

22 March 2021

Dear Sir/Madam,

Official Title: A Controlled trial of Yoga in Pediatric Inflammatory Bowel Disease

NCT No: NCT03338894

Date of document: 14 February 2021

I am writing to provide the updated study protocol of the above said study. The protocol document has been approved by the Institutional Review Board.

Thank you

Alycia Leiby, MD

Title of Project:

A Controlled trial of Yoga in Pediatric Inflammatory Bowel Disease

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Lay Summary:

Approximately 25% of Inflammatory bowel disease (IBD) is diagnosed in the pediatric age group, with the peak age of onset in the adolescent years¹. IBD adds additional stressors of a chronic disease with unpredictable and potentially embarrassing symptoms to the expected challenges of psychological and social adjustment that teenagers face. Various techniques, such as psychotherapy programs and IBD overnight camp experiences, have been studied to decrease psychological distress and improve quality of life. Stress, and particularly how stressful events are perceived, may play a role in triggering IBD flares. Complementary and alternative medicine (CAM), especially mind-body techniques are used often by pediatric IBD patients and may be beneficial in decreasing stress and improving quality of life (QOL). Yoga may be well suited as an adjunct to conventional IBD therapy to decrease stress, provide a greater sense of bodily control and improve QOL.

The primary goal of this project is to determine if a structured Yoga program, in addition to standard medical therapy, improves HRQOL in pediatric patients diagnosed with inflammatory bowel disease (IBD). We will also examine if the yoga program improves self-efficacy, which is a person's belief about their ability to influence events that affect their lives. Disease response and remission rates will be followed as well, in order to stratify HRQOL outcomes in the yoga group.

Patients will each serve as their own control and complete questionnaires at enrollment and at the start and end of the 12-week group yoga class sessions. They will also complete the questionnaires three months after finishing the class sessions. . The program will consist of a live group class session over 12 weeks. Baseline and follow-up questionnaires will be used to determine there are changes in QOL, self-efficacy, and disease response.

I. Specific Aims:

1. Primary Aim: To determine if a structured Yoga program, in addition to standard medical therapy, improves health related quality of life (HRQOL) in pediatric patients diagnosed with IBD

2. Secondary Aim:

To determine if, in pediatric patients recently diagnosed with IBD, a structured Yoga program:

- Improves self-efficacy

II. Background and Significance:

Approximately 25% of Inflammatory bowel disease (IBD) is diagnosed in the pediatric age group with the peak age of onset in the adolescent years¹. Adolescence is a time of great psychosocial growth. IBD adds additional stressors of a chronic disease with unpredictable and potentially embarrassing symptoms. Side effects of steroid treatment, such as acne, weight gain, and mood changes, as well as delayed puberty, may further ostracize youth with IBD. The incidence of psychiatric disorders, is increased compared to healthy children and is comparable to other chronic diseases such as cystic fibrosis². HRQOL may be impaired by issues of pain, school absences, and concerns about the chronic nature of IBD and patients with increased disease severity often have worse HRQOL².

Various strategies have been tried to improve HRQOL and psychosocial functioning in pediatric IBD patients. A prospective analysis of HRQOL and anxiety in children attending a one week camp sponsored by the Crohn's and Colitis foundation of America demonstrated improvement in the quality of life³. A cognitive behavioral therapy (CBT) program, which included relaxation training and pain-coping strategies, increased a feeling of control and decreased helplessness in adolescents⁴. More recently a skills based psychological intervention program, which included relaxation, imagery and deep-breathing as part overall CBT program, showed significant reductions in somatization symptoms in a group of adolescent girls with IBD and their parents when pre and post-treatment variables were compared⁵.

The role that stress may play in triggering flares of IBD has been investigated in the adult IBD population. Stress has been shown to alter gut permeability and cause the release of neuropeptides with immune modulatory effects⁶. Although some studies suggest conflicting results, several prospective studies have found a positive association with stress and IBD flares, particularly the perception of stressful events, as opposed to discrete events⁶.

Complementary and alternative medicine (CAM) use in pediatric IBD patients ranges from 40-50%⁷⁻¹⁰. Heuschkel et al reported that 41% of IBD patients used CAM because of adverse effects from conventional medications and 59% of respondents not using CAM were interested in learning more about it⁹. In a similar study by Day et al, 72% of children with IBD were noted to have tried CAM therapies, often due to parental frustration with managing their child's illness. Use of CAM was increased particularly in patients with worse QOL^{8, 11}. Mind-Body CAM techniques, especially relaxation, meditation and prayer are popularly used by adolescents with IBD and patients with more severe disease are more willing to consider relaxation strategies¹¹.

Yoga is a mind-body practice that originated in India more than 2000 years ago and is used by greater than a million children in the United States¹². Rates of yoga use in pediatric IBD patients are low^{8, 11}, with one study reporting only 1.4 % use⁸. This presents an opportunity to explore this underused CAM modality in pediatric IBD. Yoga may be well suited as an adjunct to conventional IBD therapy to decrease stress, provide a greater sense of bodily control, and improve HRQOL.

III. Preliminary Studies/Progress Report:

There have not been any studies to date looking at the role of Yoga in IBD. A recent systematic review of the clinical applications of yoga in the pediatric population found 34 studies¹², including a number for psychological health, as well as one for irritable bowel syndrome¹³ which suggested benefit. Unfortunately, many studies suffered from low methodological quality secondary to lack of randomization and inadequate statistical analysis¹².

IV. Research Design and Methods:

Participants and Enrollment:

The study will prospectively enroll patients seen at the Pediatric IBD center of the Goryeb Children's Hospital. All pediatric patients diagnosed with IBD will be offered enrollment in the study. Data collection surveys will be initially completed at the time of consent (time 0), start of the yoga (time 1) session, end of the yoga session (time 2) and three months after completion (time 3) to determine if the effects of yoga are lasting. Each patient will serve as their own control with the difference between time of enrollment (time 0)/start of yoga (time 1) and start of yoga (time 1)/end of yoga (end of 2) being compared. Patients will enroll in a twelve class series offered twice a year. The classes will be open to a maximum of ten students and will continue to be offered once a week with encouragement to practice daily at home. Patients will have the option to attend a fall or spring set of classes to increase flexibility and improve enrollment.

Through the entire study period patients will receive standard medical therapy as determined by their specific pediatric gastroenterologist. Clearance by their primary gastroenterologist will be required in the 8 week time period prior to starting yoga to confirm they are healthy enough to start yoga.

Sample Size: Based on what has been determined to be the minimal clinically significant difference¹⁴ of HRQOL using the pedQL survey, we would need 34 patients in total as each patient will serve as their own control. . With a sample size of 34 patients, there will be 80% power to detect a 10-point increase (improvement) in average total PedsQL score (0-100 scale)]. The sample size calculation was based on standard deviation of the total score in the Control group = 15.4, probability of Type I error (alpha) of 0.05, and probability of Type II error (beta) of 0.20. That is, in only 20% of the times we will fail to reject the null hypothesis when it is in fact false; i.e. there is a difference.

Recruitment will be feasible over a two-year study time frame as we care for over 800 active IBD patients in our center.

Inclusion Criteria:

- Both male and female patients with IBD.
- Age 10-17 years
- Not currently practicing specific mind-body techniques (yoga, pranayama, biofeedback, hypnosis, guided imagery)
- Diagnosis of IBD

Exclusion Criteria: Other Chronic systemic disease ex. RA, CF, Celiac. Any chronic neurologic condition.

Yoga Introduction:

Yoga is one component of Ayurveda, which is the complete traditional system of healthcare practiced in India and Sri Lanka. Understanding an individual's constitution and energy is a key part of Ayurvedic medicine. Each person's constitution is felt to be a balance of three types of energy, also known as the doshas. In Ayurveda, inflammatory disorders of the gut are primarily due to an imbalance of 'pitta' dosha of the Anna Vaha Srotas (Digestive System). Anna vaha srotas has the important functions of digestion, absorption, and assimilation. Anna vaha srotas and respiration have integrated functioning according to Ayurveda. If one breathes deeply, it increases the secretion of digestive enzymes. People who do pranayama (deep breathing regularly, in general tend to have a strong appetite, because pranayama stimulates anna vaha srotas agni (digestive fire).

Pitta pacifying poses include forward bends and twisting yoga poses stimulate the digestive system. Forward bends are calming and reduce stress. Inversions stimulate the endocrine system. All of these effects are felt to be beneficial for a healthy digestive system.

Our yoga program will consist of a 12 week program, one class session per participant, per week. Classes will be offered once a week at Goryeb Children's Hospital/Atlantic Health System, Morristown, NJ. Classes will be one hour in duration. We will offer two sessions a year.

The yoga teacher will be certified in Hatha yoga, which is the most common form in America, and be registered with the Yoga Alliance. We will require a minimum of 500 training hours.

Yoga Class description:

WARM UP/COOL DOWN:

- Breathing Techniques, Relaxation-Guided Imagery, Progressive Muscle Relaxation
- Yoga poses - see appendix 1

- Contraindications: Glaucoma, neck injury
- Poses will be modified to adjust for these contraindications

MODIFICATIONS TO ROUTINE:

Certain symptoms dictate modification of some of the yoga poses. All patients will be advised at the start of class to inform the teacher if they are menstruating, have nausea/vomiting, are dizzy, or are experiencing severe pain/flare/active bleeding. Patients will also be reminded to let the teacher know if they have a cold/cough/bronchitis/asthma exacerbation on the day of class, or if they have had a recent neck/back injury. They may be instructed not to participate in class at all that day, or to refrain from participating in certain asanas/poses that day.

The teacher will present modifications to the routine (such as avoiding inverted poses) for patients who are menstruating or having an active flare of GI symptoms.

Data collection measures :

- Impact III:

This is a validated, disease-specific pediatric questionnaire that measures HRQOL in pediatric IBD¹⁶ patients age 9-17 years. It consists of 35 questions and six domains: IBD symptoms, systemic symptoms, emotional functioning, social functioning, body image, and treatment/interventions. The answers are scored on a 5 point Likert response scale.

- Peds QL:

This is a validated pediatric questionnaire that measures general HRQOL in children ages 8-17 years¹⁴. It consists of 23 questions in areas of social, school, emotional and physical functioning. The answers are scored on a 5 point scale and then reverse scored and linearly transformed to a 0-100 scale.

- General Self-Efficacy Scale:

This is a widely used simple 10 item scale that measures a patient's a general sense of perceived self-efficacy, aiming to predict coping with daily life as well as adaptation after stressful life events¹⁷. It is a measure that has been validated in adolescents age 12 and above.

- PCDAI and PUCAI :

The Pediatric Crohn Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI) are validated disease activity indices that include patient symptoms in the previous seven days, physical exam findings, growth parameters

and laboratory studies¹⁸. The information needed to complete this index will be available through the patient's chart as the data collected is part of routine care.

- Physician Global Assessment :

This is a global assessment is part of routine care and determined by the patient's primary GI doctor. The assessment is a global measure of disease activity with the following five categories: inactive, mild, moderate, severe, NA/unknown.

- Short Crohn Disease Activity Index (SCDAI):

This tool has been validated for use in adult crohn's disease patients but is particularly useful for measurement of short-term disease activity and wellbeing. This data will be collected in the crohn's disease patients and includes liquid stools, well-being and abdominal pain²⁵.

- Medication use data:

We will record what medications the patient is currently using, including steroids, biologics and immune modulators. The dose of medications will also be recorded in order to determine such information as the total dose of steroids, per patient over the study period.

- Yoga Questionnaire:

The yoga questionnaire will consist of questions about past exercise experience, use of other non-mind/body CAM such as probiotics, herbs and supplements. Post yoga the questionnaire will consist of questions if they plan to continue to practice after the study is complete.

- Follow up questionnaire:

Questionnaire will be sent for those subjects who have completed at least nine classes. The follow up questionnaire consists of 5 questions to evaluate if they are still practicing yoga, any benefit from being in the yoga study, has it helped manage their IBD and would they participate in a follow up yoga study.

In addition to the questionnaire/outcome measure collected at baseline and at the different endpoints (Impact III, peds QL, self efficacy scale, PCDAI, PUCAI), baseline demographic and clinical data will be gathered for each patient in the study. Those include age, gender, race, disease type (crohn's, UC), date of diagnosis, areas of bowel involved, medications and dose of steroids.

V. Planned Data Analysis:

Baseline demographic data will be collected and descriptive statistics will be used to profile the patient population. Clinical factors collected at baseline and post intervention and the differences will be

analyzed between the yoga and control group. Categorical data will be analyzed using chi-square or Fisher's exact tests. The distribution of all continuous data will be examined. For continuous variables whose distributions approximate normality, a t-test will be used for comparisons. When normality assumptions are not satisfied, the non-parametric Mann-Whitney U test will be utilized.

The data from the questionnaires will be collected via REDCap secure access.

Statistical significance is considered at $p < 0.05$. All statistical analyses will be performed using MINITAB 17.

VI. Benefits and Risks:

We anticipate the participants who complete the yoga program will have improved HRQOL and self-efficacy. All participants may experience a personal satisfaction by their contribution to a clinical investigation.

We anticipate minimal risk from participation in the yoga program. A systematic review of yoga in the pediatric population found no adverse events reported and suggested that yoga was a low-risk intervention¹². Hatha Iyengar yoga is a very low-intensity physical activity and is less taxing on the cardiovascular system than walking¹⁹. There have been rare case reports of complications following yoga and these were primarily neurologic in origin²⁰⁻²². Patient with any chronic underlying neurologic condition will be excluded. There will be formal "live" instruction to assist in proper technique of the poses.

VIII. Human Subject/Ethical Issues

After the investigators have entered the data from outcome measure questionnaires, all further analysis will be done with "de-identifiable information". All personal identifiers (name, date of birth, medical record number, address etc.) will be removed. Only the previously mentioned investigators will have access to the master list that associates the child's answers to personal information that he or she could be identified with. All data will be kept on a password protected computer database/REDCap secure access. Data will be entered into the database using the alphabetical/numeric codes. A copy of the signed parental permission form will appear in the patient's medical record. The original completed questionnaires will be kept in a locked filing cabinet in the principal investigator's office. The identity of the subjects will not be disclosed in any publication related to this study.

IX. Data Safety Monitoring Plan

The principal investigator (PI) will oversee and assume responsibility for subject safety monitoring. Data monitoring will be the responsibility of the PI in conjunction with the other investigators. A staff member during the course of the study will follow the progress of the study and data entry, to assure utmost accuracy of the data and to detect the possible errors at an early time point. The PI will review all the results. Participant safety data that will be monitored include any adverse experiences, although this is unlikely given the nature of yoga as discussed above.

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