242150

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Application

Residency Grant Project 2018-2019

Section I

Project Leader: Vikram Mehta		Credentials: ☒ MD, ☐ DO, ____
☒ Male ☐ Female	Date of birth: 12/21/1987	NC medical license no.: 217754

Preferred mailing address (☐ business or ☒ home) DUMC Box 3271, Durham, NC 27710	City, State, Zip Durham, NC 27710	Business Telephone 919-684-3053
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Current Residency program Duke University Medical Center		Est. completion date 06/2023
Program Director Dr. Michael Haglund MD PhD	Director's phone 919-684-6936	Director's email Michael.haglund@duke.edu
Program Coordinator Sherolyn Patterson	Coordinator's phone 919-684-3053	Coordinator's email Sherolyn.patterson@duke.edu

Additional Project Team Members

Name	Credentials	Email address
Isaac Karikari	☒ MD, ☐ DO, ____	Isaac.karikari@duke.edu
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Section II

Personal Statement: Please indicate how this grant, if funded, will help toward your career goals and intended area of specialization. Outline your expected career path and how this aligns with the Residency Research Grant program objectives and criteria. (500 words max.)

Throughout my life, I have been fortunate to be surrounded by individuals who inspire me. My parents, older brother, teachers, and mentors have fostered an intellectual curiosity. This has stimulated a desire to help the most number of individuals to the highest degree possible.

My parents were the first to teach me how important it is to be brave and to help others. They were the first in their family to immigrate to America with the hopes of starting a new life. They were lucky to find success and have since assisted many others in obtaining citizenship and a better life. Their work with the vulnerable immigrant population taught me how important it is to help others who do not have the tools to help themselves and clarify existing questions. I decided to obtain a masters of public health to better understand how to implement and conduct clinical research including clinical trials. I then worked in clinical trials as a clinical research coordinator but found that I wanted to be more involved with patient care and decided to go to medical school.

My decision to enter the field of neurosurgery is a culmination of multiple factors, most noteworthy being my brother, an early exposure to the field of neurosurgery, and the influences of my neurosurgical mentors. My brother is completing his neurosurgical training this year. As an undergraduate, I vividly remember seeing his love for the field and his enthusiasm to teach me about the brain and spine. I had hoped to find a field that I was infatuated with as much as my brother was to neurosurgery. As I entered medical school, I had a piqued interest in neurosurgery, however it was only after I rotated with neurosurgeons and worked with Drs. Edward Benzel, and Warren Selman that I knew I wanted to be a neurosurgeon. These mentors helped further foster a desire to do what is best for my patients and conduct research to optimize patient outcomes and contribute to the field.

Thus far, my academic focus has been on the spine: spinal fusions, cost analysis, conservative management of spinal pain, and spinal metastasis. My current projects continue to focus on the spine. My focus now is analyzing the National Cancer Database CNS and spine tumors, both primary and metastatic.

These experiences have allowed me to contribute to the field of neurosurgery and help elucidate questions. I have decided that I would like to dedicate my academic career to spinal pathology with a focus on spinal metastasis. The NCSS Resident Research Grant will help provide me with the resources to further the field of neurosurgery and advance patient care.

Section III – Details of the proposal

Short title

The influence of ketamine after spine surgery

Abstract summary

Adult spinal deformity surgery has become more prevalent in the older patient population because of multiple etiologies. Spinal deformity is defined as a curvature in the spine where alignment is outside of the defined normal limits [6]. Patients undergoing spine surgery commonly complain of pain postoperatively. The mainstay of treatment has been opioids with adjuvant analgesia such as local analgesia, acetaminophen, gabanoids, and lidocaine patches. This patient population is especially vulnerable as the pain and clinical situation often predisposes them to depression and additional medical expenditures. Ketamine is a promising medication as it acutely provides analgesia, but also shows promise as an antidepressant. The current literature has shown ketamine to be effective in the acute phase, however few studies have followed patient analgesic needs over time to determine if ketamine has lasting effects, which could be mediated by its antidepressant treatment. The current study would like to further analyze the efficacy for postoperative ketamine analgesia as well as determine if there is a long-term change in chronic pain and depression after ketamine exposure.

Outline of the problem

The prevalence of spinal deformity surgery in the adult population is 2 to 32% [1,5,6]. Spinal deformity is defined as any curvature in the spine that is where the alignment is outside of defined normal limits [6]. Post-operative back pain is expected, severe and will commonly last three days [4]. Post-operative pain management is critical to improve the patient experience, reduce delirium, and encourage early ambulation, which will reduce the incidence of pneumonia, deep vein thrombosis, ileus, and other complications. Post-operative spine patients are a unique population because they have a high cross over of chronic back pain, depression, as well as other psychiatric and psychiatric symptoms [7,8]. Post-operative analgesia is typically multi-modal and centered around opioids with adjuvants such as local analgesia injection, lidocaine patches, acetaminophen, gabanoids, and intravenous lidocaine and ketamine.

Ketamine is an interesting molecule as the current literature does not have a clear mechanism of action. It is thought to block N-methyl-d-aspartate (NMDA) receptors to cause anesthetic responses, but it is also linked to interacting with the hyperpolarization-activated cyclic nucleotide channels (HCN1), nicotinic ion channels, delta and mu opioid channels and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) channel among others [14,15]. Ketamine is a unique agent in that it can treat acute pain as well treat depression and other mood disorders such as suicidal ideation even at low concentration, and single dose exposures [2,3,9,13]. Current antidepressants can take upwards of six weeks to provide relief of symptoms.

To date, there are no retrospective of prospective studies analyzing the long-term effects of post-operative ketamine exposure in relationship to both acute and subacute opioid usage as well as mood disorders such as severity of depression according to the patient health questionnaire-9 (PHQ9). The PHQ9 is a validated depression scale measuring depression symptoms [11]. Our study will be the first prospective study to analyze these effects in the setting of post-operative spinal deformity surgery patients immediately after surgery and at their follow up appointment.

State of the art in this field

Current staples of post-operative pain management include opioids, local analgesic injections, acetaminophen, gabanoids, and intravenous lidocaine and ketamine. Ketamine is an effective post-operative analgesic. A systematic review by Laskowski et al in 2011included 47 studies and found that ketamine reduced acute pain compared to placebo ($P<0.001$) [10]. A meta-analysis by Niesters et al found that single dose ketamine also significantly reduced ketamine at four weeks post infusion ($P=0.036$) [12]. Placebo controlled trials have found single dose ketamine to be an effective treatment of depression symptoms for up to seven days, with remission of symptoms for three to five days [13,16]. The state of the art does not have any prospective studies concerning acute and subacute effects of ketamine on opioid intake and mood disorders in the post-operative spine population.

Past research of the applicant in this field

None applicable

Open questions

Does ketamine provide reduce opioid requirements in the acute and subacute setting and does it provide any improvement in the depression scale in the acute and subacute period after adult spinal deformity surgery?

Hypothesis

1. We hypothesize that ketamine will significantly reduce the post-operative opioid intake after spinal deformity surgery in the acute setting when compared to those who were not administered ketamine.
2. We hypothesize that ketamine will significantly reduce the post-operative opioid intake after spinal deformity surgery in the subacute setting when compared to those who were not administered ketamine.
3. We hypothesize that ketamine will significantly improve depression symptoms after spinal deformity surgery in the acute setting when compared to those who were not administered ketamine.
4. We hypothesize that ketamine will significantly improve depression symptoms after spinal deformity surgery in the subacute setting when compared to those who were not administered ketamine.
5. We hypothesize that ketamine will significantly reduce post-operative length of stay when compared to those who were not administered ketamine.

6. We hypothesize that ketamine will reduce post-operative complications related to immobility while in the hospital when compared to those who were not administered ketamine.

What are the aims you want to reach with this study?

Our **global aim** is to determine if ketamine has an impact on opioid intake and depression in both the acute and subacute period after spinal deformity surgery.
Specific aim #1: To determine whether low dose intravenous ketamine infusion can reduce opioid requirements 0-3 days after adult spinal deformity surgery and the initiation of ketamine infusion.
Specific aim #2: To determine whether low dose intravenous ketamine infusion can reduce opioid requirements in an outpatient setting 7-14 days after discharge from adult spinal deformity surgery.
Specific aim #3: To determine whether low dose intravenous ketamine infusion can improve depression symptoms to a minimal clinically significant difference of 5 points on the PHQ9 scale 0-3 days after adult spinal deformity surgery and the initiation of ketamine infusion.
Specific aim #4: To determine whether low dose intravenous ketamine infusion can improve depression symptoms to a minimal clinically significant difference of 5 points on the PHQ9 scale 7-14 days after adult spinal deformity surgery.
Specific aim #5: To determine whether low dose intravenous ketamine infusion can reduce length of stay as compared to those without ketamine infusion after adult spinal deformity surgery.
Specific aim #6: To determine whether low dose intravenous ketamine infusion can reduce immobility related complications such as pneumonia, deep vein thrombosis, and ileus as compared to those without ketamine after adult spinal deformity surgery.

Anticipated results

We anticipate that low dose intravenous ketamine infusion will reduce both acute and subacute post-operative opioid requirements, as well as result in a reduction in post-operative depression symptoms according to the PHQ9 depression scale when compared to those who were not administered ketamine. Lastly, we anticipate that ketamine will improve analgesia, which will result in a reduction in immobility related complications such as pneumonia, deep vein thrombosis and ileus compared to those who were not administered ketamine.

Study subjects, specimen or materials

Patients with spinal deformity who have undergone adult deformity operative correction at Duke University Medical Center (DUMC). Patient population will be between the ages of 18-80 years-old. Patients will be surveyed pre and post operatively to determine the opioid requirement, PHQ-9 scale. Patients will be surveyed post operatively at days 0-3 after ketamine infusion as well as at their post-operative follow up appointment, typically 7-14 days after discharge. Patients who are pregnant will not be included. All indications except for spinal tumors will be included in the study. Spine tumors will not be included as cancer related pain will confound and be superimposed on expected post-operative pain.
Patients will be primarily selected and recruited from DUMC without regard to gender, race, age, language preference, or socioeconomic status. All patients who are eligible and who agree to participate in the prospective portion of this study will be asked to sign an IRB approved consent to participate in the study. A patient's treatment will not be affected if the patient chooses not to participate in the study.

Materials:

PHQ9; opioid equivalency scale; VAS; Clinical and demographic data obtained from the patient's electronic medical record. Data variables will be collected and stored using the web-based platform REDCap (Research Electronic Data Capture).

Effect and outcome variables

The Primary Outcomes will include PHQ9, VAS, and opioid intake equivalences in the post-operative phase at the intervals of 0-3 days after infusion of ketamine and 7-14 days after discharge.

Secondary Outcomes: Post-operative mortality and complications, which may include pneumonia, ileus, deep vein thrombosis, pulmonary embolism, ileus, and disposition.

Methods for taking measurements

Once a patient is enrolled, baseline PHQ9, VAS, and opioid equivalence will be obtained at the pre-operative visit. Opioid intake from the last 7 days will be considered. Patient demographics and clinical information will then be obtained from the electronic medical record. If the patient is to have ketamine, we will again obtain PHQ9, VAS, and opioid requirements 0-3 days after infusion has started. These measurements will be obtained again 7-14 days after patient discharge at their first post-operative appointment.

Patients who have had ketamine exposure will be matched to a patient without ketamine exposure based on demographics, operative intervention, and baseline opioid intake.

These data will then be uploaded into REDCap for secure storage and analysis of data.

Methods for data management and analysis (including biostatistical check)

Data Management

All clinical and surveyed data will be stored on the DUMC Neurosurgery file server that requires a DUMC computer as well as a secured password to view. The server is secured by encryption and is HIPAA compliant. patient information will not be stored or viewed on personal computers or on portable drives. Information obtained will include age, gender, zip code, date of birth, dates of service, operative history, medical history, inpatient and outpatient medications, VAS data, and PHQ9 data.

Data stored on paper or non-digital mediums will be kept under lock and key within the Duke Neurosurgery key-accessed office. The office will be kept locked and secured when not used by the study. Study specific data will be extracted from the paper documents and the electronic medical record and will be stored on the DUMC password secured and encrypted servers.

Patient information will be de-identified to ensure confidentiality. Data will initially be obtaining with patient identifiers, however prior to dissemination of information within the database and/or servers, the patients identifying information will be deleted and patient, study-specific numbers will be assigned. A private log of patient identification information to study-specific identifiers will be kept and stored under password security, encryption in the secure DUMC server. The adequacy of the Research Data Security Plan will be evaluated and approved by the Duke Neurosurgery clinical research unit prior to study conduct.

Analysis

This will be a two-cohort study, a ketamine exposure group, and a control. This will be a Patient's baseline PHQ9, VAS, and opioid equivalence intake will be obtained pre-intervention. This will act as a baseline. After surgery and if the patient is started on intravenous ketamine, the patient will again be surveyed in terms of PHQ9,

VAS, and opioid equivalence intake 0-3 days after ketamine exposure. PHQ9, VAS, and opioid equivalence intake will again be surveyed 7-14 days post-discharge, at the post-operative visit.
Patients who have had ketamine exposure will be matched with patients who were not administered ketamine based on demographics, medical history, surgical history, baseline opioid requirements, and operative intervention.

Quantitative data will be analyzed as means or median for continuous data and non-parametric variables and frequency for categorical variables. One-sample t-tests will be utilized for continuous parametric data and Wilcoxon one-sample test will be used for non-parametric data when comparing a single cohort over time. One sample chi-squared test will be utilized for categorical data when comparing a single cohort over time.
Two sample t-tests will be utilized for continuous parametric data and Wilcoxon two sample test will be utilized for non-parametric data when comparing data between cohorts. Fisher's exact test will be utilized for comparing categorical, independent data between cohorts.

Estimation of sample size and power

A sample size of 32 patients is needed to achieve 80% power to reject the null hypothesis under the alpha equal to 0.05 and the cohorts one sample size assumption. When comparing two cohorts in terms of opioid intake, we are currently unsure what the anticipated means of the two populations will be and cannot calculate sample size in relationship. In terms of depression scale, we will assume that patients who have had ketamine will achieve a minimal clinical significant difference of five points on the PHQ9 scale. We will assume our patient population will have a moderate to severe depression, which makes their PHQ9 score 17. This would mean our second population, after treatment, would have a PHQ9 score of 12. Based on these assumptions, we need to have 16 patients in our study to achieve 80% power and reject the null hypothesis under the area equal to .05 and the cohorts two sample size assumption. We will therefore aim for at least 32 patients in our study but will continue to enroll until our enrollment period is over.

Animal model

If an in vivo animal model is used in the planned research work, please describe the model in detail. The description should include: anesthesia protocols, treatment protocols, pain management, surgical techniques, post-operative care, criteria for removal from the study if necessary, and euthanasia protocols.

AAALAC accreditation (Association for assessment and accreditation of Laboratory Animal Care International) www.aaalac.org

Please indicate whether the institution (main applicant and co-applicants) is AAALAC accredited and specify in which institution the animal research will be carried out. If the institution is not AAALAC accredited, please detail what agency and standards are used to oversee animal use and care.

Not Applicable. No animal model will be used.

Relevance of the project

There is a high comorbidity of psychiatric mood disorders such as depression and chronic back pain. Those patients undergoing adult spinal deformity surgery often will have intravenous ketamine infusion to help with analgesia. Ketamine is a promising agent for acute and subacute pain reduction as well as potential treatment for depression and other mood disorders. The goal of our project is to follow PHQ9 depression scale scores, VAS, and opioid intake equivalence over time to assess if ketamine has an acute or subacute change in depression symptoms and opioid intake. This could lead to a new standard treatment algorithm for treating adult spinal

deformity surgery and the associated psychiatric co-morbidities. This will result in improved outcomes for patients both physically, and mentally.

Time schedule

0 month - 6 months: Set up PHQ9, VAS, and opioid requirement surveyance at outpatient clinics. Obtain IRB approval for prospective observational study. Train orthopedic and neurosurgical house staff on research protocol.

6 months – 2 years: Enrollment of patients into the study at DUMC for prospective study.

2 years-3 years: End of enrollment and beginning of analysis of data, manuscript drafting

Relevant literature by the investigators

1. Adogwa, O., Elsamadicy, A.A., Fialkoff, J., Vuong, V.D., Mehta, A.I., Vasquez, R.A., Cheng, J., **Karikari, I.O.**, Bagley, C.A., 2017a. Assessing the effectiveness of routine use of post-operative in-patient physical therapy services. J Spine Surg 3, 149–154. https://doi.org/10.21037/jss.2017.04.03
2. Adogwa, O., Elsamadicy, A.A., Sergesketter, A., Vuong, V.D., Moreno, J., Cheng, J., **Karikari, I.O.**, Bagley, C.A., 2018a. Independent Association Between Preoperative Cognitive Status and Discharge Location After Surgery: A Strategy to Reduce Resource Use After Surgery for Deformity. World Neurosurg 110, e67–e72. https://doi.org/10.1016/j.wneu.2017.10.081
3. Adogwa, O., Elsamadicy, A.A., Sergesketter, A.R., Black, C., Tarnasky, A., Ongele, M.O., Vuong, V.D., Khalid, S., Cheng, J., Bagley, C.A., **Karikari, I.O.**, 2017b. Relationship Among Koenig Depression Scale and Postoperative Outcomes, Ambulation, and Perception of Pain in Elderly Patients (≥65 Years) Undergoing Elective Spinal Surgery for Adult Scoliosis. World Neurosurg 107, 471–476. https://doi.org/10.1016/j.wneu.2017.07.165
4. Adogwa, O., Elsamadicy, A.A., Vuong, V.D., Mehta, A.I., Vasquez, R.A., Cheng, J., Bagley, C.A., **Karikari, I.O.**, 2018b. Immediate Postoperative Pain Scores Predict Neck Pain Profile up to 1 Year Following Anterior Cervical Discectomy and Fusion. Global Spine J 8, 231–236. https://doi.org/10.1177/2192568217706700
5. Cook, C.E., Frempong-Boadu, A.K., Radcliff, K., **Karikari, I.**, Isaacs, R., 2015. Older Age and Leg Pain Are Good Predictors of Pain and Disability Outcomes in 2710 Patients Who Receive Lumbar Fusion. HSS J 11, 209–215. https://doi.org/10.1007/s11420-015-9456-6
6. Elsamadicy, A.A., Adogwa, O., Fialkoff, J., Vuong, V.D., Mehta, A.I., Vasquez, R.A., Cheng, J., Bagley, C.A., **Karikari, I.O.**, 2017a. Effects of immediate post-operative pain medication on length of hospital stay: does it make a difference? J Spine Surg 3, 155–162. https://doi.org/10.21037/jss.2017.04.04
7. Elsamadicy, A.A., Wang, T.Y., Back, A.G., Lydon, E., Reddy, G.B., **Karikari, I.O.**, Gottfried, O.N., 2017b. Post-operative delirium is an independent predictor of 30-day hospital readmission after spine surgery in the elderly (≥65years old): A study of 453 consecutive elderly spine surgery patients. J Clin Neurosci 41, 128–131. https://doi.org/10.1016/j.jocn.2017.02.040
8. Phan, K., Moran, D., Kostowski, T., Xu, R., **Goodwin, R.**, Elder, B., Ramhmdani, S., Bydon, A., 2017. Relationship between depression and clinical outcome following anterior cervical discectomy and fusion. J Spine Surg 3, 133–140. https://doi.org/10.21037/jss.2017.05.02
9. Wang, T.Y., Sakamoto, J.T., Nayar, G., Suresh, V., Loriaux, D.B., Desai, R., Martin, J.R., Adogwa, O., Moreno, J., Bagley, C.A., **Karikari, I.O.**, Gottfried, O.N., 2015. Independent Predictors of 30-Day

Perioperative Deep Vein Thrombosis in 1346 Consecutive Patients After Spine Surgery. World Neurosurg 84, 1605–1612. https://doi.org/10.1016/j.wneu.2015.07.008

Relevant literature by other authors

1. Abrishamkar, S., Eshraghi, N., Feizi, A., Talakoub, R., Rafiei, A., Rahmani, P., 2012. Analgesic effects of ketamine infusion on postoperative pain after fusion and instrumentation of the lumbar spine: a prospective randomized clinical trial. Med Arh 66, 107–110.
2. Ames, C.P., Scheer, J.K., Lafage, V., Smith, J.S., Bess, S., Berven, S.H., Mundis, G.M., Sethi, R.K., Deinlein, D.A., Coe, J.D., Hey, L.A., Daubs, M.D., 2016. Adult Spinal Deformity: Epidemiology, Health Impact, Evaluation, and Management. Spine Deformity 4, 310–322. https://doi.org/10.1016/j.jspd.2015.12.009
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Section IV – Budget for proposed project period

Personnel			**Amount**
Surname / First name	Academic qualification	Effort in %	
Mehta/Vikram (Project manager)	Medical Doctor	2%	$1559.52
Sankey/Eric (Programming assistant)	Medical Doctor	0.5%	$389.88
Wang/Timothy (Data acquisition)	Medical Doctor	0.5%	$374.76
Total Cost			**$2324.16**

Material	**Amount**
GraphPad Prism (academic use)	$313.20
Adobe Illustrator	$183.60
Statistical analysis (software and consultation)	$451.44
Supplies/copies of VAS and PHQ-9	$108.00
Total Cost	**$1056.24**

Supplies	**Amount**
Computer (uploading data to REDCap and data analysis)	**$1620.00**

Rental of equipment	**Amount**
Itemize below	**$0.00**

Total Funding Request (max. $5000):	**$5000.00**

Section V

If selected for participation in the program, the grantee agrees to conduct herself/himself professionally according to the principles of medical ethics and to be governed by the Bylaws of the North Carolina Spine Society.

Applicant's signature: _____ Date: 6/14/18

Program Director's signature: _____ Date: 6/14/18

To be considered for the 2018-2019 grant year, submit the following by July 2, 2018:

1. Completed application form
2. Applicant's CV
3. Completed W-9 form of the recipient organization (IRS W-9)

Please sign your completed form and return it along with your CV by email, mail or fax to:
NCSS, PO Box 27167, Raleigh, NC 27611 | Fax: 919-833-2023 | ncspine@ncmedsoc.org