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Intestinal Microbiota Transplantation, a Paradigm in Remission

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Keywords

Fecal Microbiota Transplantation (FMT); Intestinal Microbiota (IM); Intestinal Microbiota Transplantation (IMT); Microbiota; Microbioma

Introduction

The Fecal Microbiota Transplantation (FMT) is the administration of processed fecal matter, through dilution, filtration and precipitation, with passage in a laminar flow hood, from a healthy person, to the digestive tract of a patient.

It has also been called: Reconstitution of faecal flora, transfer of intestinal microbiota and bacteriotherapy. We prefer to call the Intestinal Microbiota Transplantation (IMT), therefore, it´s a process that converts stool into microbiota.

In the history of humanity the first Fecal Microbiota Transplantation (FMT) was made in the 4th century B.C. with good results. It was Ge Hong who described it for the first time, and stool suspension served to stop intense diarrheas.

Li Shi Zhen describes the administration of feces (fermented or fresh), to treat several digestive pathologies, among which stand out from diarrhea to constipation, passing through vomiting, fever and abdominal pain. The doctors of that time denominated this preparation as yellow soup. Already in Europe, the following century, the Italian Physician Fabricius Aquapendente says that the Intestinal Microbiota Transplantation (IMT), is a transfaunación, and uses the same with good results. The term transfaunación is English origin and means: "transfer of part (or the total) of the symbiotic flora present in the digestive tract" and, they used it in veterinary medicine. The transplant has come back and it is now in the Second World War, where the Bedouins taught the German soldiers to use dromedary stools to treat dysenteric processes. Sixty one years ago Eisman B and collaborators published the article entitled "Fecal enema as an adjunct in the treatment of enterocolitis". In the report they treated four patients with pseudo-membranous colitis, with excellent results and, lay the foundations for the management of this pathology with FMT [1].

Given to different publications, the IMT is used by different authors, who use it in many conditions, among which stand out the Irritable Bowel Syndrome (IBS), Obesity, Inflammatory Bowel Disease (IBD), diarrheas, allergics, metabolic and immunological disorders, and neuro-psychiatric disorders and others [2].

The priority in the IMT is the selection of excellent donor. To select the recipient, you should try to use all the existing therapeutic methodology, before undertaking the IMT. We prefer to use the jejunal or colonic ways. The amount of microbiota to be transplanted we believe must be at least 500 milliliters, including the diluent. IMT is a harmless procedure and complications, if present, are usually reversible.

Comments

In the history of humanity the first Fecal Microbiota Transplantation (FMT) was made in the 4th century B.C. with good results. It was Ge Hong who described it for the first time, and stool suspension served to stop intense diarrheas.

Li Shi Zhen describes in the book of traditional Chinese medicine the administration of feces (fermented or fresh), to treat several digestive pathologies, among which stand out from diarrhea

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to constipation, passing, through vomiting, fever and abdominal pain. The doctors of that time denominated this preparation as yellow soup. Already in Europe, the following century, the Italian Physician Fabricius Aquapendente says that the Intestinal Microbiota Transplantation (IMT), is a transfaunación, and uses the same with good results. The term transfaunación is English origin and means: "transfer of part (or the total) of the symbiotic flora present in the digestive tract" and, they used it in veterinary medicine. The transplant has come back and it is now in the Second World War, where the Bedouins taught the German soldiers to use dromedary stools to treat dysenteric processes. 61 years ago Eisman B and collaborators published the article entitled "Fecal enema as an adjunct in the treatment of enterocolitis". In the report they treated four patients with pseudo-membranous colitis, with excellent results and, lay the foundations for the management of this pathology with FMT [3].

Recent publications indicate that babies, before they are born, obtain microbiomes and receive numerous maternal microorganisms during childbirth, in addition to breastfeeding [4,5].

It has been reported that even in healthy individuals, there are notable differences in the various microorganisms that inhabit the intestine. However, the metagenomic transport of metabolic pathways is usually stable, despite variations between community structures. The metagenome that is the set of microbial genes present in a given ecosystem or environment, is what we use (the content in the intestine). Remember that there is microbiota throughout the body and, this gives rise to the fact that in the future other metagenomes can be used, since surely the impact will be greater, when a metagenome of the skin is used in dermatological pathologies, for example [6,7].

The comparative studies of IM in breastfed children and with artificial formulas establish that human milk is a potent inducer of immunological maturation [8].

The concentrations of cytokines of TGF-β in breast milk are generally high, the increase of this biomolecule improves intestinal maturation in the newborn and has immunoregulatory function that induces immune tolerance towards maternal commensal microorganisms and the inflammatory response to the IM developing [9,10]. The immaturity of the mediators and effectors of the immune response does not allow the neonate to have a mature immune system [11,12]. Commensal microorganisms play a very important role and represent one of the first immunogenic stimuli facing the newborn [13]. Its recognition is the responsibility of the Toll Like Receptor (TLR), after which a series of biochemical signals are activated within the dendritic cells and macrophages that lead to immune tolerance, that is, the absence of the magnitude and the quality of this response depends on the type of microorganism, concentration and microenvironment, which includes the action of cytokines (proteins secreted by the immune system), which act, also as mediators of the immune response [14]. The cytokines involved in the regulatory process are: transforming growth factor beta (TGF-β) and interleukin 10 (IL-10).

A healthy IM can be defined by the presence of groups of microorganisms that enhance the host's metabolism, confer resistance to infections, inflammatory processes, and the development of neoplasms or autoimmunity, favor endocrine functions or collaborate with neurological function through of the so-called intestine-microbiota-brain axis.

Although it seems strange, the IMT it is not a new therapeutic concept. Both among folk remedies and among the knowledge of primitive veterinary and human medicine there are very old data that refer to it more or less directly. Or the indications given by the Bedouins in the North African desert to the soldiers in the Second World War regarding the intake of dromedary stools to treat dysentery [15].

The interactions between the microorganisms, the epithelium and the intestinal lymphoid tissues are diverse and continuous, so they constantly remodel the local and systemic mechanisms of immunity adapting them to the microbial environment [16]. The epithelial cell plays an important role in the immune system. Among the most important functions of the gut microbiota is the protection against harmful microorganisms. For this there are cytokines and enzymes capable of producing inflammatory mediators. Epithelial cells produce signals to attract and trigger leukocytes, as well as increase blood flow, generate capillary permeability, etc. The enterocytes act as presenters of antigens; and suggests that its function is not limited to defense [17].

Some experiences in other clinical conditions. Mizoguchi A. Points out that recent advance in genetic engineering have brought novel concepts about IBD, such as inducible knockout for specific cells, as well as knockin mouse systems, have brought novel concepts about IBD [18].

There is usually a decrease in the microbiological diversity with decrease in the microorganisms that belong to the "beneficial" edges Bacteroidetes and Firmicutes [19].

Bennet JD, in his article called: "Treatment of ulcerative colitis by implantation of normal colonic flora" [20] corroborates the beneficial effect of TMF, on self-treatment of ulcerative colitis [20]. However, some authors refer that the IMT should be extended from the area of gastroenterology to other systems and specialties, such as the immune system, dermatology, pediatrics, neurology, and psychiatry, among others [21].

Vrieze et al. [22] Were the first to analyze the efficacy of IMT in 18 patients with metabolic syndrome Randomized study, where patients received autologous IMT, from donor with BMI <23, through the naso-duodenal tube. They detected an increase in insulin sensitivity, both at the hepatic and peripheral levels, which again translates the benefit of the transplant.

The Australian Borody team published 3 cases of IMT. According to this group, all of them improvement digestive and neurological symptomatology of 2 and 15 years. In another study from the same group, a child with myoclonic dystonia syndrome and diarrhea was also benefited by the transplant. The literature includes cases with encouraging results in Parkinson's disease, chronic fatigue syndrome and autism [23-25]. Faecal microbiota transplantation has been used for sixty years to treat different diseases in addition to severe diarrhea caused by Clostridium difficile. This revision work entails the intention of demonstrating that the IMT manages to reduce, substantially, numerous alterations that are generated, when the Intestinal Microbiota (IM), becomes ill and, not necessarily the benefit of the TMI, when it is used in the correction of severe diarrheas produced by C. difficile [26-30]. United States of America has become the pioneer country in fecal transplants [31].

One of the concepts poured out by Cho and Blaser is that the

microbiome and the metagenome probably have important functions in health and disease. This concept has been reviewed, many researchers. Its evaluation is a frontier in the genetics of humanity [32]. Regulatory T cells play a central role in immune tolerance because they secrete cytokines [33].

Although we cannot disregard the written about C. difficile, and for sample, the statistics of McDonald LC, about hospital discharges in the United States of America, where the number of them doubled, so we have to stimulate the use of the IMT, since with it, this trend can be reversed [34,35].

Personal suggestions

The priority in the IMT is the selection of an excellent donor, to whom all the necessary studies are carried out, to avoid transmitting any condition. To select the receptor, you must try to use all the existing therapeutic methodology, before undertaking the (IMT). We prefer to use the jejunal or colonic ways. The amount of microbiota to be transplanted we believe must be at least 500 milliliters, including the diluent. IMT is a harmless procedure and complications, if present, are usually reversible.

We do not expect total cures, although the response is magnified, the corrections are usually between 40% to 70% improvement. The literature reports that in some patients two or more transplants are required to improve their clinical status. In our patients there has been no need, more than for a transplant, to date, in which we have 2 years of follow-up.

The literature also reports that there is a reversion of the (IMT) generally to the year. We have not noticed this circumstance yet.

The results of improvement shown by the patients have fluctuated between 2 days to 2 weeks from the date on which the transplant was performed.

Our casuistry is not very high, since it is quite expensive (IMT), given the base of the laboratory studies performed to the donor.

Discussion

Adverse effects of IMT have been observed, although they are usually mild and infrequent. Keep in mind that there are many procedures performed around the world and that there are quite long follow-up periods.

Of course, the different means of administration of the microbiota can produce specific complications, such as those produced with colonoscopy, the complications of sedation or the adverse effects of medications. For this reason we must insist that it is convenient to have expert staff to perform the procedure, in order to abate potential complications.

The procedure is usually tolerated and safe for the patient. In the first days after the transplant, diarrhea may appear in the first 3 hours. Same as almost always, yield spontaneously. There may be flatulence [36,37], constipation, [38] vomiting, pruritus, abdominal pain, paresthesias, elevation of C-reactive protein, headache, tongue lesions and thermal rise that are also clinical data that usually do not be transcendental [39].

It has been described that if a patient with Ulcerative Colitis (UC) is used as a donor, the appearance of an outbreak of this disease (UC). Although this has happened in only one case. The deaths are extraordinarily rare, so we see that an 88-year-old woman with chronic kidney disease died 3 days after the transplant due to peritonitis. I was undergoing peritoneal dialysis. It was concluded that nasogastric tube placement may have caused the death [40]. Other deaths have been related to the comorbidity of patients who are candidates for the procedure [41]. Due to the good results and the continuous communications of the specialized press, as well as successful publications, the FDA reinforced the surveillance and carried out the process, in order to standardize it and have greater protocolization in it [42].

It is suggested that the procedure is not carried out by inexperienced hands, since a death in self-administration has been reported in men of 36 years [43].

Conclusion

Although the FMT is the first clinical application of microbiota manipulation and its use has been limited to the control of severe diarrheas caused by C. difficile, some groups have gone much further and carry out the procedures in numerous conditions, both digestive and extra-digestive.

The list of the diseases sensitive to IMT every day is larger and we see improvements in such diverse cases, such as [36-42]:

Allergy to the cold, Food allergies, Alzheimer's, Anorexia nervosa, Anxiety, Rheumatoid arthritis, Autism, Colon, Gastric, Esophageal, Biliary vesicle cancer, Clostridium difficile, Colitis, Fulminating colitis, Non-specific chronic ulcerative colitis, Functional constipation, Depression, Atopic dermatitis, Diabetes mellitus type 1, Functional diarrhea, Severe diarrhea due to antibiotics, Severe diarrhea, not reversible, Functional dyspepsia, Bloating and abdominal swelling and unspecified disorders, Gastrointestinal pain of childhood disorders, Functional chest pain

Celiac Disease, Crohn's Disease (CD), Parkinson's disease, Colon diverticular disease, Inflammatory Bowel Disease (IBD), Pseudomembranous enterocolitis, Multiple Sclerosis (MS), Constipation, Fibromyalgia, Fatty liver (Non-alcoholic fatty liver), Bloating/functional abdominal distension, Hypothyroidism, Lupus erythematosus, Morbid obesity, Functional heartburn, Refractory pouchitis, Psoriasis, Idiopathic thrombocytopenic purpura, Rhinitis, Chronic Fatigue Syndrome, Irritable Bowel Syndrome (IBS), Metabolic Syndrome (MS), Bacterial overgrowth, Neurodevelopmental disorders, Functional disorders of Oddi sphincter and gallbladder, Functional gastrointestinal disorders in childhood, Gastrointestinal functional disorders in adolescents, Neurodegenerative disorders, Bacterial vaginosis.

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