Examining the Association Between Pre-existing Sleep Disturbance and Postoperative Delirium

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Principal Investigator: Oluwaseun Johnson-Akeju, M.D., M.M.Sc
Co-Principal Investigator: Jason Qu, M.D.

1. BACKGROUND AND SIGNIFICANCE

Post-operative delirium (POD), commonly encountered after surgery,[1] is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition not explained by a preexisting neurocognitive disorder.[1 2 2] Although the increased mortality rates ascribed to delirium remain debatable, delirium remains a leading cause of preventable morbidity in hospitalized elderly patients. It is also associated with prolonged hospitalization, prolonged institutionalization, and long-term cognitive deficits. The total healthcare cost attributable to delirium is estimated between $143 and $152 billion annually. Thus, principled strategies to pre-emptively identify and target patients at risk for delirium may result in significantly improved peri-operative outcomes.

Sleep is a naturally occurring state of decreased arousal that is crucial for normal immune and cognitive function.[3] Basic science and clinical studies suggest sleep disturbance as a modifiable risk factor for post-operative delirium (POD). Sleep deprivation, which is associated with increased pro-inflammatory cytokine levels including interleukin-6,[4-6] precedes the onset of delirium in some patients.[7 8]A recent investigation linking brain activity of microglia, astrocytes, interleukin-6 and delirium in humans,[9] suggests a mechanistic link between sleep deprivation, brain inflammation and delirium. Further, conditions associated with delirium are characterized by activation of the inflammatory cascade with acute release of inflammatory mediators.[10-24] Increasing age is a significant risk factor for the development of delirium. Notably, aging is associated with activated brain glia cells.[25 26] Following a systemic challenge such as critical illness, these activated glia have been suggested to facilitate an exaggerated neuroinflammatory state that predisposes to delirium.[25-28] Thus, as systemic inflammation may be involved in the pathophysiology of delirium, sleep disturbance may constitute a modifiable risk factor for POD. However, structured studies are necessary to make clear the extent to which this association exists and is modifiable.

Systematic Literature Search

We conducted a systematic search into the association between sleep disturbance and POD. The search included patients across a range of surgical specialties. The aim of the search was to capture studies that assessed a history of sleep disturbance and POD. Published literature were searched using strategies devised by a librarian using a combination of standardized terms and keywords, and were implemented in Pubmed, Embase, CINAHL, Web of Science and Cochrane from inception until May 31st, 2017. We identified 1,238 citations (328 studies in the MEDLINE database (PubMed), 939 in EMBASE, 86 in CINAHL, 266 in Web of Science and 76 in the Cochrane Library Database), and included 12 unique studies enrolling 1,878 patients. The studies were methodologically diverse with respect to metrics that were used to diagnose sleep disturbance and POD.

Search Methodology Summary

All studies were reported between 2001 and 2015. They included seven prospective cohort studies[29-35] and five retrospective studies.[36-40] Nine studies had a sample size greater than or equal to 60.[30 31 33-35 37-40] The largest study was a retrospective cohort study involving 432 patients, [40] while the smallest was a prospective cohort study with 40 patients.[29] Four studies specified obstructive sleep apnea as the type of sleep disorder evaluated.[30 32 33 37] However, the other studies did not explicitly specify the type of sleep disorder that was evaluated.[29 31 35 36 38-41] Eight studies assessed pre-operative sleep disorder,[29 30 32 33 36-38 41] three studies assessed sleep disorder immediately post-surgery but before the onset of delirium,[35 39 40] and one study assessed sleep disorder occurring after the onset of delirium.[31] Five studies evaluated orthopedic surgeries,[30 34 36 37 39] four studies evaluated cardiac surgeries[29 31 33 35] and others evaluated thoracic and non-cardiac surgeries.[32 38 40] Eight studies utilized the Confusion Assessment Method (CAM), a standardized evidence-based tool, [20, 21] to diagnose delirium;[29 30 32-35 38 39] two studies used the Diagnosis and Statistical Manual of Mental Disorders (DSM-IV);[31 40] and two studies utilized patient chart records and information obtained from caregivers to diagnose delirium.[36 37] We excluded cross-sectional studies, case reports and studies not reported in English language.

Pooled Analysis Summary

A total of 1,199 patients and 244 cases of delirium were analyzed. We found that the pooled odds ratio for the association between sleep disturbance and POD was 5.24 (95% CI: 3.61 to 7.60, p <0.001; I^2=0.0%, p=0.76). The pooled odds ratio for the association between pre-delirium sleep disturbance and POD of 5.24 (95% CI: 3.61 to 7.60, p <0.001; I^2=0.0%, p=0.76; Fig 2b) was statistically significant. The odds ratio associated with obstructive sleep apnea and unspecified types of sleep disorder were 4.75 (95% CI: 2.65 to 8.54, p <0.001; I^2=0.0%, p=0.85), and 5.60 (95% CI: 3.46 to 9.07, p <0.001; I^2=0.0%, p=0.41), respectively. We conducted a sensitivity analysis using risk ratios obtained from the prospective studies, [29 30 32-34 42] and found that the pooled risk ratio for the association between sleep disturbance and POD of 2.90 (95% CI: 2.28 to 3.69, p <0.001; I^2=0.0%, p=0.89; Fig 5) was significant.

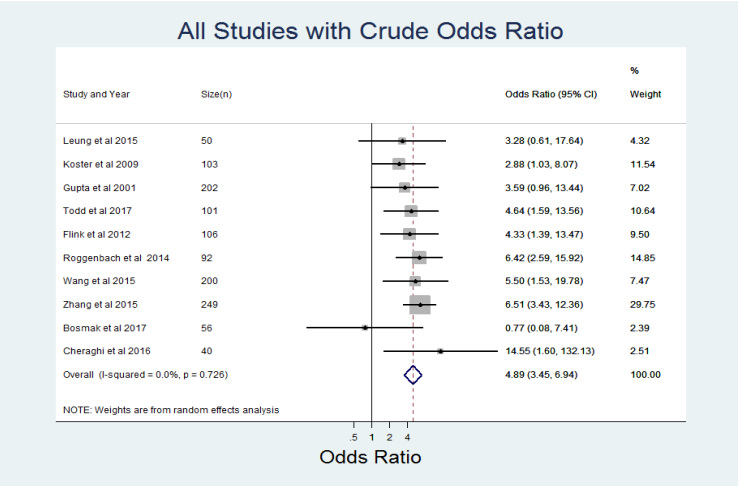

Figure 1. Pooled analysis of studies with crude odds ratio

Evans et al., in a pilot prospective study that used EEG recordings to objectively study predictors of POD, found that diminished sleep time and increased sleep latency on POD 1 is associated with increased incidence and severity of delirium.[43] Sleep disturbance is a hallmark feature of the postoperative period,[44-48] and results from this study do not resolve whether pre-existing sleep disturbance is associated with an increased incidence of POD. Other studies that have evaluated the association between sleep disorder and delirium have utilized measures such as wrist actigraphy or the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep disturbance. Unfortunately, the use of actigraphy or the PSQI in isolation do not provide accurate details on sleep quality or microstructure dynamics of sleep such as slow-delta oscillations, sleep spindles, K-complexes or REM alpha oscillations. These dynamics, which may aid the pre-emptive identification of patients that are prone to developing POD, can be obtained using a portable sleep polysomnography (PSG) device.

Therefore, we aim to study the association between preoperative sleep disturbance and POD. Our central hypothesis is that preexisting sleep dysfunction will correlate with incidence of POD. To enable assessment of objective sleep quality metrics, our cohort will be comprised of patients admitted to the hospital prior to surgical procedures. We will perform cognitive and delirium assessments, polysomnography and blood sample collection peri-operatively. Additionally, previous research has demonstrated a clear link between infection and sleep apnea. Thus, we will track subjects' postoperative infection rates in order to assess the generalizability of this outcome to sleep disturbance overall. At the conclusion of this study, we will have expanded our knowledge of the pathophysiology of POD.

2. SPECIFIC AIMS

The specific aims of this study are:

AIM 1: To use PSG and a validated sleep questionnaire to characterize sleep quality in POD patients

Hypothesis 1.1. POD will be associated with significantly decreased pre-operative total sleep time

Hypothesis 1.2. POD will be associated with a pre-existing history of sleep disruption as measured by the Pittsburgh Sleep Quality Assessment (PSQI)

AIM 2: To use serum profiling to understand the association between POD and circadian disruption

Hypothesis 2.1. POD will be associated with decreased am mRNA transcript levels of clock genes (Bmal1, Clock, Per1 and Per2).

3. Subject Selection
Primary inclusion criteria for patients: 1) age ≥ 60; 2) inpatient and scheduled for surgical procedure at MGH.
Primary exclusion criteria for patients: 1) blindness, deafness or the inability to speak English; 2) inability to provide informed consent.
Primary objective drop for patients: 1) post-operative intubation >24 hours.

4. Subject Enrollment
Recruitment: This study will be performed at the Massachusetts General Hospital in Boston, MA. We will enroll 100 male and female patients into the study. Cardiac surgical patients and orthopedic trauma patients represent the primary surgical patients that are admitted to the hospital prior to their surgical procedures. Thus, we will screen cardiac and orthopedic surgical schedules to identify potential eligible subjects. We will engage members of the patient's clinical care team to ask the patient if he/she is willing to have a study team member approach him/her to discuss a research study. This initial care patient contact will be performed by cardiac or orthopedic clinical staff (M.D., P.A, N.P, R.N), cardiac or orthopedic anesthesia care providers (M.D., C.R.N.A, S.R.N.A), or hospital geriatric clinicians (M.D., P.A, or N.P). Study team members will only approach patients that are interested in learning more about the study. They will explain the details of the study and provide a flyer summarizing study procedures to the patient. Formal written consent will be obtained prior to any study related procedures.

Retention: All subjects who provide written consent but later decline participation in the study will not be subject to any study-related follow-up.

Remuneration: There will be no monetary remuneration for this study.

Procedure for informed consent: Members of the patient's clinical care team will briefly introduce the study to the patient. Study team members will only approach patients that are interested in learning more about the study. Study team members will explain the details of study and provide a flyer summarizing study procedures to the patient. If the study team member is a non-physician (i.e. clinical research coordinator), he/she will explicitly offer the patient an opportunity to speak to physician investigators. The study team member will review and discuss the details of the research study with the patient using the informed consent document as a guide. The discussion will include all the required elements of informed consent. A formal written consent will be obtained only after all questions and concerns have been addressed.

Treatment Assignment and Randomization: Not applicable.

5. Study Design
Pre-operative Visit: We will obtain a written consent prior to conducting the Long-CAM, PSQI, Patient Health Questionnaire (PHQ-9), Trust in Physician Scale (TPS) and the abbreviated Montreal cognitive assessment. Next, we will place a portable PSG device at approximately 7 pm to record neurophysiological data using the Compumedics Portable PSG monitoring device. Due to clinical care concerns, patient acuity, patient unavailability and several other unforeseen factors, PSG may not be placed on all study subjects. A minimum of the following electrodes will be placed for sleep staging: Two central channels (C3 and C4), two electrooculogram channels to capture lateral eye movements, and two reference channels over the left and right mastoids.

Post-operative Day 0: PSG electrodes will be removed at approximately 6am. Additionally, we will obtain approximately 13ml of blood to be processed into mRNA to understand the association between peri-operative circadian cycle disruption of four circadian clock genes (Bmal1, Clock, Per1 and Per2) and POD. The PI will ensure that appropriate privacy and de-identification procedures are in place for the collection and storage of blood. All MGH ORs are equipped with a four-channel frontal EEG device (Sedline, Masimo, Irvine, CA). Thus, we will collect intraoperative routine EEG data that is recorded as part of routine anesthetic management. Due to clinical care concerns, patient acuity, Sedline electrode unavailability and several other unforeseen factors, blood and Sedline EEG data may not be obtained on all study subjects.

Post-operative Days 1-3: On post-operative day 1, we will obtain approximately 13ml of blood as a post-surgical measure of mRNA levels to understand the association between peri-operative circadian cycle disruption of four

circadian clock genes (Bmal1, Clock, Per1 and Per2) and POD. Delirium assessments may be conducted twice daily (AM and PM with at least 6 hours between tests) beginning on postoperative day 1 using the Long Confusion Assessment Method (CAM).[49 50] PHQ-9 will be assessed on POD 3 only. Subjects who elect to withdraw from the study during their hospital stay will be re-approached by the study team within 8-24 hours of study withdrawal. The study team member will elicit the reason for study discontinuation and confirm the withdrawal decision. This visit serves to ensure that the withdrawal decision was made during an informed and non-delirious cognitive state. In the event that a subject finds it difficult to complete an assessment (i.e. pain, clinical intervention), only the long-CAM domains necessary to dispel the presence of delirium will be assessed (i.e. acute onset, inattention, disorganized thinking and altered level of consciousness). Subjects who cannot complete this shortened assessment will be re-approached several hours later. Long-CAM assessments for subjects who are reintubated for clinical care or for further surgical management will be considered missing data.

Post-operative Day 30: PHQ-9 and the Pain Interference 8a (PROMIS SF v1.0) questionnaires will be administered over the phone. Subjects' infection rates will also be tracked postoperatively.

6. DATA ANALYSIS PLAN

Hypothesis tests will be performed using a two-sided significance level (type I error) of $\alpha=0.05$. Aim 1 (Hypotheses 1 and 2) outcome will be evaluated using binominal regression models with adaptive elastic net penalty to examine the association between total sleep time and POD. Patient characteristics of interest (i.e. age, gender, baseline cognitive score, pain, depression symptom score, frailty index, Charlson comorbidity index) will be included into this regression model. Because missing data rarely occur entirely at random, we will assess associations between patient characteristics with respect to missing data. If patients with at least one missing outcome value are different from those with complete outcomes data, we will use multiple imputation to assign values to missing data risk factors and outcomes in regression modeling. Aim 2 (Hypothesis 1) Wilcoxon rank-sum tests with corrections for multiple comparisons will be used to assess differences for each analyte or transcript. In other exploratory analysis, we will assess differences in the EEG (PSG and intraoperative) dynamics of delirious and non-delirious patients. To assess statistical significance for the difference in EEG spectra at each frequency, we will compute the 99% confidence interval of the median difference between groups by using an empirical bootstrap approach. The null hypothesis will be rejected only if the confidence interval of the median difference at each frequency exceeds the significance threshold over a contiguous frequency range $\geq 2W$. We will also characterize differences in sleep microstructure dynamics (i.e. spindle power, spindle rate, spindle peak frequencies, slow-delta phase- spindle amplitude modulation) between groups using algorithms developed in-house.

7. POWER ANALYSIS

The primary objective of this trial is to detect a difference in the duration of sleep between delirious and non-delirious patients. Assuming a delirium event rate of 15%, a type I error of 0.05, power of 0.90 and a SD of 60 minutes, n = 13 patients with delirium and 78 patients without delirium will enable us to detect an absolute total sleep time difference of 60 minutes between both groups (i.e., 360 minutes versus 300 minutes). Therefore, anticipating a dropout rate of approximately 10%, we aim to recruit 100 subjects.

8. RISK AND DISCOMFORT

PSG risks: The risks associated with PSG electrodes are redness, irritation at placement site, unpleasant odor from glue, and annoyance from having electrodes attached to the body.

Questionnaire risks: Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning.

Data risks: Procedures are in place to reduce the likelihood of a breach of confidentiality including the de-identification of data and storage of data only on partners approved devices/portals. However, there is a small risk that people outside of this study may be exposed to information about study subjects.

9. POTENTIAL BENEFITS

Subjects will have no direct benefit from taking part in this study. Findings from these studies will help advance our understanding of the neurobiology of delirium. We envision that in the future the information obtained from the proposed research will enhance the diagnosis and management of POD.

10. MONITORING AND QUALITY ASSURANCE

Because this study is a physiological study of sleep neurophysiology, as opposed to a clinical trial, the principal investigator and co-investigators will be responsible for monitoring and quality assurance of the study. In conjunction with the research assistants, weekly meetings will be held and documented. Current subjects in the study will be discussed at each meeting, and charts will be reviewed for completeness. The team will evaluate the progress of the study, verify that the rights and well-being of the subjects are protected, verify that the reported study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments.

Serious Adverse Events: Expedited review will occur for all events meeting the FDA definition of SAEs – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution. Reporting to the IRB will be done within 24 hours of the SAE.

Study Stopping Rules: If at any time during the course of the study, the PIs or CO-Is judge that risk to subjects outweighs the potential benefits, the PI/CO-Is shall have the discretion and responsibility to recommend that the study be terminated.

AE Reporting Guidelines: Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines, as well as the RDRC within 5 days.

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