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Prevalence of Chronotropic Incompetence in Patients with Unstable Angina and Anhedonia

A. Study Purpose and Rationale

Cardiovascular disease is the number one cause of death in the United States and affects a large number of Americans on a yearly basis. Major Depressive Disorder (MDD) is also very prevalent amongst Americans and has been shown to increase major adverse cardiac events (MACE) as well as mortality in patients with coronary heart disease with relative risk of 2.4 (95% CI 1.8-3.2) for all-cause mortality (ACM)[2, 10]. MACE is defined as a myocardial infarction (MI), urgent PCI or CABG, or unstable angina (UA) requiring admission. One in six patients with acute coronary syndrome (ACS) also has depression.

Chronotropic incompetence (CI) is the inability to adequately increase heart rate during physical exertion and is also an independent predictor of ACM in patients with ACS which includes MI and/or UA [7]. The criteria for unstable angina includes chest pain at rest for more than 20 minutes, new onset chest pain resulting in slight limitation of ordinary activity, or a progressive worsening of chest pain resulting in marked limitation during ordinary activity.

The link between depression and ACS has been studied and to further elucidate this relationship depression must be broken down into more basic components.

Anhedonia, a component of MDD, is characteristic of Melancholic depression and is defined as lacking interest in activities or people or lack of mood reactivity to previously pleasurable stimuli. Anhedonia has been shown to predict mortality in ACS patients one year after their event [3]. The focus of this project is to see if there is a higher prevalence of CI amongst patients with UA and depression than without depression. The ultimate goal is to better understand the connection between depression and ACS pts in order to be able to implement more effective treatments and therefore decrease morbidity and mortality in this population.

B. Study Design and Statistical Analysis

Data will be gathered from an observational cohort study, the Prescription Use, Lifestyle, & Stress Evaluation (PULSE) study database, lead by principle investigator Dr. Karina Davidson at CUMC. The purpose of this study is to disaggregate MDD into key sub-types, understand their biological and behavioral correlates and the mechanisms by which they lead to accelerated disease and death. The study has received NIH/NHBLI funding for the period of 9/22/2008 - 6/30/2013.

Patients with a diagnosis of ACS will be screened and randomized to the control group or experimental group depending on whether they meet the criteria for anhedonia on or before 1 month after discharge. Patients will then be followed for a period of 1 year taking into account anhedonia symptoms, medications and MACE/ACM. Cross over will be possible up to 1 month after discharge if patients are newly diagnosed with anhedonia at prior telephone evaluations. Patients that met the criteria for anhedonia at one point before the 1 month post discharge interview but then tested negative on follow up dates will remain in the experimental group. The patient's primary care doctor, with the permission from the patient, would be notified by mail if they earned a new score of $\geq$ 40 on the DBI questionnaire during the course of this study. Any patients meeting the criteria for SI/HI on screening or questionnaires would be evaluated by a psychiatrist in the hospital (Dr. Clemow contacted first) for safety.

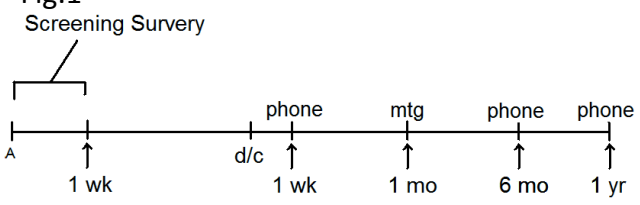
Patients recruited in the study were enrolled for a year. Patients with a diagnosis of ACS would have a screening survey done within 1 week of admission (Refer to Fig. 1 for timeline). This interview would include: informed consent, evaluation of dementia with the MMSE questionnaire, depression screening with the BDI-I, II questionnaire, alcohol abuse screening with AUDIT questionnaire, psychiatric disorder screening with questions from SCID (Structured Interview for DSM), and a review of their medications and past medical history including a past history of depression.

Three to seven days after discharge the patient would be called at home and evaluated for depression with the DISH questionnaire, the Diagnostic Interview and Structured Hamilton. This is a structured psycho-diagnostic interview used in studies of depression in post MI and other cardiac populations. It was developed for the Enhancing Recovery in CHD Patients Study (ENRICHD Trial) to eliminate redundancy between items on the modified DIS and the HAM-D and can be applied over the phone with good validity. This test could take about 10 to 30 minutes depending on whether the patient is depressed or not. After this test, a lifetime prevalence of MDD questionnaire is employed as well as questions to assess any MACE since discharge.

One month after discharge the patient returns for the baseline assessment, an in-person interview to assess if there were any depressive symptoms within the past 2 weeks with the PHQ-9 questionnaire, another review of their medications, the BDI to assess for depression at that time as well, and to assess any MACE since the last phone conversation. Any patients meeting criteria for anhedonia up to and including this point would be included in the experimental group.

At 6 months and 1 year following discharge, the patient would be called at home and again evaluated for depression with the BDI, a review of their medications would be done and MACE would be assessed since their prior telephone conversation or visit.

Fig.1



The prevalence of CI in patients referred for exercise stress testing, not including patients with heart failure, valvular heart disease, congenital heart disease or on beta blockers, has been found to be 11% in the literature [7]. Assuming 25% of patients with UA and depression have CI, using Chi-Squared Test in order to achieve a power of 80% with an alpha-error rate of 0.05 a minimum of 131 patients are needed per group. Categorical analysis can also be achieved using the Chi-squared Test. Over 500 participants have already completed the study at this point and so attaining enough participants per group should be feasible.

C. Study Procedure: N/A

D. Study Drugs: N/A

E. Medical Device: N/A

F. Study Questionnaires

Questionnaires will be implemented by clinical/research coordinators trained in CPR, HIPAA, and DISH (by Dr. Clemow) and videotaped for comparison and reliability check from time to time. New clinical/research coordinators will attend an all-day training session led by Drs. Burg, Clemow and Davidson.

Study questionnaires include:

1. BDI
2. MMSE
3. DISH
4. Lifetime Prevalence of MDD
5. MACE
6. PHQ-9

G. Study Subjects

Inclusion Criteria:

1. UA diagnosis
2. Age +18
3. Including woman and minorities
4. Exercise stress tests

Exclusion Criteria:

1. Suicidality/Personality disorder/ETOH abuse/Drug abuse
    a. AUDIT >8
2. Age <18
3. Dementia: MMSE $\leq$ 24
4. Not fluent in English or Spanish
5. Beta-blockers

6. Non-exercise stress tests
7. Terminal Illness

H. Recruitment of Subjects

Subjects will be patients at CUMC. Patients will be recruited from various services, including the CCU, ICU, ED, PA service, Medical Floors and Catheterization Lab via referrals. At that point EMR will be reviewed for exclusion criteria including: verification of ACS, terminal illness, language (does not speak English or Spanish), age less than 18, PSA and active SI/HI. If patient is deemed a good candidate then a clinical/research coordinator will approach them within 1 week of admission.

I. Confidentiality of Study Data

Patient confidentiality is incredibly important and for that matter multiple layers of security have been devised in order to secure patient privacy. All patient identifiers will be kept in a locked drawer and will be attached to a unique patient identification (ID) number also kept in a locked drawer. Patient data and questionnaires will only have their ID number and all data will be password protected. Questionnaires performed by the staff will be in private rooms, and any paperwork containing patient identifiers will be shredded.

J. Potential Conflict of Interest: N/A

K. Location of the Study

Columbia University Medical Center (CUMC) in Washington Heights which includes Columbia College of Physicians and Surgeons (P&S) and New York Presbyterian Hospital (NYPH) the Columbia Site, a 1,537 bed hospital, where the patients will be recruited. Within NYPH is the Center for Behavioral Cardiovascular Health (CBCH), the coordinating center for the study.

L. Potential Risks

Potential risks include a new diagnosis of depression which might lead to new medications provided by the PMD. Another potential risk is the need for a formal psychiatric evaluation by a psychiatrist if meet the criteria for HI or SI.

M. Potential Benefits

On the same token, an early diagnosis of depression which might lead to early intervention can also be deemed a benefit. Access to referrals and a formal evaluation by a psychiatrist would be deemed a benefit if a patient is in need of help.

N. Alternative Therapies: N/A

O. Compensation to Subjects

Patients will be paid $25 cash for completing the baseline visit during the hospitalization. If they agree to participate in different arms of the project, they can be paid up to an additional $35 cash. In total, a patient can receive up to $60 cash.

P. Costs to Subjects

Patients would be responsible for their travel costs at the 1 month visit to CUMC.

Q. Minors as Research Subjects: N/A

R. Radiation or Radioactive Substances: N/A

References

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