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# Behavioral Therapy and its Impact on Acute Stress in Ulcerative Colitis

## A. Study Purpose and Rationale

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, characterized by exacerbations and remissions of symptoms[1], and there are approximately 30,000 new cases of IBD diagnosed each year[2]. IBD consists of a grouping of Ulcerative Colitis (UC) and Crohn's Disease (CD), and the etiology of the disease involves a complex interaction between genetics and environment[3,4]. IBD is now thought to result from the body's inappropriate activation of the mucosal immune system against normal luminal flora. This irregular response is thought to be facilitated by defects in both the barrier function of the intestinal epithelium and the mucosal immune system[5].

While we have learned a great deal about IBD and its pathophysiology, the "environmental" causes of the disease flares and the mechanisms by which they act continue to be explored. Psychological stress has long been associated in an anecdotal manner with disease exacerbation [6,7,8,9]. In the 1950's, UC was even regarded as a model of psychosomatic disease [10]. Recent studies suggest that adverse life events, chronic perceived stress, and acute daily stress can increase the incidence of subsequent symptoms and disease relapse in patients with IBD [11].

Examining stress and its contribution to IBD is particularly difficult due to the study designs themselves. Numerous case studies suggest that adverse life events can be a causal factor in relapse of IBD; however, these observations are significantly limited by recall bias. Also, controlling for confounding factors has proven difficult in the past. Several researchers have attempted to conduct well-designed trials to assess stress and its relation to IBD. Bitton et al [12] showed in a prospective study of UC patients that an increased number of life stress events in the preceding months were, in fact, a risk factor for relapse within 1 yr. Similarly Mardini et al [13] in a two year prospective sample of patients with Crohn's found that depression, and, to a lesser extent, stressful life events are truly a predictor of relapse. It has also been shown that acute daily stress in IBD can be positively associated with disease relapse and exacerbation [14,15].

While these previous studies relied on surveys and are subject to various biases including recall and reporting bias, there have been several studies that attempted to evaluate real-time stress in these patients. The experiments involved creating an artificial stressful situation both physically and psychologically. One protocol involved placing a subject's hand in ice cold water and studying the physiological changes between IBD patients and healthy controls [16]. This study focused on the brain-gut axis and hypothesized that it is this axis which is hyperstimulated in the setting of stress. With hyperstimulation, the experimenters theorized that this would lead to exacerbation and symptomatology. The study focused on histological changes and found increased mast cell activation and degranulation as well as oxidative tissue injury. In similar works, Mawdsley et al [17] and Murray et al [18] used rectal mucosal blood flow (RMBF) to help

assess the extent of stress experienced by subjects during their experiments and the subsequent toll on the body. This measure is a reflection of the activity of the autonomic innervation, specifically to the gut. The theory is that a decrease in rectal mucosal blood flow would lead to ischemia and subsequent relapse. Murray [18] had previously shown that anxiety and depression can cause altered levels of autonomic innervation of the gut. Both studies were conducted using an experimental stress situation (though patient populations were different, with UC patients in one study and irritable bowel syndrome patients in another). These investigators both found a significant decrease in the RMBF in diseased patients during an acute stressor. Healthy volunteers also had a decrease in RMBF, but they were able to return to baseline after the stressor, whereas the diseased patients were unable to do so.

Serum markers of inflammation are also an emerging aspect of IBD research. The effects of stress on inflammation in IBD are likely to be mediated through changes in hypothalamic-pituitary-adrenal function, alterations in bacterial-mucosal interactions, activation of mucosal mast cells, and peripheral release of corticotrophin releasing factor [11]. These have been shown in a variety of animal models and have spawned some promising research in humans. In addition, IL-6 and TNF-alpha are supposed to be reduced by glucocorticoids through an inhibitory effect on transcription factors, but low dose steroids are actually stimulators. It has been shown that acute life stress or experimental stress tests lead to an acute rise in sympathetic nervous system, followed by an increase in cortisol [19]; this increase is associated with immune enhancement [20]. One particular small study to support this showed that blood taken from medical students on the day of an exam showed increases in IL-6 and TNF alpha [21]. In a related not, illustrating the clinical importance of these inflammatory findings, Infliximab, a monoclonal antibody of TNF-alpha, is being increasingly used as treatment in both UC and Crohn's patients [22,23].

Given that stress is likely a pathogenic contributor in IBD, stress reduction therapy or management strategy should be studied as a modality of treatment in IBD. While this is an important endeavor, there are several problems associated with designing trials in this field. By nature, it is difficult to have a blinded and controlled trial with this type of intervention. Also there are placebo rates as high as 40% [24,25] in patients with IBD.

Schwarz and Blanchard [26] attempted to implement a behavioral treatment package in a randomized study in patients with UC and CD. Those that underwent the behavioral treatment did feel that they were coping better with their IBD, but in fact, it was the control group that had improvement in terms of their physical symptoms. There were differences, though, between CD and UC patients (in terms of psychological distress and response to treatment) which clouded the study's results. There have been several other trials with mixed results, in which a stress reduction course and other cognitive techniques were used as treatments. However, none of these experiments have been defining (for either a positive or negative effect).

Thus, there have been many observational studies assessing stress and its relation to IBD. There have also been numerous animal models and several human studies attempting to study the physiological effects of stress on patients with IBD. There even have been new medical treatments developed that act on the inflammatory component of IBD. However, it is important to try and find other therapeutic modalities which can help

IBD patients prevent relapses. Stress reduction and psychotherapy are potential remedies which need to be further tested in clinical settings. The particular study that I am proposing would analyze the effect of psychotherapy on acute stress in the IBD patient and would assess the physiologic and psychological changes experienced.

**B. Study Design and Statistical Analysis**

This will be a prospective randomized single blind study (physicians blinded as to which subjects are enrolled in the treatment arm) to assess the impact of stress reduction therapy on Ulcerative Colitis patients. The patients will have two visits to the research center. The visits will be held in the morning, and the patients will come to the center in a fasting state. The first visit will entail completing baseline questionnaires (regarding anxiety, anger, stress, and depression), drawing blood, and checking rectal mucosal blood flow measurements. Baseline blood pressure and pulse will be taken as well once the patient has had a chance to become acclimated to the office. The subjects will then undergo a stressor for one hour. This stressor will be the dichotomous listening test, which has been used multiple times in experiments [17]. The dichotomous listening test will be described below. RMBF will continue to be monitored during the stressor every 10 minutes. This procedure will be detailed below. Heart rate and blood pressure will be followed during the stressor as well. The subjects will complete questionnaires at the end of the session assessing their present state of anger, anxiety, and stress. The RMBF will be checked approximately 5 minutes after the end of the stressor. They will have their blood drawn once again to assess the change in serum markers of inflammation 30 minutes after the stressor has been completed.

The subjects will then be randomized in a 1:1 basis, stratified for baseline rectal mucosal blood flow and baseline stress/anxiety level from the questionnaires. This will attempt to ensure that our groups will have even distribution in terms of their baseline physical and psychological characteristics. The subjects randomized to the treatment arm of the study will receive eight one-hour treatment sessions consisting of training in cognitive coping strategies, muscle relaxation techniques, stress management courses, and information about IBD and symptomatology in addition to their conventional treatment. This is based on the Schwartz and Blanchard study which found a psychological improvement in coping with the IBD after psychotherapy. These sessions will be on an individual basis and will be performed by the same therapist to eliminate bias. The other group of UC patients will not have any intervention (they will continue with their conventional therapy).

The second visit to the research center will be similar to the first experience (3 months after the first visit). Similar measurements will be taken, including baseline questionnaires, blood pressure, heart rate, serum blood markers, and rectal mucosal blood flow. The subjects will then experience a stressor (slightly different from the first stressor) where RMBF, blood pressure, heart rate, and serum blood markers will be evaluated. Questionnaires will be completed by the subjects at the end of the new stressor.

Because such an experiment has not been performed in the past, determining the effect size will be difficult. We assume that this will be a feasibility study to assess if there is, in fact, a difference seen in a small population of subjects in response to psychotherapy. There has been a previous study in IBS patients measuring RMBF in the

setting of acute stress, which found the standard deviation in the findings to be 9.8%. In studies where RMBF changes were measured in the setting of acute stress, the results were similar in finding an average of 23% reduction in RMBF in both healthy and diseased patients (with subsequent return to baseline of the healthy volunteers). For this study, we will assume that the psychotherapy will help these patients deal with the acutely stressful situation. Therefore, we will look for an effect size of 12% (approximately half the effect seen by just stress alone). Using an unpaired t test calculation, each group should have 13 participants to achieve a power of 80% with a P value of 0.05.

The questionnaires are quantifiable, and we will therefore be able to assess anger, stress, and anxiety using unpaired t tests. This will enable our stratification by baseline stress level. Also, the visual analog scales will be converted to millimeter measurements; therefore, when a subject marks a location on the visual analog scale, we can then quantify the response. This, too, will allow us to use unpaired t tests to compare the means of the two groups. The serum blood markers as well can allow us to do this statistical measure. However, depending on what our baseline values are and the variability encountered, we may be forced to use ANOVA with repeated measures in order to completely assess the data. This will allow us to look at each subject individually and allow the subject to be their own control.

**C. Study Procedures**

There will be multiple serum markers measured during the baseline period and 5 minutes after the stressor. ACTH and cortisol will be measures to assess the stress response. Similarly, we will measure LPS stimulated IL-6 and TNF-alpha.

In order to measure rectal mucosal blood flow, the laser Doppler probe (DRT4 laser Doppler flow meter) will be used. A rigid sigmoidoscope will be inserted with minimal air insufflation to assess that the rectum is empty, and the probe will be placed (under direct visualization) against the rectal mucosa 10 cm above the lower limit of the anal margin. The probe uses a low intensity beam which then measures the change in light frequency as reflected by the red blood cell [27]. The tissue is relatively constant in this case, and the volume flow (flux) can be used to estimate the ml of blood per minute for 100 g of tissue. We can then use the difference in the flux units at baseline and post-stressor to assess the difference ascribed to the stressor.

The first stressor will be the dichotomous listening test. This method has been used in previous experiments and has been shown to increase stress levels and pulse rates in patients. The test involves playing one type of music in one ear, and another type of music in another. For example, Murray et al [18] used folk music in one ear and rock music in another to elicit stress. This will be played at relatively loud levels, and the patient will not be able to change the volume of the music. The second stressor in this experiment will be similar; though it will follow a different study. In that particular study [17], the participants were subjected to the dichotomous listening test, but simultaneously, they were forced to complete a one hour IQ test in less than 45 minutes (without being told of the test time limitation and while continually hearing reminder in their ears of the importance of completing the exam) [28, 29]. This caused an increase in pulse and blood pressure and caused a decrease in RMBF. The goal in using a different stressor in the

second experiment is to try and avoid any attenuation or learning by the subjects and to be able to produce a similar stressor response in this second meeting (as compared to the first session).

**D. Questionnaires**

There will be several questionnaires used in this study. At baseline, the patients will complete the Beck's Depression Inventory (BDI) on both the first and second visit (patients with inactive IBD had an increased chance of relapse over next 18 months if the baseline score was increased) [29]. The Perceived Stress Questionnaire (PSQ) [31] will be given after the stressor during the first and second visit. The patients will mark a 10 point visual analog scale (VAS) [18] before and after each stressor which will assess their current level of stress and anger. The State Trait Anxiety Inventory (STAI) and the Spielberger Trait Anger (STA) scale will be completed as well at the beginning of each session.

**E. Study Flowsheet**

Visit → BDI, VAS, STAI, STA→ blood markers drawn→RMBF, Blood pressure, heart rate→STRESSOR (with RMBF, BP, HR being measured)→ PSQ, VAS, RMBF, blood markers

**F. Study Drugs**

There are no study drugs in this protocol. The treatment arm will involve psychotherapy for stress reduction.

**G. Medical device**

The medical devices used in this procedure will include the ABPM (ambulatory blood pressure monitor) and the laser Doppler probe. The ABPM will monitor both the pulse and blood pressure at set intervals before, during, and after the stressor (at 5 minute intervals). This is a device which has the blood pressure cuff on the arm, and the monitor can be attached to one's belt.

The RMBF will be measured as stated above.

**H. Recruitment of Subjects**

The group will be recruited using the Webcis database, which will provide the ICD code for Ulcerative Colitis. These patients will be arranged into alphabetical order (so as to attempt to eliminate differences in length of time patients have had the disease). They will be called and screened by phone for the inclusion/exclusion criteria. Recruitment will stop after 30 patients have been enrolled.

**I. Study Subjects**

Patients in the study will range from ages 18 to 60. They must have documented Ulcerative Colitis, confirmed by biopsy. We will only use UC patients at this time, as these patients usually have anal or rectal involvement, as opposed to Crohn's patients who can have skip lesions throughout the colon. Also, there have been several studies with both UC and Crohn's patients and this has led to mixed results amongst the patients. However, the UC must be quiescent, with no relapses within the past 6 months. They

should have an endoscopic score of zero on flexible sigmoidoscopy as per their most recent visit. They should score a 0 on the symptom scale:
-Hematochezia or presence of mucus (0 for absent, 1 for present < 50% of time, 2 for present>50% of time
-stool consistency (0 for formed, 1 for pasty, 2 for liquid)
-tenesmus (0 for absent, 1 for occasional, 2 for constant)
-number of daily bowel movements (0 for 0-3, 1 for 4-5, 2 for >6)

The subjects can use medications for their IBD including oral or rectal 5-aminosalicylate or oral azulfidine as sole therapy, but they should not be taking anti-inflammatory agents such as Infliximab or any form of systemic steroids. Females enrolled in the study must be in the follicular phase of their menstrual cycle for their visit sessions, due to changes in rectal mucosal blood flow. The patients should otherwise be medically well with no diabetes, HTN, or renal disease. They cannot be smokers, and their BMI must be less than 30 (due to changes in RMBF). The subjects should have no prior psychiatric diagnosis and cannot be on any anxiety, depression, or psychiatric medications. They cannot be undergoing therapy of any sort at this time. Informed consent will be obtained from all subjects.

**J. Potential Conflicts of Interest**
None

**K. Potential Risks and Benefits**

The subjects could have a possible benefit from psychotherapeutic intervention, though this is simply for research purposes only. If the patients feel they are benefiting from psychotherapy, they are encouraged to continue it on their own once the study is complete. The rectal mucosal blood flow measurements have minimal risk and have the side effect of discomfort. Also, the patients will initially be subjected to a sigmoidoscopy. This is only for the purpose of proper placement of the Doppler probe. Minimal air insufflation will be used. The risk of perforation is extremely low.

**L. Compensation of Subjects**

The psychotherapy will be free of charge for the subjects. They will also be compensated for their time (pending the funds from grant)

## Citations


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