Bispectral Index: A Comparison of Bifrontal Montage Agreement

NCT04062240

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General Study Information

Principal Investigator: Dr. Matthew Ritter

Study Title: Bispectral Index: A Comparison of Bifrontal Montage Agreement

Protocol version number and date: version 1.0 - 5/19/2019

Research Question and Aims

Hypothesis: Bispectral index (BIS) sensors applied in a bilateral frontal montage will show similar readings for the duration of the study.

Aims, purpose, or objectives: The objective of this study is to determine measurement difference and variability of BIS values when monitored in a bilateral frontal montage. The results will be utilized to determine a sample size for further study.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc.*):
BIS monitors are FDA approved to gauge depth of sedation by analyzing segments of electroencephalogram (EEG) waves. The BIS monitor utilizes a proprietary algorithm to process the EEG information second by second, and outputs a number (0-100) that corresponds with a patient's level of consciousness. A level of 0 indicates no EEG activity; a level of 100 indicates awake EEG activity. Several studies demonstrated that BIS monitors may not be useful in paralyzed patients, as patients who were paralyzed and not sedated unexpectedly showed a large decrease in their BIS values following administration paralytic medications.[2-4] Vivien et al[2] found BIS values dropped an average of 24 points in already sedated patients when the patients were given paralytics. In the same year, Messner and colleagues paralyzed unsedated volunteers and found a dramatic drop in BIS values until paralysis wore off or was reversed.[3] Schuller et al[4] repeated the Messner experiment and found similar results with 18 of 20 unsedated volunteer's BIS values dropping to levels expected of patients who were sedated. These results suggest that BIS monitors are integrating electromyography (EMG) data into its algorithm to derive a BIS value. Our hypothesis is that a BIS monitor commenced after paralysis, thereby lacking exposure to any "awake" EMG activity, will result in a cleaner data set and more accurate representation of a patient's level of sedation. Studying in this manner will require the subject to wear two BIS sensors in a frontal montage. The manufacturer of the sensors gives no guidance as to which side of the forehead an individual sensor is placed, and no studies demonstrate BIS validity with the use of concurrent sensors. The purpose of the present investigation is to assess the measurement difference and variability associated with use of concurrent bifrontal BIS sensors. The data obtained will be used as a framework for additional BIS study (separate IRB form to follow this research study).

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Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

We are proposing a nonrandomized, prospective, comparative, observational study in patients undergoing elective cardiac surgery with general anesthesia.

Patients will be screened for eligibility based the provided inclusion/exclusion criteria. Informed consent will be obtained.

The current standard of care in cardiovascular surgery calls for the placement of a BIS sensor to the patient's forehead per the manufacturer's recommendation on arrival to the operating room. The sensor is then connected to the BIS LoC2 module, which is connected to the BIS II module on the anesthesia monitor (Philips MX800). Our study will add an additional BIS sensor to the patient's forehead connected to a second monitor (Philips MX550) fitted with the same BIS LoC2 and BIS II modules as the anesthesia monitor. The sensors will be delineated as left (L) and right (R). The two monitors will be synced for time. After ensuring appropriate skin contact and signal quality of both sensors, BIS monitoring will commence. BIS readings will be available every 12 seconds during the 5 minute duration of the study. For the current analysis, data obtained from the BIS sensor at each interval will include BIS value, Signal Quality Index, EEG level, EEG Suppression Ratio, EEG asymmetry and Burst Suppression Level. Our primary interest, though, is the BIS value.

Potential limitations to the study include the following:

- Convenience sampling with no randomization
- Limited frequency of sampling (12 seconds) compared to other studies due to equipment limitations
- Manual transcription of data from monitor to data collection sheet; manual entry from data collection sheet to digital spreadsheet.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

- The study will be performed in the cardiac operating room.
- Dr. Matthew Ritter is the project advisor and primary investigator. He is available as needed for questions, guidance, and troubleshooting, and oversight.
- Sean Loughlan, CRNA is the faculty advisor for the project, serves as a liason between the clinical area, project advisor, and research activities. He helped find opportunities related to funding, and will provide guidance related to dissemination.
- Wade Kreun, SRNA will obtain informed consent and perform all data gathering activities.
- Equipment
    - BIS Quatro sensor (Medtronic, Dublin, Ireland)
    - BIS LoC2 module (Medtronic, Dublin, Ireland)
    - Intellivue MX550 monitor (Philips, Madison, WI)
    - Intellivue MX800 monitor (Philips, Madison, WI)
    - IntelliVue M1034B Bispectral Index BIS II Module (Philips, Madison, WI)

- The portable anesthesia transport monitor (Philips MX550) assigned to each operating room and fitted with the BIS LoC2 and BIS II modules will be used as the secondary monitor
- Statistical analysis will be performed with JMP software, with support provided by Darrel Schroeder from the Center for Clinical and Translational Science.

- Budget: This study has no budgetary needs as it utilizes already existing equipment and materials.

- A poster will be generated to disseminate results. Per institutional guidelines for poster development and preparation, Media Support Services will provide support and print the poster at no charge.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 15 subjects

Subject population (children, adults, groups): adults undergoing elective cardiovascular surgery

Inclusion Criteria:
1. Adult patient having elective cardiac surgery.

Exclusion Criteria:
1. Patient refusal.
2. Pediatric patients.
3. Emergency procedure.
4. Patients with known or suspected carotid or cerebrovascular disease.
5. Patients with prior stroke.
6. Skin condition or anatomy preventing proper sensor placement.

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Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☒ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

(3) Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range:

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☒ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name		
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☒ None

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Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement: The sample-size for this investigation was determined after weighing statistical considerations along with the logistical and resource constraints inherent in the study design. A sample-size of 15 patients will provide a total of 450 paired data-points that will be used for the analysis.

Data Analysis Plan: For each patient, 30 data points will be obtained for each parameter monitored per BIS sensor. The agreement between (L) and (R) sensors will be assessed using the methods of Bland and Altman, as Bland-Altman plots allow identification of any systematic difference between measurements and possible outliers.[4]

Endpoints
Primary: Difference and variability of BIS values obtained from (L) and (R) sensors.

Secondary: Difference and variability of the other parameters measured from (L) and (R) sensors: Signal Quality Index, EEG level, EEG Suppression Ratio, EEG asymmetry and Burst Suppression Level.

References:

1. Messner M, Beese U, Romstöck J, Dinkel M, Tschaikowsky AK. The bispectral index declines during neuromuscular block in fully awake persons. *Anesth & Analg*. 2003;97(2):488-491. doi:10.1213/01.ane.0000072741.78244.c0.

2. Schuller P, Newell S, Strickland P, Barry J. Response of bispectral index to neuromuscular block in awake volunteers. *Brit J Anaesth*. 2015;115:i95-i103. doi:10.1093/bja/aev072.

3. Vivien B, Maria SD, Ouattara A, Langeron O, Coriat P, Riou B. Overestimation of bispectral index in sedated intensive care unit patients revealed by administration of muscle relaxant. *Anesthesiology*. 2003;99(1):9-17. doi:10.1097/00000542-200307000-00006.

4. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *J R Stat Soc Ser D*. 1983;32(3):307-317. doi:10.2307/2987937.