SedLine EEG-Guided Depth of Anesthesia: Effect of Anesthetic Dosage

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1.0 Background & Rationale

Electroencephalogy (EEG) was first described in 1875 in dogs and apes.[1] The technology was shortly after applied to humans and within 10 years the changes to the EEG tracing was studied when certain sedatives drugs were administered.[1] Over the last several decades EEG based monitors have been developed with the hopes of aiding anesthesiologists at evaluating the "depth" of a patient's anesthetic while under general anesthesia. Currently, typical anesthesia practice is to measure and adjust depth of a general anesthetic based on the medications administered and hemodynamic parameters of the patient, potentially exposing high risk patients to un-needed excessive depths of anesthesia which can potentially result in adverse post-operative outcomes.[2,3]

The use of intraoperative EEG monitoring to guide the depth of an anesthetic seems to have the potential to reduce the total dose of anesthetic required. Use of the EEG based monitor called the Bispectral Index Monitor (BIS Monitor) in an older study was shown to reduce sedative use and total cost in ICU patients who were receiving intravenous infusions of sedatives and neuromuscular blockers.[4] And recently, the BIS monitor was used in a large randomized control study in order to investigate whether providing an anesthetic guided by an EEG based monitoring device in individuals at high risk for postoperative delirium would significantly reduce postoperative delirium. While the primary results reported a negative results, the study did have other interesting findings – most notably a significant reduction in the dosage of volatile anesthetic (the primary anesthetic agent used in general anesthetic procedures). Furthermore, the study showed using a protocolized adjustment in anesthetic depth using an EEG based monitoring system for guidance in human subjects resulted in no significant change in adverse outcomes in a large trial of patients in this population[5]

The Masimo Sedline Brain Function Monitor (SedLine), is an EEG based monitoring device that is approved by the Food and Drug Administration for monitoring of brain function under anesthesia. This new generation device provides processed EEG information (as the BIS monitor does) as well as raw EEG waveforms and a Density Spectral Array (DSA) display – providing information of the power of the EEG signal over a spectrum of frequencies. This additional

information allows the anesthesiologist to evaluate the depth and appropriateness of the anesthetic in detail.[6]

We hypothesize that the use of a Sedline processed EEG monitor (using a protocolized adjustment in anesthetic depth using this EEG monitoring device) will allow anesthesiologists to reduce the doses of anesthetic drugs during general anesthesia in patients 65 or older (resulting in less exposure of anesthetic medications to a high-risk patient population as well as a potential reduction in cost). In addition, an added benefit of safely reducing the amount of volatile anesthetic used in everyday anesthesia practice may prove to also be helpful to environment and cut down on their contribution to ozone layer depletion.[7]

We plan to investigate this hypothesis in a study in which we will randomize patients to either anesthetic drug doses guided by Sedline processed EEG characteristics or standard anesthesia care. We plan to evaluate the hypothesis that SedLine monitoring reduces anesthetic drug doses.

Of note, we have recently completed a pilot study with a similar study design and have confirmed we have the capabilities and resources to conduct this study.

2.0 Objective(s)

2.1 Primary Objective

The primary objective of this study will be to determine whether an anesthetic guided by the Sedline EEG based monitor will reduce the total dosage of anesthetic under general anesthetics in this population (patients 65 or older).

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measures

The primary outcome measured will be the total average percent of volatile anesthetic (sevoflurane) utilized while subjects are under anesthesia (maintenance phase). The time considered “maintenance phase” under general anesthesia will be measured starting 5 minutes after the induction agents are administered and measurements will stop following

administration of neuromuscular blocker reversal drugs. Data will be collected from computerized anesthetic records.

3.2 Secondary Outcome Measures

The secondary outcomes measured will be the total dosage of hypnotic agents administered while in the maintenance phase of anesthesia. These agents include: midazolam, lorazepam, diazepam, fentanyl, sufentanil, ketamine, propofol, morphine, and hydromorphone. Additional secondary outcomes measured will include episodes of hypotension (this will be defined as an episode of mean arterial pressure of <65 mmHg), total dosage of vasopressors (such as phenylephrine, ephedrine, vasopressin, or norepinephrine), and the occurrence of EEG isoelctricity, or burst suppression. SedLine images will be recorded for both groups in order to compare rates and duration of burst suppression events. Of note, if the patient has a functioning arterial line in place, we will use measurements from this in preference to a non-invasive blood pressure cuff).

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- Patients undergoing a scheduled surgery (laparotomy, hepatobiliary surgery, gynecologic surgery, and/or urologic surgery procedures) at Indiana University Health University Hospital that is expected to have at least a 3 day post-operative hospital stay.
- ASA class 1, 2, 3, or 4.
- Age 65 years or older.
- Male or Female
- Surgical procedure requiring general anesthesia.

4.2 Exclusion Criteria

- Any previous diagnosis of dementia or other cognitive impairment.
- Any patient undergoing emergency surgery.
- Any patient undergoing surgery who is currently an inpatient.
- Patient refusal to participate in study.

- Any patient undergoing surgery that would prevent placement of the Sedline monitor leads (for example – surgery on the patient's forehead/scalp).
- Any physical, mental, or medical conditions which, in the opinion of the investigators, may confound the ability to assess the patient for delirium in the post-operative period.

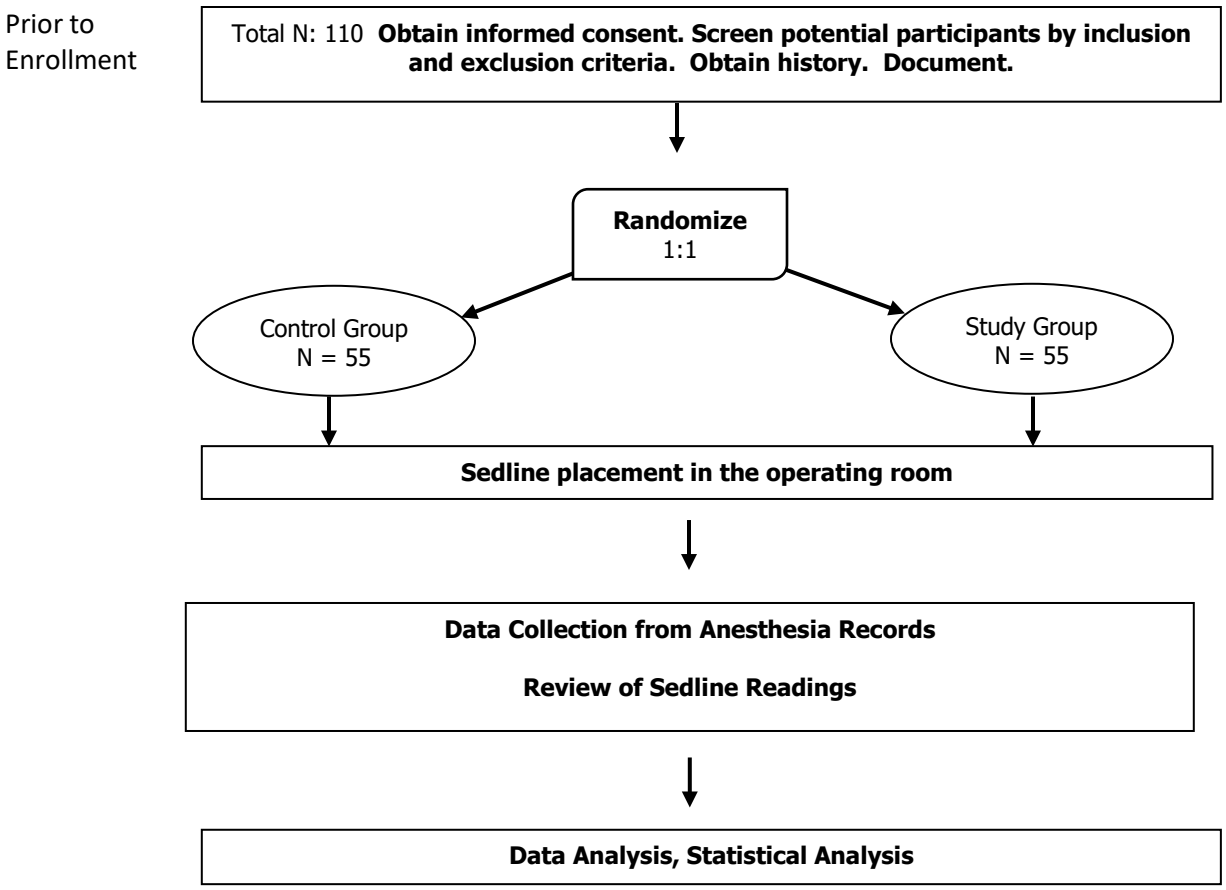
5.0 Study Design

- Prior to study commencement, select anesthesiologists from the Indiana University Health University Hospital Anesthesia Group will be trained on usage and interpretation of the Sedline. Training for this group of providers will include a PowerPoint presentation recording presented by Dr. Wolfe to aid in interpretation of the Sedline data. Representatives from the study will also be available as needed to answer questions as they arise. They will also be given certain guidelines for anesthetic administration based on the processed EEG findings. These will include the following:
  - Usage of sevoflurane as the primary anesthetic agent
  - Reducing sevoflurane dosage if the EEG indicates signs of burst suppression (excessive anesthetic depth), if the PSI on the Sedline reads less than 25, or if hypotension is occurring and the anesthesia provider believes that depth of anesthesia may be a contributing factor.
  - Increasing sevoflurane dosage if the EEG pattern is not consistent with general anesthesia (not enough depth of anesthetic).
- We anticipate 5-10 anesthesiologists being included in this group. Given that this group of anesthesiologists will be assigned to both groups (study and control), the size of the groups, and the instructions regarding the maintenance phase of anesthesia, diazepam, and dexmedetomidine we anticipate the difference in practice patterns between providers will not affect the data. We will discourage the use of nitrous oxide as well as IV anesthetics including midazolam. In the control group, the anesthesiologist will be asked to provide the anesthetic as he or she would under normal care with the exception of avoidance of nitrous oxide and IV anesthetics during the maintenance phase of anesthesia. We anticipate

that the surgical procedures included in this study will be similar enough that the type of surgical procedure will not affect anesthetic dosing.

We will identify subjects who meet inclusion/exclusion criteria on the day of surgery. Following explanation of the study and completion of informed consent, the patient will be randomized into 1 of 2 groups – study group or control group. We plan to use block randomization to keep the groups relatively balanced throughout enrollment. The patient will then be taken to the operating room in normal fashion. Prior to the induction of anesthesia, the Sedline monitor will be placed on the patient's head to ensure the monitor is working properly. For those in the study group, the monitor will be in full view of the anesthesiologist administering the anesthetic. For those in the control group, an apparatus will be placed over the monitor will not be in view of the anesthesiologist. The monitor will still be processing and recording EEGs for both groups. The patient will then be placed under anesthesia and surgery will commence. While under anesthesia, images of the display screen of the Sedline will be collected for later evaluation. Once the surgery is complete, the patient will have the monitor removed and image capture of the display will be stopped prior to exiting the operating room.

Following finalization of the anesthetic record by the staff anesthesiologist, the primary and secondary outcomes will be collected by investigators. The images of the Sedline EEG monitor will also be reviewed by investigators to ensure that appropriate depth of anesthetic was utilized throughout the maintenance phase of anesthesia in the study group. Blinding of the study investigators will not be possible due to the manner in which images of the Sedline readings are collected (it will be readily apparent on the images whether the SedLine data was readily available or concealed from the anesthesia team).



6.0 Enrollment/Randomization

The surgical schedule will be assessed daily to identify patients scheduled for surgery who may be eligible to participate in this study. A member of the research team, either principal investigator, co-investigator, or study coordinator will approach the potential subject the day of their scheduled procedure. They will conduct the visit in a private area such as a patient's room, secluded hospital room, or an area free from the general public. All study procedures will be reviewed, questions answered, and the subject will be given ample time to discuss and determine if they will sign the consent to participate in the study.

We plan to enroll 110 subjects in this study. Patients will be randomized to either the control or the study group.

7.0 Study Procedures

As noted above, following enrollment on the day of surgery, the Sedline device will be placed on the patient just prior to the induction of anesthesia. Anesthesia

will then be induced, and surgery will proceed as usual. Images will be captured of the display of the Sedline monitor while under anesthesia during the surgical procedure using a recording device. The study group will have the Sedline readings visible to the anesthesiologist in the room and will use the Sedline to guide anesthetic depth. The control group will have the monitor out of view and not visible to the anesthesiologist, but the images of the Sedline monitor will be recorded.

Once the procedure is complete, the Sedline monitor will be removed from the patient and the collection of images will be stopped prior to the patient exiting the operating room.

Following the finalization of the anesthetic records, the desired data will be collected from the anesthetic record. The images of the Sedline readings will also be reviewed by investigators to confirm an appropriate depth of anesthetic was achieved in the study group.

8.0 Study Calendar

We will begin to enroll patients once we receive approval for study commencement from the IRB and following selection/training of the anesthesiology study team. We plan to enroll 110 patients total. Following data collection of the last patient the study will be closed.

9.0 Reportable Events

Patients will be monitored by the primary team during the postoperative period, and any adverse events or unanticipated problem will be reported to the anesthesia service and research team. All unanticipated problems will be reported to the IRB committee using the prompt reporting form.

10.0 Data Safety Monitoring

In order to protect the privacy of our patients, any data which has identifiable patient data attached to it will be stored in the REDcap system. Of note, the images obtained from the Sedline monitor display will not contain ANY identifiable patient data (these images will be stored on a research computer).

11.0 Study Withdrawal/Discontinuation

The patient can withdraw from the study at any time by contacting the research team or the anesthesia service.

12.0 Statistical Considerations

Primary outcome: total average percent of volatile anesthetic (sevoflurane) utilized while subjects are under anesthesia.

Secondary outcomes: total dosage of hypnotic and opioid agents administered while in the maintenance phase of anesthesia. These agents include midazolam, lorazepam, diazepam, fentanyl, sufentanil, ketamine, propofol, morphine, and hydromorphone during the maintenance phase of anesthesia. Additional secondary outcomes measured will include episodes of hypotension, episodes of burst suppression, and total dosage of vasopressors and hypnotic agents.

Statistical analysis will be performed using a standard statistical program (SAS or Stata). All data will be summarized (either means and standard deviations or medians and quartiles for continuous variables; frequencies and percentages for categorical variables) by treatment group. Demographic data will be compared between the two groups using t-test or Wilcoxon rank sum test as appropriate for continuous variables, and chi-square tests or Fisher's exact test for categorical variables as appropriate. The primary outcome, total average percent of volatile anesthetic (sevoflurane) utilized along with secondary outcomes of total dosage of hypnotic agents administered, will be compared between the two groups using t-test or Wilcoxon rank sum test as appropriate. To account for the possible effects of covariates age, sex, and BMI and anesthesiologist, a mixed model with a random effect for anesthesiologists will be employed. Here we could treat surgery type and duration as fixed effects if needed. The secondary outcome of episodes of hypotension which will be compared using chi-square tests or Fisher's exact test for the occurrence of hypotension. Distributions of the continuous variables will be examined, and a transformation of the data (e.g. natural logarithm) or nonparametric tests will be used as necessary. A 5% significance level will be used for all comparisons.

From a similar study using an outcome (minimum alveolar concentration or MAC) comparable to ours we were able to estimate a coefficient of variation for total average percent of volatile anesthetic to be 0.15.[4] Working with a feasible sample size of 44 per group and using a power of 90%, 5% significance level, and employing a two-sided test, the study will be able to detect a reduction of 10% in for total average percent of volatile anesthetic between the two groups. Assuming a dropout rate of up to 20%, we will enroll up to 55 patients per group for this study. Here we used a "Tests for the Ratio of Two Means" using sample size software PASS 2019.

13.0 Statistical Data Management

Primary data will be collected via review of electronic medical records, anesthesia records, and screenshot images of the SedLine EEG monitor and will be stored electronically in REDCap. The storage location will be backed up automatically. Quality assurance steps will include, built-in range checks and testing of the database by the study team prior to moving to production mode. The following quality control methods will be used: 1) single data entry with random checks of accuracy; and 2) extraction and cleaning of data that will be used for analysis every 6 months.

14.0 Privacy/Confidentiality Issues

Any private data or potentially identifiable patient data will be stored in the REDcap system.

15.0 Follow-up and Record Retention

The study will start upon approval of the IRB and following selection/training of the anesthesiology study team and the study will stop following completion of data collection from the 110th subject. We anticipate that this should not take longer than 24 months.

16.0 References

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