be run at 1.33 mg/kg/hour for 48 hours. A 2-day infusion was chosen because the level of pain after this period of time is significantly less. Dosing weight will be an adjusted body weight using the formula Adjusted Body Weight=Ideal Body Weight+1/3*(Actual Body Weight–Ideal Body Weight). We will use the ideal body weight if patient's actual body weight is less than the ideal body weight. This dose was chosen based on prior studies showing a significant reduction in opioid usage, but with no significant incidence of lidocaine toxicity.

Baseline assessments

All assessments are performed by trained research assistants. Patients that consent to participate in the study will receive a baseline delirium (CAM) and cognitive status evaluation. Preoperative cognitive status will be measured by the Telephone Interview for Cognitive Status (TICS) test which was adapted from the MMSE for use either in person or over the telephone.[39] To minimise patient test burden, we used the nine-item word list test in lieu of the word naming in the TICS test during the preoperative testing. The following cognitive tests will be administered: the Word List Learning, the Digit Symbol Test and the Controlled Verbal Fluency Test. Patients will also complete the Short Form 36 Health Survey Questionnaire (SF-36) and Oswestry Disability Index (ODI) questionnaires preoperatively, which are routinely administered in our surgical clinic.

Primary outcome

Our primary outcome is the incidence of postoperative delirium in the first 3 days after surgery. Delirium is assessed during both the preoperative and three postoperative interviews. At approximately 24 hours after surgery, the patient will be rated on the Richmond Agitation and Sedation Scale (RASS).[40] If a patient is too sedated to be interviewed (RASS score of −4 or −5), delirium status will be considered unevaluable. The presence of delirium will be measured using the CAM, a delirium screening instrument. CAM assessments will be performed once daily using a structured interview. The CAM assessment was developed as a screening instrument based on operationalisation of Diagnostic and Statistical Manual of Mental Disorders III-R criteria for use by non-psychiatric clinicians in high-risk settings. Based on a structured interview, the CAM algorithm consists of four clinical criteria: (1) acute onset and fluctuating course, (2) inattention, (3) disorganised thinking and (4) altered level of consciousness. For delirium to be recorded, both the first and second criteria must be present, plus either criterion three or four. CAM has a sensitivity of 94%–100% and specificity of 90%–95%, with high inter-observer reliability and convergent agreement with four other mental status tests. All cases of delirium will be validated by a second investigator.

Secondary outcomes

Secondary outcomes of interest include delirium severity, changes in cognition, pain scores, opioid usage, opioid-related side effects and functional recovery. The severity of delirium will be measured using the Memorial Delirium Assessment Scale, an instrument that contains 10 items using information from the MMSE and structured interview to rate delirium severity.[41] Postoperative intravenous opioid use will be measured daily during the infusion of the study drug, at 72 hours, and total for the hospitalisation. We will convert all opioids to morphine equivalents as follows: hydromorphone and fentanyl doses will be converted to morphine equivalents using the conversion formula: 1.5 mg of hydromorphone equals 10 mg of morphine equivalents, 0.1 mg of fentanyl equals 10 mg of morphine equivalents.[42–44] See table 1 for details regarding the specific outcomes and associated tests.

Sample size

There is little direct evidence about the effect of a lidocaine infusion on the incidence of postoperative delirium. There are data on other opioid sparing adjuncts that show a reduction of approximately 50% in the incidence of postoperative delirium.[45] Based on our prior work showing an incidence of postoperative delirium of 28% in elderly spine surgery patients, a sample size of 132 patient/group (264 in total) will provide an 80% power to detect a significant effect on postoperative delirium (with 2-sided alpha error set at 0.05).[9] Because we do not randomise patients until they are in surgery, we assume a

Table 1 Primary and secondary outcomes

Domain	Outcome	Definition
Delirium	Incident delirium (primary outcome)	CAM (+) assessment
	Delirium severity	MDAS Score
	Number of days of delirium	Number of CAM (+) days
Cognition	Change in MMSE/TICS	
	Change in other test scores	Digit symbol substitution test, timed verbal fluency test, word list learning task
Pain/opioid consumption	Post-Anaesthesia Care Unit (PACU)	Last pain score in PACU Total morphine equivalents
	During infusion	Daily pain scores (rest/movement) Total morphine equivalents during infusion, at 72 hours
	Analgesic satisfaction	Daily assessment during hospitalisation
Opioid-related side effects	Respiratory depression	RR <8, SPO_2 <95%, naloxone administration
	Sedation	Comparison of the Passero Opioid Sedation Scores or RASS for ICU patients
	Nausea/vomiting	Daily review of chart and MAR for anti-emetic administration, daily interview of patient for symptoms
Lidocaine safety	Local anaesthetic toxicity	Daily questionnaire for symptoms of toxicity including perioral numbness, metallic taste, dizziness, tinnitus, nausea/vomiting, decreased hearing, slurred speech and tremors.
Functional recovery	PT/OT	Ability to participate with PT (daily note reviews)
	Time to discharge	Days in hospital following surgery
	Disability: ODI	Change in ODI score from preop to 3 months postop
	Quality of life: SF-36	Change in SF-36 score from preo to 3 months postop

CAM, Confusion Assessment Method; ICU, Intensive Care Unit; MAR, Medications Administered Record; MDAS, Memorial Delirium Assessment Scale; MMSE, Mini-Mental State Examination; ODI, Oswestry Disability Index; OT, Occupational Therapy; PT, Physical Therapy; RASS, Richmond Agitation and Sedation Scale; RR, Respiratory Rate; SF-36, Short Form 36 Health Survey Questionnaire; SpO2, Oxygen Saturation; TICS, Telephone Interview for Cognitive Status.

very low dropout rate of 5% and so we need to enrol 139 patients per group (or 278 total).

Statistical analysis

Data are entered using an electronic tablet directly into an online database application called Research Electronic Data Capture (REDCap). All REDCap databases are password protected and accessible only to authorised users. Data will be exported from REDCap to a statistical package for data analysis. Data will first be evaluated for errors and patterns of missing data.

We will use descriptive statistics to summarise the characteristics of the study population by treatment groups. Patients will be compared by group with respect to baseline characteristics including age, gender, race, comorbidities and medications. Intraoperative data will be compared including length of surgery, intravenous fluids administered, estimated blood loss, blood transfusion, intraoperative medications administered (including total opioids) and depth of anaesthesia (assessed using SEDline brain function monitor) among other variables.

We will use an intention to treat paradigm in assessing the effect of the intervention on the outcomes of interest.

We will compare the primary outcome of incident postoperative delirium using the χ^2 test. Differences in secondary outcomes will be assessed using parametric and non-parametric tests where appropriate, and a p value of <0.05 will be considered statistically significant.

The Student's t-test or Mann-Whitney non-parametric test for continuous outcomes will be used to evaluate continuous secondary outcomes including the severity of delirium in CAM positive patient, changes in cognition, pain scores, opioid consumption, time to discharge from the hospital and the change from baseline scores on the SF-36 and ODI. χ^2 test or the Fisher exact test will be used to assess the incidence of opioid related side effects, the incidence of lidocaine-associated toxicity symptoms, the proportion of patients that develop plasma lidocaine levels greater than the toxic threshold and the proportion of patients able to participate with physical and occupational therapy on each postoperative day.

Data monitoring and safety

A data and safety monitoring board has been established to monitor participant safety, data quality and to evaluate the progress of the study. The Data Safety Monitoring Board (DSMB) includes three independent experts who are not directly involved in the study. The DSMB is charged with performance, safety and treatment oversight. Performance parameters include subject recruitment, retention, follow-up, flow of data forms, protocol adherence and quality of data. Safety parameters include

the magnitude and frequency of adverse events including any plasma lidocaine levels in the toxic range. Treatment parameters include efficacy metrics such as pain scores and amount of opioid used. The DSMB will meet regularly based on the progression of the study, but we do not plan an interim analysis. However, the DSMB will regularly examine accumulating data and make recommendations regarding the continuation, modification or termination of the trial. All adverse events that are related to the trial (as determined by the Principal Investigator) and protocol violations will be reported to the DSMB and the IRB in a timely manner.

Based on the accumulated literature, the risks associated with this study are anticipated to be low. The potential risks include complications from intravenous administration of a medication, including an intravenous infiltration, less effective analgesic management in the treatment arm and side-effects of systemic administration of a local anaesthetic. To minimise these risks, patients will be assessed by nursing staff every 4 hours to evaluate intravenous patency, administer analgesics as requested and assess for signs of toxicity. Additionally, our acute pain service will see patients at least once per day for similar assessments.

In the event of concern for local anaesthetic systemic toxicity from a high lidocaine plasma level, for example, seizure or cardiac arrest (eg, inadvertent overdose), the study can be immediately unblinded by removing the opaque sticker covering the study drug.

We anticipate high compliance and low drop out since we will not randomise patients until after they have entered the operating room and are under anaesthesia. Criteria for discontinuing the study intervention include patient request and/or unwillingness to continue with the study, a request from the treating physician or a severe adverse event that could be related to the study drug (seizure or cardiac arrest).

The University of California will provide necessary medical treatment in the event of adverse events, however, the costs of the treatment may be billed to the patient's insurer just like any other medical costs, or covered by the University of California, depending on several factors. The University or study does not normally provide any other form of compensation for injury.

Ethics and dissemination

This protocol, questionnaires, and patient consent forms have been reviewed and approved by the UCSF Human Research Protection Program IRB prior to enrolling any patients in this trial. All the patients will be informed about the aims and procedures of the trial, possible adverse events and possible hazards to which they may be exposed. The results of this study will be published in a peer-review journal and presented at national conferences as poster or oral presentations. Participants wishing to know the results of this study will be contacted directly on data publication.

Confidentiality

Only research staff have access to patient health information. Electronic data are stored on password-protected department networked drives and are only accessible on hospital servers. REDCap is being used at the study database. A study ID is used to identify all participants.

Dissemination

Results of this study will be published in peer-reviewed journals. Study data may be made available on request to the principal investigators with an appropriate research and data-protection plan agreed on.

Patient and public involvement

No patient involved.

DISCUSSION

Reconstructive spinal surgeries continue to increase in frequency and complexity, particularly in the elderly. Older patients, especially those undergoing complicated reconstructive spinal surgeries are at significant risk of postoperative delirium. While the problem is well documented and the risk factors are well defined, there are few effective therapies for its prevention and or treatment once it has developed. Our study will be one of the few interventional studies to investigate the association between pain, postoperative delirium, and other postoperative opioid-related adverse effects. Our approach uses a geriatric perspective which recognises baseline vulnerabilities that place older patients at risk for poor postoperative cognitive outcomes combined with a disease-oriented focus to identify and minimise the effects of precipitating factors of postoperative delirium, including pain and opioid use.[2 46] In this model, we hypothesise that the proposed intervention reduces pain and opioid use, both of which are known precipitants of delirium. Additionally, although lidocaine has been used intraoperatively for years, with prior data supporting its efficacy for improved analgesic and functional outcomes, the evidence supporting its postoperative use is scant. Our study will be one of the first to standardise the intraoperative anaesthetic and separately investigate the potential postoperative benefits of a continuous postoperative lidocaine infusion. Because lidocaine is an approved anaesthetic and has many generic versions, the use of postoperative infusions of lidocaine will potentially be a very economical means to provide effective postoperative analgesia to patients who have undergone complex spinal surgeries. Lastly, proving our hypothesis that postoperative lidocaine is associated with a reduction in postoperative delirium will provide insight into the pathophysiology of postoperative delirium, particularly as to how delirium is associated with pain and opioids.

In a comprehensive systematic review of postoperative cognitive changes after non-cardiac surgery, the authors

concluded that after a systematic review of previous studies, 'one area that requires further examination is the possibility that symptoms such as pain and/or some type of postoperative medication may lead to a poorer neuro-psychological performance'.[47] Our proposed research is therefore extremely timely and critical to further our understanding of the pathophysiology of this condition. From the geriatric perspective, preventing delirium may have a direct impact on preventing functional dependence (disability), as delirium is a clear precipitant of disability, and disability is also a geriatric syndrome. Therefore, in addition to its value in preventing delirium, better pain management may have direct effects on preventing or limiting functional dependence.

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