A Prospective, Randomized, Double-Blind, Placebo-controlled Pilot Study of Single-dose Intraoperative Ketamine for the Prevention of Delirium in Otolaryngeal Cancer Surgery Patients

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Short Title: Delirium Prevention with Ketamine in ENT patients

Winship EU3268-16

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2. Abstract

The goal of this prospective randomized double blinded placebo controlled study is to investigate if a single dose of ketamine in addition to standard anesthesia will reduce the risk of delirium in otolaryngeal cancer patients postoperatively. Ketamine's effect on post-operative pain and opioid use will be measured as well. Electroencephalogram (EEG) will be utilized during the surgical procedure to evaluate its potential as a possible predictive device for delirium. The study will be a single center study at Emory University Hospital Midtown (EUHM).

Up to 100 patients will be consented in order to achieve at least 60 patients who will be randomly assigned and administered 0.5 mg/kg, 1mg/kg or placebo intravenous bolus after induction of anesthesia. A processed EEG device (SEDline, Masimo Corporation) will be used to gather raw EEG data for off line analysis among patients developing post-operative delirium. Patients will be screened for delirium with the CAM-ICU once per shift (3 times daily) for three days postoperatively. Currently, the CAM- ICU is performed by ICU nursing and documented in the electronic medical chart. Both CAM-ICU screens and SEDLine monitoring are part of the usual and customary practice associated with these cases at EUHM and it would be unusual for a case such as this to be performed without this clinical data. Pain will be assessed according to hospital protocol and postoperative opioid consumption will be determined from the medical charts. Preoperative and postoperative cognitive assessment will be completed at the ENT clinic preoperative, and postoperative follow up visit (done by research assistant). Adverse

effects (e.g., hallucinations or nightmares) will also be evaluated for three days postoperatively.
Chart review, data collection/entry will be done by Candace Stearns, PharmD, research assistant and the research staff.

3. Background and Significance:

Delirium is a frequent post-operative complication of major surgery with a reported incidence of 10-70 % [1] [2] [3]. After major head and neck cancer surgeries the incidence of delirium is reported to be over 25% [3]. Delirium is associated with increased morbidity and mortality, prolonged length of hospital and intensive care unit (ICU) stay and functional and cognitive decline [4] [5] [6] [7]. A history of dementia or depression, chronic medical illness, male gender and age>60 years are consistently described as risk factors for delirium [8] [9]; in the head and neck cancer patient population length of surgery and alcohol consumption have been identified as well [3] [10]. Currently there is no effective prophylactic treatment for delirium identified. Even the treatment of delirium remains difficult [11]. A Cochrane review on delirium prevention in hospitalized patients came to the conclusion that there is a paucity of research in this area resulting from difficulties in delirium detection and confounding factors like pre-existing cognitive impairment or multiple medical problems [12].
Recently a small randomized trial in cardiac surgery patients found a significant reduction in postoperative delirium (31% to 3%) when sub-anaesthetic doses of ketamine (0.5mg/kg) were given upon induction [13]. The same group further published data for improved postoperative cognitive function with ketamine in cardiac patients [13]. A follow up randomized prospective study in cardiothoracic patients looking at ketamine and delirium is currently recruiting (PODCAST).
Ketamine's benefits are thought to be based on its NMDA antagonism, HCN1 inhibitory effects and its anti-inflammatory properties [14]. Multiple studies have shown decreased post-operative pain with decreased post-operative opioid use when ketamine was administered during the surgery [15]. Interestingly a recent study showed that a single dose of ketamine had a prolonged two week lasting effect on patients with refractory depression [16].
Ketamine is a drug that has been in use for more than half a century, is inexpensive and has a wide margin of safety.

We are proposing a prospective randomized placebo controlled study to elucidate the effects of ketamine on postoperative delirium in the head and neck cancer population receiving “flaps”, administered peri-operatively.

4. Objectives:

Primary Aim:

Optimize our intraoperative treatment protocol for head and neck cancer patients to reduce the incidence of delirium and associated postoperative cognitive dysfunction. The hypothesis is that ketamine decreases delirium postoperatively in this high risk surgical patient population.

Secondary Aims:

1. Determine the dose response relationship for intraoperative ketamine and delirium reduction. Our hypothesis is that higher dose ketamine will lead to a more profound reduction in postoperative delirium.
2. Determine if a single dose of ketamine will reduce post-operative pain and opioid requirements. Our hypothesis is that the higher dose of ketamine will lead to a more profound decrease in objective pain scores.
3. Determine if raw EEG data can predict postoperative delirium during general anesthesia. Our hypothesis is that EEG patterns will correlate with incidence of post-operative delirium.
4. Evaluate length of ICU and length of hospital stay (done by medical chart review). Our hypothesis is that ketamine administration will not increase ICU/hospital stay.

5. Innovation, Impact & Leverage.

The successful completion of this study will provide critical data on a therapeutic and/or prophylactic effect of perioperatively administered ketamine on postoperative delirium. Delirium has been associated with increased length of ICU and hospital stay, increased cognitive impairment/decline and mortality. Despite increasing evidence of ketamine’s ability to reduce postoperative delirium in cardiac patients, its opioid sparing effects and decreased postoperative opioid needs, ketamine is not widely used. Clinicians are concerned that psychoactive properties (e.g., hallucination and dissociative states)

interfere with post-operative cognitive function. These side effects however are rarely seen when ketamine is used in subanaesthetic doses.
Additionally, EEG data will be used to determine if this tool can be a possible predictor of delirium.
Currently, the most common way to monitor brain function during surgery is via processed electroencephalogram (EEG) monitors (SEDLine). These devices use frontal or fronto-temporal EEG electrodes, to measure the electrical activity of the brain. A special computer program translates these brain waves into a dimensionless number that roughly correlates to the dose of anesthesia administered. A purpose of our research is to utilize the electrical information from the raw EEG signals to determine if EEG patterns can predict a propensity to develop postoperative delirium. Our approach is to probe deeper into the analysis of the EEG signal than simply depth of consciousness by developing a taxonomy of specific states leading up to and through emergence.
EEG technology measures the electrical potential generated by synaptic input onto the dendrites of cortical neurons. Although higher frequencies are attenuated somewhat by the skull, a wide range of frequencies can be observed even with the abbreviated montage typical for the commonly available devices. With a minimal amount of effort the EEG file is available for download from the device via USB stick. The sensors are pre-packaged with gentle adhesive and applied to the patient's forehead while the patient is awake and removed with a minimal amount of discomfort (similar to a Band-Aid). Although these EEG devices are not considered an ASA standard monitor for general anesthesia, many practitioners elect to place these sensors for routine cases as a monitor of depth of anesthesia. Several other benefits of these devices have been proven through the use of these devices and their utility as a standard monitor has been considered [17]. Previous experiments using abbreviated EEG records in this fashion have shown variations in the post-operative pain that correlated with their EEG patterns just before emergence from general anesthesia [18]. This is in contrast to the majority of the past studies using these devices that have focused on the predictive value of the number derived from the proprietary algorithm developed by the manufacturer. These algorithms reduce the EEG information into a single dimensionless number which roughly correlates with depth of anesthesia, although this concept has come under criticism. Our study involves quantitative EEG analysis of multiple electrodes placed over frontal brain regions of patients with co-morbid conditions. The value of EEG frequency

analysis in predicting delirium is unknown, but it has the potential to be an important tool in determining risk of delirium.

6. Approach:

Our aim is to optimize our perioperative treatment protocol for head and neck cancer patients in the operating room to positively impact ICU outcomes, by improving the incidence of delirium, associated postoperative cognitive dysfunction and pain control. This is a single center prospective randomized double blinded placebo controlled study that will be conducted at EUHM

Study arms:

1. 0.5mg/kg pre-incision bolus
2. 1.0mg/kg pre-incision bolus
3. Saline placebo pre-incision bolus

Standard general anesthesia will be applied with following standardized drugs: Sevoflurane, fentanyl, hydromorphone, succinylcholine, rocuronium, cis-atracurium, lidocaine, propofol. Dosing and choice of above medications is at the discretion of the anesthesiologist.

Primary Outcome:

Delirium (measured by Confusion Assessment Method for Intensive Care Unit criteria, CAM-ICU) Measurements: Prior to surgery (baseline assessment upon study enrollment in ENT clinic) and postoperative days 0-3 (afternoon/evening on postoperative day 0, POD 1-3 measurements per shift as per Emory delirium protocol)

Secondary Outcomes:

1. Pre- and postoperative cognitive dysfunction (assessed in ENT clinic at pre- and post-operative visits or at anesthesia preoperative clinic) with the Mini-Cog, Mini-Mental Status Examination (MMSE) and the Cognitive Failure Questionnaire (CFQ).
2. Pain assessment (Prior to surgery (baseline assessment upon study enrollment in ENT clinic) and postoperative days 0-3 (afternoon/evening on postoperative day 0, and POD 1-3 per Emory protocol every 4 hours). Assessed by observer-based Behavioral Pain Scale or Behavioral Pain Scale (Non-Intubated) with subsequent administration of patient-reported Visual Analog Scale.

3. Post-operative use of narcotics (assessed POD 0-3 from medical chart)

4. Off line EEG analysis to correlate with postoperative delirium

7. Participant Selection

Inclusion criteria:

Inclusion criteria:

1. Patients 18 years of age and older, with otolaryngeal cancer receiving surgery with general anesthesia.

(Please note we are purposefully including patients with higher predisposition to delirium as we are investigating potential preventive strategies for this diagnosis of multiple etiologies. Patients at higher risk of delirium (e.g., advanced age, chronic hypertension) will be included in our study. Additionally, other common risk factors that exist in this patient population (e.g., alcohol or nicotine use) are thought to contribute to delirium postoperatively. [19])

2. Competent to provide informed consent.

Exclusion criteria:

1. Emergency surgery

2. Monitored Anesthesia Care (i.e., regional anesthesia alone without plans for general anesthesia)

3. Surgery involving the eye, eyebrow, forehead, or frontal scalp near the sensor placement

4. Poor health literacy (see next section)

5. Patients with an allergy, or have experienced any drug reaction to ketamine will be excluded.

6. Pregnant or lactating patients

7. Patients in active alcohol withdrawal

8. Patients with chronic pain who are taking buprenorphine

Subject Replacement

Subjects who are not admitted to the Intensive Care Unit after surgery, will be replaced, but will be followed per protocol through the final visit 2-6 weeks post-operatively.

Recruitment Plan/Eligibility Screening:

Patients undergoing surgical procedures requiring general anesthesia will first be approached for participation during the patient's preoperative visit, at the preoperative ENT clinic visit or on the day of surgery. A clinical research coordinator or other research personnel will be available to answer questions and obtain informed consent from the patient. It will be made clear to the patient that study participation is optional and that they can "opt out" at any time even if they have signed a consent form. In order to assure that our study participants are capable of understanding the information provided in the informed consent a single question screen will be used to detect inadequate health literacy: "How confident are you filling out medical forms by yourself?". This has been used in previous hospitals to detect poor health literacy [20]).

We intend on enrolling up to 100 male and female patients that meet eligibility criteria in order to have 60 patients who complete all study assessments. In addition to examining the potential effects of age, anesthetic drugs, and other patient and clinical factors on cognitive trajectories post-anesthesia, gender will be recorded and statistically examined as a potential contributor to different EEG patterns among our patients in this observational study.

8. Procedures:

- Upon enrollment, demographic data and medical history will be collected, subjects will be questioned about obstructive sleep apnea (OSA) using the STOP-Bang Questionnaire [21]). They will also be screened for cognitive impairment using Mini-Cog, Mini-Mental Status Examination (MMSE) and the Cognitive Failure Questionnaire (CFQ). A baseline pain assessment will be performed using the Visual Analog Scale. A baseline assessment of delirium will be obtained using the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) criteria.
- Patients will be randomized to one of three groups on the morning of surgery by the Investigational Drug Service, before they enter the operating room. A randomization table will be provided and the subject assignment will be the next available number on the list. The study staff will be blinded to the list and the assignment. Group 1 will be given 0.5mg/kg of ketamine pre-incision as an intravenous (IV) bolus. Group 2 will receive 1.0mg/kg of ketamine pre-incision as

an IV bolus. Group 3. Will be administered saline/ placebo pre-incision an IV bolus. The provider will be blinded to the treatment assignment.

- Upon arrival in the operating room, before the induction of anesthesia, disposable EEG sensors (SEDLine) will be applied over the forehead according to the manufacturer's instructions.
- The pads will be placed out of the surgical field. For surgical cases where patient positioning or surgical skin preparation may interfere with good sensor contact, tape or Tegaderm® patches will be applied over the sensors to ensure they stay dry and in place.
- The patient will then be induced according to standard of care at the anesthesiologist's discretion. After induction a single bolus dose of ketamine (0.5mg/kg or 1mg/kg) or saline placebo will be given intravenously.
- The operation itself will proceed in the usual fashion using the standard monitors placed in all such cases according to institutional practice. Operative characteristics will be recorded.
- At the conclusion of the operation, the anesthesia practitioner will press the event marker button to aid in synchronizing the EEG raw data. The provider will adhere to specific guidelines (Provider Instructions), data will be recorded and the EEG file (without patient identifiers) will be downloaded and stored securely.
- The sensor will be removed and EEG data will cease to be collected before transport to the recovery room.
- While in the recovery room, the patient's pain level will be assessed (observer-based Behavioral Pain Scale or Behavioral Pain Scale (Non-Intubated) with subsequent administration of patient-reported Visual Analog Scale) as standard of care. The patient will be screened for post–operative delirium using the CAM-ICU delirium score and the Richmond Agitation and Sedation Score (CAM-ICU; RASS) 30 minutes after arrival and at discharge.
- While in the ICU pain assessment will be performed on postoperative days 0-3 (afternoon/evening on postoperative day 0, and POD 1-3 per Emory protocol, that is typically recorded by staff every 4 hours). Assessed by observer-based Behavioral Pain Scale or Behavioral Pain Scale (Non-Intubated) with subsequent administration of patient-reported Visual Analog Scale. Available data will be

gathered from the medical chart including vasopressor use, ICU and hospital length of stay.

- The patient will be screened for post-operative delirium using the CAM-ICU delirium score and the RASS during the ICU stay, typically recorded three times a day per Emory SOC. Available data will be gathered from the medical record for POD 1-3.

- At the routine outpatient ENT clinic postoperative visit that may occur from 2 to 6 weeks after surgery, cognitive impairment again will be screened with the Mini-Cog, Mini-Mental Status Examination (MMSE) and the Cognitive Failure Questionnaire (CFQ). Pain assessment will be performed using the Visual Analog Scale.
- This will be done by our research assistant.
- Post-operative use of narcotics will be assessed POD 0-3 from medical chart and at postop clinic visits at the ENT clinic visit postoperatively. The subject's study participation will end at the postoperative ENT clinic visit. 30 day readmissions, as well as mortality will be captured.

9. Risks

a. Risks regarding EEG sensors:

There is a very small chance of minor skin irritation from applying sensor strips (as the conductive gel has a minimal amount of latex-free adhesive similar to EKG leads); these skin reactions typically go away in 30 minutes without treatment. There is no more risk of skin irritation or discomfort from application or removal of these sensors than occurs during the removal of a Band-Aid. It should be noted that SEDLine sensors are routinely placed on the forehead of surgical patients without adverse effects. However, an information sheet with general instructions on care for minor skin problems after sensor removal will be made available. This sheet will also have recommendations for recognizing and treating minor skin irritation (i.e., mild soap and water) and the contact information for the study coordinator.

b. Risks regarding ketamine are as follows:

According to the manufacturer the anesthesia induction dose is as follows: the initial dose of ketamine administered intravenously may range from 1 to 4.5 mg/kg. The average amount required to produce 5–10 min of surgical anesthesia has been 2 mg/kg. The short-term side effects of ketamine at higher doses (>1–2 mg/kg) than the dosages proposed for this study (0.5 or 1 mg/kg) include tachycardia, nystagmus, hypersalivation, euphoria, emergence reactions, hallucinations and nightmares [22] In the doses used in this study (low dose ketamine at 0.5 and 1mg/kg after induction), it is very unlikely that these side effects will happen. [23]

c. ADE reporting and Data Safety Monitoring Plan:

The Emory School of Medicine, section of Anesthesiology Research, will conduct this study according to the national rules, regulations and guidelines governing human clinical research. In addition, procedures cited by the US Code of Federal Regulations (Title 21) will be followed as these apply to the principles of Good Clinical Practices and approval by the Emory Institutional Review Board (IRB). Investigators will complete Emory University required research training. All individuals involved in the study and data collection will be made aware of the unanticipated event reporting policy.

The research team will monitor subjects randomized and treated in the study for adverse events related to the research through the final study visit in the ENT clinic. If the change from baseline is considered by the investigator to be part of the normal fluctuations of an underlying disease process, this shall not be reported as an adverse event (AE). If the change in baseline is considered by the investigator to be an untoward medical occurrence different from the standard of care, this medical occurrence shall be reported as an AE. Any event meeting serious adverse event criteria will be reported by the research team immediately to the PI via email or telephone and will be reported to the Institutional Review Board (IRB) per policy. The PI will also inform all investigators of the event via email. The common grading system will be used for adverse event reporting where Grade 1 is mild, Grade 2 moderate, Grade 3 severe, Grade 4 life-threatening or disabling, and Grade 5 death related to AE. Should emergency unblinding be required for the safety of the patient, the PI will contact the Investigational Drug Service responsible for the preparation and dispensing of the study medication.

All enrolled subjects will be followed and monitored per Emory standard of care for postoperative surgery. Subject data will be evaluated on an ongoing basis during the study visits to ensure continued subject safety. There will be no pre-specified formal stopping rule for safety. An interim safety analysis will be performed after 10 participants are enrolled in each arm to ensure ongoing subject safety.

This monitoring plan is appropriate, since ketamine, an anesthetic drug, has an excellent safety profile and is commonly used in anesthetic practice. In addition, the doses used in this study are unlikely to cause major or minor side effects (e.g., emergence reactions, hallucinations).

10. Statistical analysis

a. Sample size:

It was assumed about 30% delirium incidence in our population by standard care [1] [2] [3].

Estimating 5-8 oropharyngeal cancer surgeries per week with a conservative enrollment rate of 50%, we will be able to recruit 130-208 patients in 12 months. We plan to enroll about 85 eligible patients in order to achieve 20 completed patients in each randomized group. For this pilot study, with this sample size we will have 85% statistical power under significant level of 0.05 to detect delirium incidence rate drop at least 30$ (placebo) to 5% (two treatment arms combined) by one-sized Mantel Haenszel test, and such effect size is supported by an existing trial [13].

b. Data analysis:

For primary aim, the incidence of delirium will be calculated in each of three randomized group with 95% confidence interval (CI), and compared between each ketamine treated group with placebo group through Fisher's exact test. For secondary aims, the dose response effect of ketamine on delirium reduction will be tested by Cochran-Armitage trend test. For other outcomes, such as pain (and/or change from baseline), MMSE (and/or change from baseline), EEG data, length of stay (LOS), and use of narcotics will be first described by summary statistics (mean, median, standard deviation, frequency, and etc.) by three randomized groups and then compared by Chi-square test/Fisher's exact test, ANOVA, or Krusal-Wallis test wherever appropriate. The analysis will be

conducted by the Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute.

The Winship OnCore system will be used for data entry and analysis.

11. Confidentiality

The privacy of the research subjects will be ensured through standard procedures for securing research data. Whenever possible, a study number, rather than a name, will be used on study records. Identifying information will not appear when we present or publish the study results. All interactions with subjects during the study will occur in a private setting. Only Emory owned computers will be utilized to store data with any identifiers and these are compliant with the Emory disc encryption policy.

12. Literature:

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Assessments	Screening (up to 6 weeks prior to surgery)	Treatment Visit/DOS	Recovery Room	POD 0	POD 1	POD 2	POD 3	ENT clinic visit 2-6 weeks after surgery
Inclusion/Exclusion Criteria Review	**X**							
Informed Consent	**X**							
Randomization		**X**						
Treatment with Ketamine/Placebo		**X[1]**						
Connection to EEG Device (SEDLine Monitoring) and data capture during operative procedure		**X**						
Medical History and Demographics	**X**							
STOP-Bang Questionnaire	**X**							
Mini-Cog	**X**							**X**
Mini-Mental Status Exam (MMSE)	**X**							**X**
Cognitive Failure Questionnaire (CFQ)	**X**							**X**
Pain Assessment using Visual Analog Scale (VAS)	**X**		**X**	**X[2]**	**X[3]**	**X[3]**	**X[3]**	**X**
Follow provider guidelines		**X**						
Confusion Assessment Method fo Intensive Care Unit (CAM-ICU) delirium score	**X**		**X7**	**X[4]**	**X[4]**	**X[4]**	**X[4]**	
Richmond Agitation Score (RASS)			**X7**					
Pain assessment (Observer based Behavior Pain Scale or Behavior Pain Scale)			**X**	**X[2]**	**X[3]**	**X[3]**	**X[3]**	
Use and amount of narcotics daily				**X**	**X**	**X**	**X**	**X**
EEG Analysis								**X**
Adverse Events[6]			**X**	**X**	**X**	**X**	**X**	**X**
Surgery Characteristics		**X**						
Length of ICU and Hospital Stay								**X**

APPENDIX A- Study Flowchart and Schedule of Assessments

1 Just after anesthesia induction time
2 Assessment to occur in afternoon or evening, obtain VAS if possible
3 Pain assessments recorded for SOC, as available
4 CAM-ICU scores as recorded per SOC, during ICU stay, as available
5 Post op visit may occur at ~ 2 weeks **and/or** ~6 weeks
6 Adverse Events to be collected only after treatment with study product/placebo
7 30 minutes after PACU arrival and at PACU discharge

CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the pt different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?	Either question Yes →	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate Pictures) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. S A V E A H A A R T **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 →	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** Command Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If pt is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1→	☐

Overall CAM-ICU Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive		
	Criteria Met →	☐ CAM-ICU Positive (Delirium Present)
	Criteria Not Met →	☐ CAM-ICU Negative (No Delirium)

The Cognitive Failures Questionnaire (Broadbent, Cooper, FitzGerald & Parkes, 1982)

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the past 6 months. Please circle the appropriate number.

		Very often	Quite often	Occasion-ally	Very rarely	Never
1.	Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find you confuse right and left when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0
12.	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0

		Very often	Quite often	Occasion-ally	Very rarely	Never
14.	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15.	Do you have trouble making up your mind?	4	3	2	1	0
16.	Do you find you forget appointments?	4	3	2	1	0
17.	Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18.	Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19.	Do you daydream when you ought to be listening to something?	4	3	2	1	0
20.	Do you find you forget people's names?	4	3	2	1	0
21.	Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22.	Do you find you can't quite remember something although it's "on the tip of your tongue"?	4	3	2	1	0
23.	Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24.	Do you drop things?	4	3	2	1	0
25.	Do you find you can't think of anything to say?	4	3	2	1	0

References

Broadbent, D.E., Cooper, P.F., FitzGerald, P., & Parkes, K.R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology*, *21*, 1-16

Mini-Mental State Examination (MMSE)

Patient's Name: Date:

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Interpretation of the MMSE:

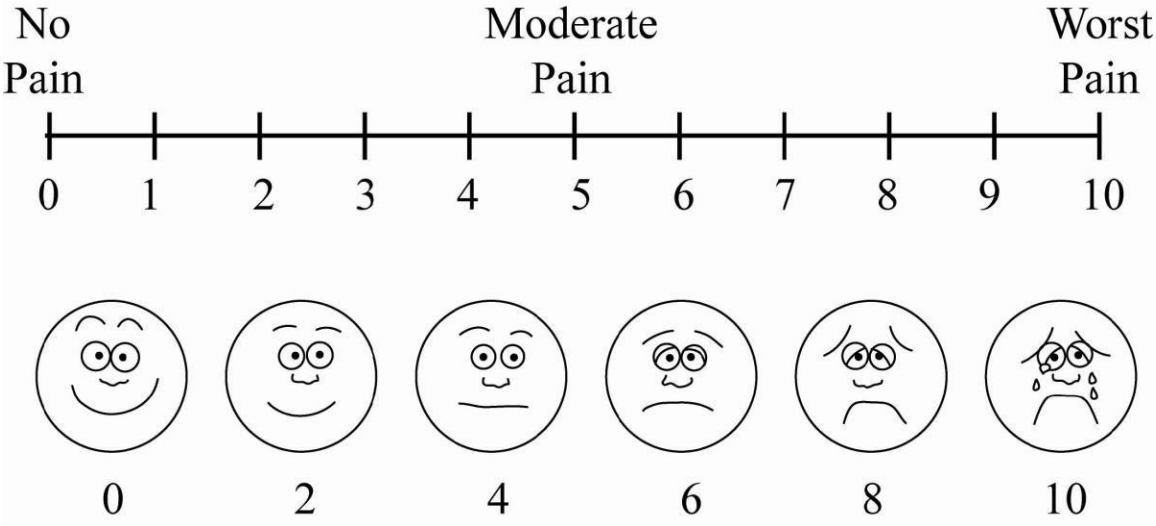
Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21 >25	Increased odds of dementia Decreased odds of dementia
Education	21 <23 <24	Abnormal for 8th grade education Abnormal for high school education Abnormal for college education
Severity	24-30 18-23 0-17	No cognitive impairment Mild cognitive impairment Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Source:

- Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." *J Psychiatr Res* 1975;12:189-198.


No Pain
Moderate Pain
Worst Pain
0 1 2 3 4 5 6 7 8 9 10
0 2 4 6 8 10

A Randomized Placebo-controlled Pilot Study of Single-dose Intraoperative Ketamine for the Prevention of Delirium in Otolaryngeal Cancer Surgery Patients

A Randomized Placebo-controlled Pilot Study of Single-dose Intraoperative Ketamine for the Prevention of Delirium in Otolaryngeal Cancer Surgery Patients

Provider Instructions-Emory University Hospital Midtown (EUHM)

Subject ID:_____ Date:_____

On behalf of the anesthesiology research personnel, we would like to thank you for your willingness to assist with capturing data for our study. During different time intervals you may be asked to provide our team with specific information as patients emerge from anesthesia. In attempting to execute this protocol, do not compromise the patient's safety. Should you have any questions regarding this protocol please contact Dr. Moll, Dr. Lee, or Dr. Dooley at 404-686-2316.

Table 1. Proposed Standard Emergence Protocol

Clinical Sign / Event	Practitioner action
Pre-induction	Apply EEG electrodes while patient has received minimal sedation and can still follow verbal commands.
Induction	Tap electrodes 2 times to signal induction.
Study Drug Administration	Tap electrodes 2 times when given
End of Surgery	Tap electrodes 2 times to signal end of surgery time.

(Request for noise to be kept at a minimum at time of emergence)	
Return of spontaneous breathing (after last NMB dose)	Record time
Cessation of maintenance anesthetic & FGF > 8 Lpm OR If Gas off at OR exit, check here: ☐	Record time. Tap electrodes 4 times to signal emergence. At this time, suction oropharynx, remove eye tape, apply nasal or oral airways if anticipated.
Increase in HR, BP, tearing, salivating, posturing, choking, gagging, coughing, grimacing	Avoid suction of the oropharynx, avoid tactile stimulation to face and endotracheal tube/trach. Record drugs and doses (if administered) on anesthesia record.
End of emergence if in OR	Record time
MAC Awake *Expired gas concentration has reached:* *Sevoflurane < 0.4%,* *Isoflurane < 0.2%,* *Desflurane < 0.6%,* OR Propofol off for 5 min.	Record time. Use clinical judgment regarding reversal agents (naloxone, flumazenil).
Extubate (If applicable)	Record time

- Please notify _____Number:_____ when nearing the end of the case (~30 minutes before end)
- Please place this provider sheet _____
- SedLine Monitor Instructions: Press event marker at end of case; Turn monitor off when you exit room; study staff will be in by the next morning to collect the machine.

Person Contributing to this Form:_____ Date:_____
Signature

Person Contributing to this Form:_____ Date:_____
Signature

v. 05.15.17

MINI-COG™

Instructions

ADMINISTRATION	SPECIAL INSTRUCTIONS
1. Get patient's attention and ask him or her to remember three unrelated words. Ask patient to repeat the words to ensure the learning was correct.	• Allow patient three tries, then go to next item. • The following word lists have been validated in a clinical study:[1–3] **Version 1**: • Banana • Sunrise • Chair **Version 2**: • Daughter • Heaven • Mountain **Version 3**: • Village • Kitchen • Baby **Version 4**: • River • Nation • Finger **Version 5**: • Captain • Garden • Picture **Version 6**: • Leader • Season • Table
2. Ask patient to draw the face of a clock. After numbers are on the face, ask patient to draw hands to read 10 minutes after 11:00 (or 20 minutes after 8:00).	• Either a blank piece of paper or a preprinted circle (other side) may be used. • A correct response is all numbers placed in approximately the correct positions AND the hands pointing to the 11 and 2 (or the 4 and 8). • These two specific times are more sensitive than others. • A clock should not be visible to the patient during this task. • Refusal to draw a clock is scored abnormal. • Move to next step if clock not complete within three minutes.
3. Ask the patient to recall the three words from Step 1.	Ask the patient to recall the three words you stated in Step 1.

Scoring

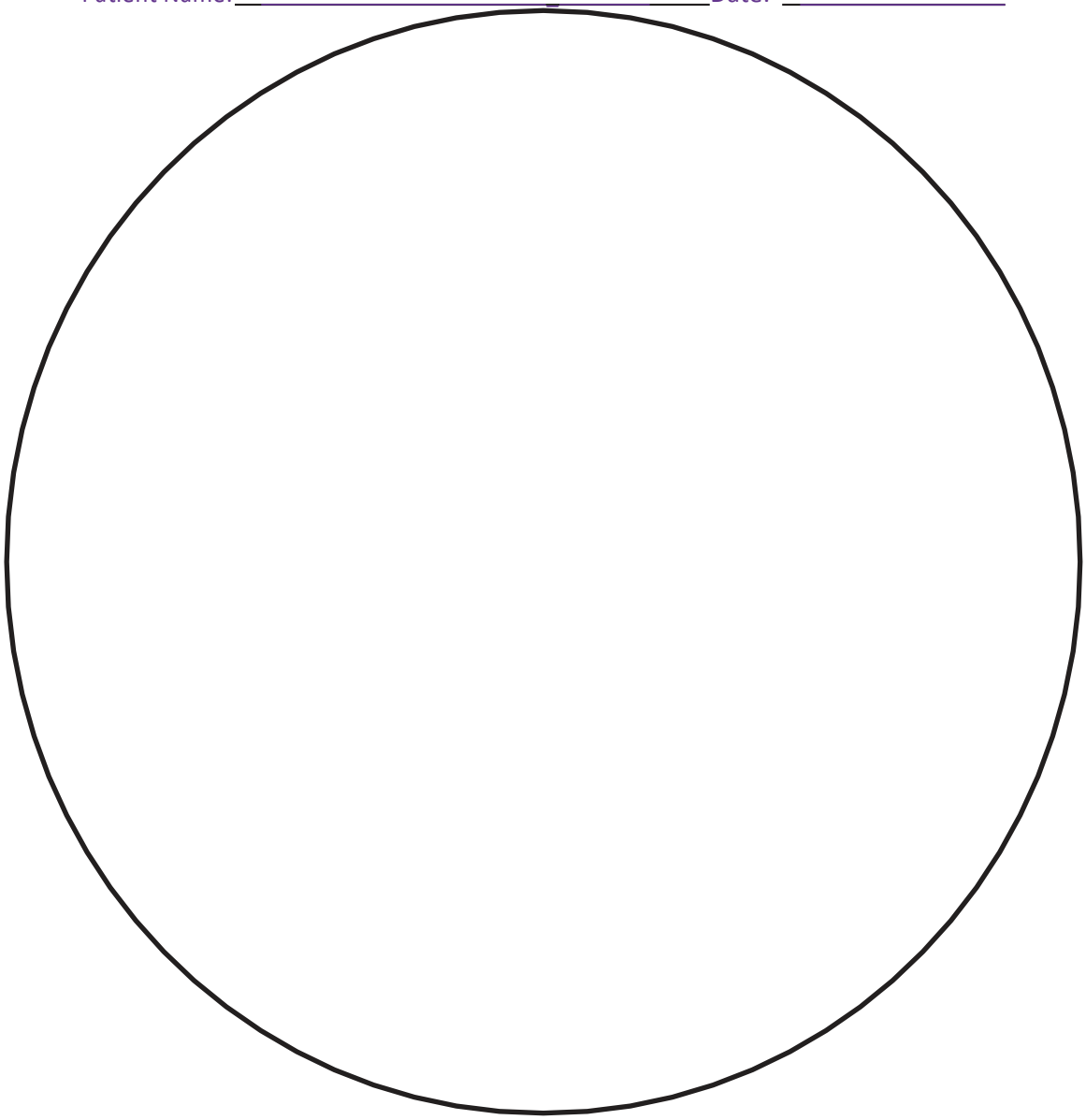
3 recalled words	Negative for cognitive impairment
1-2 recalled words + normal CDT	Negative for cognitive impairment
1-2 recalled words + abnormal CDT	Positive for cognitive impairment
0 recalled words	Positive for cognitive impairment

References

1. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive "vital signs" measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry. 2000;15(11):1021-1027.
2. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc. 2003;51(10):1451-1454.
3. McCarten JR, Anderson P Kuskowski MA et al. Finding dementia in primary care: the results of a clinical demonstration project. J Am Geritr Soc. 2012;60(2):210-217.

CLOCK DRAWING TEST

Patient Name:_____Date: _____



Richmond Agitation Sedation Scale (RASS) *

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to *voice* (≥**10 seconds**)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* (<**10 seconds**)	
-3	Moderate sedation	Movement or eye opening to *voice* (**but no eye contact**)	
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation	Physical Stimulation
-5	Unarousable	No response to *voice or physical* stimulation	

STOP – Bang Scoring Tool

To Detect Suspected Obstructive Sleep Apnea (OSA)

Directions for Use: Ask your patient the following questions.

Snore **T**ired **O**bserved **P**ressure **B**MI **A**ge **N**eck **G**ender	1. Do you **S**nore loudly? *(louder than talking or loud enough to be heard through closed doors)*	Yes / No
	2. Do you often feel **T**ired, fatigued, or sleepy during daytime?	Yes / No
	3. Has anyone **O**bserved you stop breathing during your sleep?	Yes / No
	4. Do you have, or are you being treated for, high blood **P**ressure?	Yes / No
	5. **B**MI more than 35? *(see BMI chart on reverse side, ht (in)_____ wt (lbs) _____)*	Yes / No
	6. **A**ge – Over 50 yr old?	Yes / No
	7. **N**eck circumference greater than (17"-male) or (16"-female) ?	Yes / No
	8. **G**ender- Male / or Post-Menopausal?	Yes / No

Acuity: Five "Yes" responses place the patient in the category of suspected high risk Of having **O**bstructive **S**leep **A**pnea (OSA).

Microword.mjh 3/16