Klinika anesteziologie a resuscitace
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Šrobárova 50, 10034, Praha

PATIENT INFORMED CONSENT TO PARTICIPATE IN THE STUDY

Clinical study: Fecal bacteriotherapy for the treatment of postantibiotic diarrhea in critically ill patients

Faecal Bacteriotherapy in Intensive Care, ACRONYM: FEBATRIC

Unique Protocol ID: 2021-002290-25

Patient (name, surname, ID number, date of birth, insurance company):

Department (clinic, department):

Dear Madam, dear Sir

A study is currently underway at the intensive care workplaces of the Royal Vinohrady University Hospital (FNKV), dealing with the effectiveness and safety of therapeutic transmission of bacteria from the stools of healthy volunteers to the recipient's colon (so-called fecal bacteriotherapy, FBT). This method has already been tested and is commonly performed on patients outside the intensive care unit (eg treatment of certain types of diarrheal diseases, intestinal inflammations, metabolic diseases, etc.). We hypothesize that it may also be effective and safe to treat diarrhea after antibiotic therapy in patients in the intensive care unit. The study, in which we offer you (or your loved one), compares the FBT treatment method with the standard treatment procedure for postantibiotic diarrhea.

Fecal bacteriotherapy (FBT): the method of fecal bacteriotherapy means the transfer of stool and with it the microflora (especially bacteria) from a healthy donor to the recipient's digestive tract. The goal of this medical procedure is to restore the damaged intestinal microflora by transferring healthy microflora from the donor. Fecal bacteriotherapy (FBT) has long been an established treatment method for the treatment of recurrent Clostridial enterocolitis and in recent years is a method used in many other indications – inflamatory bowel disesases (ulcerative colitis, Crohn's disease), gastrointestinal dysfunction (irritable bowel syndrome), gastrointestinal disorders (irritable bowel syndrome), metabolic diseases (type 2 diabetes mellitus, metabolic syndrome), psychiatric disorders (autism, etc.) and many others.

The administration of the graft to the gastrointestinal tract will be performed in this study by the lower route, i.e. in the form of an enema, directly into the rectum. The transplant will be used from processed and subsequently frozen stools from a thoroughly tested donor.

For assessment and analysis of possible side effects, infectious complications or for further scientific analysis, the serum and stool of the donor and recipient will be frozen at -80 ° C, properly labeled and stored. This will allow possible subsequent analysis or further testing in the research of the composition of bacteria in the stool (intestinal microbiome).

<u>Why the study is running and what is its purpose:</u>

Most critically ill patients receive antibiotics during their intensive care unit. A side effect of this treatment is that it often eradicates the symbiotic ("friendly") bacteria that live in the large intestine, thus increasing the "hostile" bacteria that resist the antibiotic. The resulting bacterial imbalance can cause persistent diarrhea, which not only prolongs the healing process (stay in the intensive care unit), but can very rarely lead to serious complications of colonic enlargement, sepsis (blood poisoning) or death. As a treatment, probiotic therapy

has been used in some studies, but due to the results of these studies in patients in intensive care units, this therapy is not recommended by default. In these patients, it remains to wait for a healthy intestinal bacterial population to recover spontaneously after discontinuation of antibiotics. By this time, in some critically ill patients, a stool drainage tube is inserted into the rectum to prevent stool skin damage and bedsores, but can be a source of discomfort and odor.

The purpose of the present clinical study is to test the hypothesis that administration of an enema containing "friendly" bacteria, made from the stool of healthy volunteers (FBT), will accelerate the recovery of intestinal bacteria and lead to a shortening of postantibiotic diarrhea in ICU patients. The efficacy and safety of FBT have been established in a number of clinical trials in patients with post-antibiotic diarrhea caused by C. difficile.

Stool donors are thoroughly screened for communicable diseases before FBT, reducing the potential risk of infection from donor to recipient. The population of critically ill patients in whom we plan to conduct this clinical study is certainly specific in a number of respects.

We believe that the treatment of diarrhea in these patients by the FBT method has great therapeutic potential and will lead to an improvement in their condition. At the same time, however, it is likely to be associated with certain risks arising from the characteristics of fragile patients in intensive care units.

This study raises the following questions:

1) Is the FBT method effective in patients with postantibiotic diarrhea? Will it lead to a faster remission of the problem compared to the standard treatment procedure?

2) Is the administration of an FBT enema easy to perform in an intensive care unit?

3) Will any side effects of this method be observed in patients in the intensive care unit who undergo FBT?

How does the study work in practice?

The study will include 36 patients who meet the entry criteria. Entry criteria include the presence of diarrhea early after antibiotic withdrawal in adult patients hospitalized in the intensive care unit. Patients meeting the exclusion criteria will be excluded from the possible

selection of patients. Patients will be randomly divided 1: 1 into 2 groups. The first group will be treated with fecal bacteriotherapy (FBT). The second, control group, will be treated in the standard way (ie as if the patient were not included in the study). The expected duration of patient participation in the study is 6 months.

Day 0: The patient with diarrhea, after treatment with antibiotics, will be acquainted in detail with the planned study by the doctor. If the patient agrees to be included in the study, he or she will sign an informed consent. If the patient is unable to sign the informed consent, the patient's fully informed legal representative or independent physician will sign it. If it is a woman of childbearing age, a pregnancy test will be performed. Furthermore, the treatment plan will be checked with an event. discontinuation of all drugs that may contribute to diarrheal disease, unless this will increase the patient's health risk. All patients in the study will be discontinued from enteral nutrition (feeding directly to the gastrointestinal tract) no later than 6 pm on day 0. Patients enrolled in the study will be randomized 1: 1 to the experimental or control group. The patient also undergoes an initial examination: an X-ray of the abdomen (to rule out intra-abdominal complications), a stool and blood sample is taken for routine examinations, including the determination of fecal calprotectin.

The stool and blood sample will be further subjected to a special study analysis and part of the blood and stool sample will be frozen at -80 ° C for possible later analysis.

Day 1: The patient will be physically examined in the morning, including the determination of the degree of SOFA score (a set of laboratory results and examinations estimating organ function) and the frequency, amount and structure of the patient's stool will be recorded. Blood will be taken for analysis. Monitoring of vital functions (body temperature, heart rate and heart rate, blood pressure and blood oxygen levels) is part of standard patient care. In both treatment groups, adequate hydration of the patients will be ensured by fluid replacement. Patients will be treated for their primary disease throughout the study according to established standard procedures.

The control group will wait for spontaneous diarrhea recovery with symptomatic therapy, which is a standard treatment.

In the experimental group, a drug to slow down intestinal peristalsis (bowel movements), Loperamide 2mg, will be given orally (by mouth) 2 hours before fecal bacteriotherapy (FBT). Then, in the position on the left side, an FBT treatment enema will be applied. It is a 350 ml solution, applied through the rectum to the lower part of the large intestine with an irrigator (aid for enema). After application, the FlexiSeal fecal system will be temporarily closed and the patient will be tilted upside down by approximately 30 ° in the left side position. After 15

minutes, it turns to the right side for another 15 minutes. Positioning the patient is important so that the beneficial bacteria from the donor's stool spread as much and as far as possible into the recipient's gut.

If a patient is confirmed to have a Clostridial infection from a stool sample (expected to be 20% of patients), then the non-absorbable antibiotic Vancomycin (standard treatment for this type of diarrhea) 250 mg is given every 6 hours **in the control group**.

In the experimental group, when the Clostridial infection is confirmed, a cleansing enema is performed with 1 liter of saline and fecal bacteriotherapy (FBT) is repeated with an enema at least 6 hours apart. We will not administer any antibiotic treatment in the experimental group. Only if the patient's condition worsens, Tigecycline i.v. as a rescue treatment.

Day 2.3: All patients in the study perform standard examinations including: physical examination, SOFA score control, stool structure, frequency and amount control, and evaluation of laboratory results. Any change in health or medication will be recorded in the documentation.

Day 4: In addition to the standard examination, we will take a stool sample to assess the change in the microbiome and a plasma sample to examine anti-inflammatory markers. Stool and plasma samples will be frozen at -80 ° C and stored throughout the study for possible further analysis.

Day 5.6: Standard examination (see day 1, 2, 3)

Day 7: In addition to the standard examination, stool and plasma sampling and subsequent freezing of part of the plasma and stool sample, an efficacy assessment will take place - ie. presence or absence of diarrhea by an independent evaluator.

If the patient is not in the ICU but remains in the hospital, the study nurse will bring a special form to the appropriate ward and inform the patient and the nursing team to record stool volume, frequency and consistency over the next 24 hours (according to the Bristol scale). In addition to the stool record, the results of the physical examination will also be entered on the form. The protocol includes a stool and blood sample (see day 1, 2, 3).

If the patient has been discharged from the hospital, the patient is contacted during the sixth day by a study nurse who asks him to come to the anesthesiology and resuscitation clinic the

next day for a blood sample and at the same time for the patient to bring a stool sample. If the patient is unable to come to the hospital, the patient will be excluded from the study.

Adverse events, antibiotic therapy, and stool volume, structure, and structure are monitored daily throughout patients in the ICU. Follow-up examinations (see day 4) are performed on all patients in the ICU with a fecal system at intervals of 7 days up to 28 days or until the fecal system is removed or discharged from the medical facility.

In patients who remain in the ICU but have the fecal system removed, the same checks are performed at seven-day intervals as in the group of patients in the ICU with the fecal system (see day 4), except for faecal sampling. Stool collection should always be performed as close as possible to the collection day after the patient has spontaneously emptied.

Patients who are not in the ICU but remain in the hospital are visited by a study nurse at seven-day intervals (7, 14, 21 and 28 days) until discharge. The visit includes monitoring the patient's general condition, the presence / absence of diarrhea, monitoring for side effects, recording of antibiotic therapy, or other therapies affecting the intestinal microflora. At the same time, the study nurse takes a blood sample for a standard study examination (see day 1).

After six months, the participant will be contacted by phone and asked for a follow-up visit or asked in detail about his / her medical condition by phone.

Duties and rights of the patient:

The patient is obliged to provide the caregiver with all information that could be significant from the point of view of the effectiveness, but especially safety, of the tested FBT method (especially to report possible side effects).

Participation in the study is completely voluntary. It is the patient's right to withdraw from the study at any time (even without giving a reason) without any effect on further treatment. If at the time of enrollment he was unable to give his consent and was enrolled based on an independent review, he has the option not only to withdraw from the study at any time, but also to request permanent and irreversible deletion of all data collected until he withdrew his consent to participate in the study.

study exclusion / exclusion criteria:

newly diagnosed contraindications to treatment, noncompliance, the patient wishes to withdraw from the study voluntarily, if the investigator thinks that participation in the study is not in the patient's best interests or if the patient cannot comply with the study requirements.

Patients excluded from the study will not be followed up in the study.

In the case of damage to health, according to paragraph 52, para. 3 letter f of the Act on Medicinal Products, the contracting authority is insured in case of damage to health or death of the subject of the clinical trial.

If you think that your health has been damaged in connection with your participation in the study, contact the examining physician (contact details are given on the last page of this document). Appropriate medical care will be provided and reimbursed for you. You have the right to compensation in accordance with applicable law. By signing this informed consent, you do not waive any of your legal rights.

What are the risks of participating in the study and what is the potential benefit to the participant?

Potential benefits of FBT for the patient: FBT is a simple, minimally burdensome treatment method with a high success rate depending on the indication. The main potential benefit of the proposed experimental treatment in this study is the restoration of optimal intestinal microflora, which is needed for proper functioning of the intestinal mucosa (absorption of essential nutrients from food, motility (movements) of the digestive tract, synthesis of vitamins and much more). Restoration of bowel function leads to faster disappearance of diarrhea and thus improve the patient's health. Because the colon is a reservoir of antibiotic-resistant bacteria, it can be hypothesized that FBT can reduce the incidence of infectious complications (so-called nosocomial infections such as pneumonia).

Potential risks of FBT to the patient:

The main risks of FBT are the risk of transmission of infection from the stool donor. However, the donor stool is applied to places where intestinal bacteria already occur normally and therefore the risk of infectious complications is very small. The donor is

examined in detail before collection to exclude possible transmission of pathogens. Donor stool is tested for the presence of HIV, jaundice type A, B, C, Syphilis, cytomegalo virus infections, intestinal bacterial and parasitic infections, including Clostridium difficile. Donor blood, blood count + differential, sedimentation, glycemia, CRP (laboratory parameter of inflammation), liver enzymes and blood group are also examined. Due to the need to exclude other possible infectious diseases of the donor, a questionnaire is completed with the donor reducing the risk of his unrecognized infectious disease. Furthermore, there is a theoretical risk of changes in the metabolic properties of the intestine after FBT in connection with changes in the microflora (changes in weight, changes in insulin resistance, changes in moods, etc.). Other possible risks include perforation of the intestine of the GIT or bleeding in connection with the introduction of an enema in FBT.

The risks of FBT to pregnant or breast-feeding mothers are not known, however, patients of childbearing age will be screened prior to enrollment.

Can I end and leave the study?

Your participation in the project is not associated with any deviations from the recommended procedures, so it does not lead to an increase in health risk. This is an academic project of Charles University carried out at the Faculty Hospital in Královské Vinohrady (FNKV), completely independent of pharmaceutical companies. The implementation of the project was approved by an independent Ethics Committee. Your participation in this scientific project is voluntary and not rewarded. Your decision to (not) participate in this project does not affect the healthcare provided. Participation in the project does not represent financial costs for you. During the follow-up, you can decide to end your participation in the study at any time. If new information becomes available at the time of the study that could affect your decision to continue in a clinical trial, you will be notified immediately by the physician who will monitor you in the study. Your participation in the study may be terminated if the study sponsor decides to terminate the study early, or based on the decision of the ethics committee or regulatory authority.

More information:

When included in the study, your personal data will be kept with full confidentiality protection in accordance with applicable Czech laws, including the General Data Protection Regulation (GDPR). The personal data processing notice is a separate document that you will receive.

All data and samples obtained in the clinical trial will be sent to the sponsor only in coded form. The data enabling the identification of your identity will not leave the workplace of the examining physician. Only the examining physician, authorized representatives of the sponsor (eg monitor and auditors), persons authorized by national control authorities (State Institute for Drug Control - SÚKL) and members of the ethics committee have access to your personal records in medical documentation, ie. persons in charge of supervising the course of the clinical trial. These persons are bound by professional secrecy. During the study, genetic information is archived in the form of a frozen stool and plasma sample.

For further information you can contact the main investigator doc. MUDr. František Dušek, PhD on tel 608405541.

The examining physician informed the patient in detail and answered additional questions:

name and surname:

date:

signature:

Confirmation:

I declare that I understand all the data, instructions and written consent that have been communicated and explained to me. I consider the lessons to be sufficient and I agree to participate in this scientific project. I have been informed of the possibility to withdraw from participating in the said scientific project at any time.

date:

signature:

Close / Family: I hereby confirm that I understand the above information that I have had the opportunity to ask additional questions that have been answered.

date:

signature:

Independent physician: I hereby confirm that the patient meets the inclusion criteria and is unable to give informed consent on his own. I believe that inclusion in the study is in his best interest

date:

name:

signature: