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STUDIO 170485. CARATTERISTICHE DELLA DISFUNZIONE INTESTINALE IN PAZIENTI CON SCLEROSI MULTIPLA: EFFICACIA DELLA PROCEDURA DI IRRIGAZIONE TRANSANALE CON IL DISPOSITIVO PERISTEEN NEL TRATTAMENTO DELLA STIPSI E DELLA INCONTINENZA ANALE CORRELATA ALLA MALATTIA

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Study protocol 170485. Approved on 29/06/2017 2017 by UNIQUE ETHICAL COMMITTEE OF THE PROVINCE OF FERRARA, ITALY

Characteristics of INTESTINAL DYSFUNCTION in patients with MULTIPLE SCLEROSIS. Effectiveness of the TRANSANAL IRRIGATION PROCEDURE with the PERISTEEN DEVICE in the treatment of constipation and disease-related anal incontinence.

Abstract

MS (Multiple Sclerosis) is the most common neurological disease involving disabilities in young adults, with bowel symptoms such as constipation and fecal incontinence. The main objectives of the study are to assess the prevalence, characteristics, severity and impact on the Quality of Life of intestinal disorders in this population, to correlate the severity and characteristics of constipation and fecal incontinence with Intestinal Transit Time and the time dedicated to the evacuation, and how these items change in relation to the use of transanal irrigation (TAI). Another objective is to identify the composition of the intestinal microbiota in MS patients in relation to the type of bowel characteristics, comparing it with microbiota profile of the healthy population of the same region of origin, Emilia-Romagna, Italy.

Study Protocol

MS (Multiple Sclerosis) is the most common neurological disease involving disabilities in young adults, with Central Nervous System involvement in both the brain and spinal cord. In a recent review, its incidence in the United Kingdom is estimated at 7 new cases per 100,00 inhabitants per year, with a prevalence of about 100,000 patients. Bowel symptoms, in particular constipation and faecal incontinence, affect more than two thirds of MS patients, and have a significant impact on patients' quality of life (QoL) by significantly limiting their social, occupational and emotional life.

Recently, bowel management based on Transanal Irrigation (TAI) has also been proposed in patients with MS, but TAI efficacy on intestinal transit time and patient's compliance with TAI have not been defined yet.

The primary objective of the study is to assess the prevalence, characteristics, severity and impact on the Quality of Life of intestinal disorders in patients who consecutively refer to the neurological clinic for the diagnosis and treatment of Multiple Sclerosis at Ferrara University Hospital, Italy.

Secondary objectives are to correlate the severity and characteristics of constipation and fecal incontinence with intestinal transit time and the type of faeces evacuated according to the Bristol Stool Form Scale; to evaluate the costs in terms of the precautions (diapers, traverses, drugs, medicated clysms, etc.) and the time dedicated to the evacuation, and how these items change in relation to the use of TAI; and finally, to study the composition of the intestinal microbiota in MS patients in relation to the type of bowel characteristics, comparing it with the profile of the healthy population of the same region of origin, Emilia-Romagna, Italy.

The study proposed is a monocentric prospective observational study. The study population will be composed of patients who will consecutively refer to the Neurological Clinics of the University Hospital of Ferrara, Italy for a number of about 150 patients.

The study will consist of two phases. The first phase will be the selection of eligible patients by administering two self-filling questionnaires: PacQol (Patient Assessment of Constipation Quality of Life) and NBD (Neurogenic Bowel Dysfunction Score).

Patients with PacQol score ≥ 32 will be sent to the surgical clinic for the second phase. During the latter phase, patients will undergo a number of visits varying from 1 to 4 depending on the patient's willingness to continue the study. After the illustration of the purpose and protocol of the study to the patient,

classification of constipation and/or faecal incontinence in accordance with the Rome III Diagnostic Criteria will be assessed, with consideration of other possible etiopathogenetic factors other than MS. Further questionnaires will be filled in to evaluate the disease status (Constipation scoring system by Agachan-Wexner, Obstructed defecation score by Altomare et al, Fecal Incontinente grading scale by Jorge-Wexner); if the patient will consent to the continuation of the study, he will be given 7-days food diaries, evacuation diaries, radiopaque markers, stool collection container and appointment date for plain abdominal X-ray which may coincide with the appointment for examination number 2 (visit 2 or 3).

In particular, radiopaque markers Intestinal Transit Study will be performed according to the Bouchoucha procedure revised by Abrahamsson, which involves ingestion of 10 markers for 6 days at the same time and execution of a plain abdominal X-ray on the 7th day. During this week the patient will complete an evacuation diary recording the time and number of evacuations, the method of eventual bowel care, the consistency of faeces according to the Bristol Scale, any episode of fecal incontinence, the type of hygiene measures in general, the number of enemas, diapers, and any other garrison used in relation to the evacuation.

Patients will be asked to collect a faecal sample in a container during the last week before the following inspection at Visit 2.

During the second visit, the outcome of the plain abdominal X-ray will be discussed, the completed diaries will be collected, and the faecal sample will be stored at -20 C° and subsequently sent to the Laboratory of the Department of Pharmacy and Biotechnology of the University of Bologna, Italy for the analysis of the intestinal microbiome composition.

Patients with severe NBD impairment will be offered the adoption of TAI as a way to manage their own evacuation, replacing any other measure used until that moment (suppositoires, enemas) with the exception of the possible intake of macrogols and/or prebiotics and/or probiotics which instead can be continued. This treatment will be proposed to all patients with severe impairment of intestinal function.

The TAI training with Peristeen will be carried out at the surgical clinic of the Surgical Department of the Ferrara University Hospital, Italy, by the personnel involved in the study, usually in a single session, but more sessions may be necessary.

During the following 4 weeks, patients will continue to use the Peristeen at home according to the instructions provided by the training staff collecting a stool sample each week. During the last of the four weeks of TAI use patients will repeat the compilation of food diaries, evacuation diaries, the radiopaque markers Transit Time, and collection of the stool for microbiota analysis. The appointment for the radiography could coincide also in this case with the following visit (visit 3 or 4).

During the last visit the outcome of Transit Time X-ray will be discussed, completed diaries and stool samples will be collected, and PAC-QoL questionnaire will be submitted to patients who completed the study pathway.

Patients will be asked about overall satisfaction of TAI treatment with Peristeen by means of a numerical assessment from 0 to 10.

Finally, any comment will be noted as well any events that might be related to TAI irrigation with Peristeen will be recorded.

Patients will undergo a neurological examination 3 months after the start of treatment.

The whole duration of the study will be of 2 years.

Group Cohort

This group will be composed by 150 MS patients who, consecutively, from the start of the study, will refer to the MS clinic of the Neurology Unit of the Ferrara University Hospital, Italy. The first 50 patients with a PACQoL score ≥ 32 will be asked to be willing to enter the next phase of the study that continues at the Coloproctological Outpatient Clinic of Ferrara University Hospital, Italy with an appointment provided by the neurologist with a pre-established schedule (with written consent).

Intervention

Patients with severe intestinal dysfunction impairment (PAC QoL score ≥ 32) will be offered the adoption of the TAI (Transanal Irrigation) with Peristeen Device as a way to manage their own evacuation, replacing any other measure used until that moment (suppositoires, enemas) with the exception of the possible intake of macrogols and/or prebiotics and/or probiotics which instead patients can continue. This treatment will be proposed to all patients with severe impairment of intestinal function.

The TAI training with Peristeen will be carried out at the surgical clinic of the Surgical Department of the Ferrara University Hospital, Italy, by the health personnel involved in the study, usually in a single session, but more sessions may be necessary, documented in CRF as VISIT 3, VISIT 3 bis and so on, until the end either with the continuation of the TAI independently for 4 weeks or with patient's exclusion from the study if the guarantees of appropriate use of the device will not be reached.

Primary Outcome Measure:

Outcome 1) Incidence and prevalence of intestinal dysfunction in Multiple sclerosis. Calculation of % of patients with a PACQoL score ≥ 32 for items B.1 to B.6 and/or a score ≤ 11 for item B.7 of the questionnaire.

Outcome 2) Characteristics of intestinal dysfunction in MS. Calculation of Agachan-Wexner scores, the Cleveland Clinic Index, the Altomare Questionnaire, and the NBD Score on the patient population that report a significant impact on their QoL of problems related to their bowel management and bowel disorders in general (Score ≥ 32 to PAC-QoL).

Outcome 3) Intestinal transit time in SM patients with intestinal dysfunction. Calculation of % of patients with a slowed Intestinal Transit Time (≥ 60 hours for women and 55 hours for men)

Secondary Outcome Measures

1) Correlation between Intestinal Transit Time and constipation scores in MS patients with intestinal dysfunction. To calculate the Correlation Coefficient between Intestinal Transit Time and the Bristol Score, the Agachan-Wexner Score, the Cleveland Clinic Index, and the NBD Score.
2) Correlation between Diet and intestinal dysfunction in MS patients. To correlate the Intestinal Transit Time and the Bristol Scale Score to the type of diet usually followed by patients in terms of adequacy of caloric intake compared to BMI, composition of macronutrients, and dietary fibre intake.
3) Efficacy of TAI in MS patients with intestinal dysfunction. Compare the Scores of the assessment scales used before and after the 4-week TAI treatment period, in order to detect a reduction in severity and an improvement in QoL score. Calculate a possible advantage or non-benefit of the costs of treatment with TAI compared to the previous bowel management.
4) Analysis of Microbiota in MS patients with intestinal dysfunction, before and after treatment with TAI. Compare the composition of the intestinal microbiota of MS patients with the known "healthy"

profile of the Italian population of North East of Italy and assess any changes after the period of treatment with TAI.

Eligibility

Inclusion Criteria:

- Patients ≥18 years of age, both sexes - Diagnosis of MS for no more than 10 years - Residence in the Italian Region of Emilia Romagna, Italy

Exclusion Criteria:

-EDSS (Expanded Disability Status Scale) < or =7 -Diagnosis of Celiac Disease, Inflammatory Bowel Disease (Ulcerative Colitis or Crohn's Disease) -Evidence of Diverticular Colon Disease -Previous or ongoing neoplastic diseases of the digestive system -Endocrine disorders such as uncompensated hypothyroidism, diabetes mellitus in treatment, hypoparathyroidism, pheochromocytoma -Other neurological disorders such as M. of Parkinson's, S. of Shy Drager. -Taking drugs that affect intestinal transit (opiates, antiepileptic drugs, major antidepressants, calcium antagonists, anticholinergics, antidopaminergics)-Evidence of rectal or occult bleeding in the last 3 months -Infectious episodes in progress (*)

NOTES: (*) Rational: it is not considered ethical or functional to carry out such research in patients with infectious organ diseases requiring antibiotic and/or inflammatory therapies.

Study population

The study population will be composed by 150 MS patients who will consecutively refer to the MS Outpatient Neurology Clinic at Ferrara University Hospital, Italy. The PAC-QoL questionnaire will be given to every patient. This questionnaire is a self-filled instrument validated and used in various studies to document the consequences that intestinal disorders and defecation have on everyday life. The first 50 patients with a PACQoL score ≥ 32 will be asked to be willing to enter the next phase of the study that continues at the Coloproctological Outpatient Clinic of Ferrara University Hospital, Italy with an appointment provided by the neurologist with a pre-established schedule (with written consent).

Statistical analysis

Data will be expressed as median (interquartile range – IQR 25-75) and mean ± standard deviation according to distribution assessed by Shapiro-Wilk test. Categorical data will be presented as numbers. Data will be analysed using Chi-square, t-student, and Mann-Whitney tests as appropriate. Cox regression analysis will be employed to assess independent predictors of improvement of intestinal dysfunction after Transanal Irrigation (TAI). Significance will be considered for values of $p < 0.05$. Statistical analysis will be performed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp. Armonk, NY: IBM Corp.). The report will comply with the strengthening the reporting of cohort studies.