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Turmeric and LED in the treatment of sore throat

Submission date 05/06/2019	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol
Registration date 14/04/2020	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 14/04/2020	**Condition category** Respiratory	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims
In the last two decades, we have witnessed the emergence and spread of bacteria resistant to multiple antibiotics. Multiresistant bacteria are currently considered as an emerging global disease and important public health problem. Coordinated efforts are required for the development of new diagnostic and treatment strategies as well as new antibiotics. Photodynamic therapy (PDT) is a treatment that uses light to cause cells to die. It has been shown to be effective against bacteria for dental procedures and oral disinfection. Sore throat is a common complaint in outpatient medical consultations and emergencies. The conventional treatment of bacterial pharyngotonsillitis (inflammation of the tonsils and other parts of the throat) involves oral antibiotics, and there is often inappropriate and excessive use of antibiotics in pharyngitis of other causes, potentially leading to resistance. Even in streptococcal pharyngotonsillitis, at least seven days of treatment are required for a full response. The aim of this study is to assess the effectiveness of PDT with curcumin in the treatment of acute pharyngotonsillitis in adults in the city of São Carlos.

Who can participate?
Patients aged of 18 to 45 with acute pharyngotonsillitis

What does the study involve?
Participants undergo testing for the bacteria Group A beta-hemolytic Streptococcus (EBHGA). Participants with streptococcal pharyngotonsillitis are randomly allocated into two groups: Group A1 receive antibiotics and PDT, and Group A2 receive antibiotics and placebo (sham) PDT. Participants with non-streptococcal pharyngotonsillitis are randomly allocated into two groups: Group B1 receive PDT, and Group B2 receive placebo PDT. The response to treatment is assessed in terms of clinical symptoms (sore throat and fever) and microbiological response (presence of EBHGA).

What are the possible benefits and risks of participating?
Participants receive direct and frequent care with a team of specialists for a follow-up period of at least 60 days. If there is evidence of bacterial infection, they receive treatment with antibiotics provided by the study at no additional cost. Although participants may not receive PDT, they will be contributing to the development of a new form of treatment that could be

widely used in the very near future and help to decrease the use of antibiotics. It is expected that this treatment will contribute to the reduction of complications such as rheumatic fever and kidney disease (post streptococcal acute glomerulonephritis). Experimental studies show that PDT can cause mild inflammation of the mouth when used for a very long time (greater than 5 minutes). The treatment time used in the study has not caused inflammation of the mouth in either animals or humans. Still, the side effect that could occur, although rarely, is a slight inflammation of the mouth. Although completely painless, mild discomfort (vomiting) may occur at the time of collecting the pus from the throat with the special swab, but this is currently indicated for throat treatment even if not participating in the study. Antibiotics may occasionally cause an allergic reaction. If participants already know that they have some type of allergy, the researchers can change the type of antibiotic prescribed. The antibiotic will be the same as would be taken even if you not participating in the study. If participants are indicated to use analgesics or anti-inflammatories, they may occasionally also have intolerance or allergy to this medicine. The medication will be the same as they would take even if they did not participate in the study.

Where is the study run from?
University of São Paulo (Brazil)

When is the study starting and how long is it expected to run for?
February 2018 to July 2020

Who is funding the study?
Foundation for Research Support of the State of São Paulo (FAPESP) (Brazil)

Who is the main contact?
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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
RBR-5fqbj9 - Brasilian Clinical Trial Registry (ReBEC)

Study information

Scientific Title
Photodynamic action in the treatment of streptococcal pharyngotonsillitis

Study objectives
Photodynamic therapy can be used to treat infections and may be associated with or eventually replace antimicrobial use. The use of the photosensitizer dye curcumin, which has low bioavailability, allows the local use, without systemic action in diseases involving mucous membranes. Acute pharyngotonsillitis is a common disease in adults, and antibiotic therapy is usually indicated in case of EBHGA infection due to the risk of systemic complications. In cases of pharyngotonsillitis caused by Fusobacterium necrophorum (Fn), antibiotic therapy for the risk of Lemierre's syndrome is indicated, as well as treatment in the case of gonococcal pharyngotonsillitis. In pharyngotonsillitis due to other etiologies, there is no established consensus treatment. The development of new therapeutic options for pharyngotonsillitis would allow the reduction of systemic adverse effects with the use of antibiotics, the emergence of bacterial strains resistant to the available antimicrobial agents and could also lead to the less abusive use of antimicrobials. The aim of this study is to evaluate photodynamic therapy as a coadjuvant agent in adults in the city of São Carlos and region and that the study will generate a report evaluating the therapeutic efficacy of Photodynamic Therapy, generating the possibility of new studies to propose an alternative for the use of antibiotics in the treatment of pharyngotonsillitis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/05/2018, Committee on Ethics in Research in Human Beings of Santa Casa de Misericórdia de São Carlos (R. Paulino Botelho de Abreu Sampaio, 535 - Jardim Puraza, São Carlos - SP, 13561-060, Brazil; Tel: +55 (0)35091307), ref: CAAE: 83082018.4.0000.8148

Study design
Randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Pharyngotonsillitis; bacterial infections and mycoses; pharyngitis; pathological conditions, signs and symptoms; acute tonsillitis

Interventions
All patients with clinical suspicion of pharyngotonsillitis will be examined and investigated for fever, tonsillar hypertrophy, tonsillar exudates, anterior cervical adenomegaly, mucosal lesions (petechiae, vesicles, exulcerations), cough, nasal obstruction, tearing and diarrhea. Patients will then be assessed for inclusion and exclusion criteria. Once admitted to the study, oropharynx smears will be collected for rapid testing for EBHGA, Gram staining and general culture on blood, chocolate and MacConkey; polymerase chain reaction for Fusobacterium necrophorum (Bank F et al., 2010) and panel detection of respiratory viruses by polymerase chain reaction (influenza A and B viruses, adenovirus, Rhinovirus, coronavirus and EBV). According to the positivity in the rapid test for EBGA detection, the patient will be divided into groups A (TR +) and Group B (TR-). As patients are admitted to groups A and B, they will be randomly divided again to receive photodynamic therapy (PDT) or not. In this way four groups of participants will be constituted:
Group A1 = Antibiotic therapy + photodynamic therapy
Group A2 = Antibiotic therapy + placebo of photodynamic therapy
Group B1 = Photodynamic therapy
Group B2 = Placebo of photodynamic therapy

A total of 1.2 x (22 + 82) = 125 patients should be included. Thus, the distribution of a total of 126 patients will be:
Group A1: 13 patients
Group A2: 13 patients

Group B1: 50 patients
Group B2: 50 patients

Patients selected for photodynamic therapy will suck two bullets with photosensitizer (FS), the natural curcumin from PDT Pharma (http://www.pdtpharma.com.br/). The concentration of curcumin to be used will be 0.75 mg/mL or 22.5 mg/bullet. After the patient sucks the curcumin bullet, the oral cavity will be illuminated with blue light emitting system (LED), with a wavelength of 450 nm. The lighting system (Patent: BR10201601347) ensures that the illumination of the oropharynx is homogeneous with illumination intensity of 20 mW / cm2 with 2.4 J / cm2. The equipment is manufactured by MM Optics (http://en.mmo.com.br/), and has already been approved by ANVISA for photopolymerization of dental enzymes (registration 80051420018). The system is formed by a set of optical fibers having at one of its ends the flat arranged fibers. For the design, a diffuser tip will be adapted to ensure uniform hemispheric illumination. The system with diffusion tip adaptation has already been used in a disinfection study in healthy adults with no local adverse effects. The survey participant will receive the recommended lighting during five minutes of exposure, when the device automatically switches off. The tip will be placed two centimeters from the retropharynx, without physical contact with the mucous membranes, which will guarantee the recommended exposure angle.

Patients selected for placebo of photodynamic therapy will suck two gelatine-based bullet, provided by PDT Pharma. They will use as a placebo the same blue light emitting device of wavelength of 450 nm, but with metal protection on the optical fiber base that prevents 90% of the passage of light.

All patients diagnosed with streptococcal pharyngotonsillitis (Group A) by rapid positive test (TR +) will receive antibiotic treatment consisting of the antibiotic amoxicillin in 500 mg capsules, Amoxil® brand, Smith-Kline Laboratory Beecham, in the dosage of 500 mg orally for 8/8 hours for 10 days. If the patient is allergic to amoxicillin, he or she will be given the antibiotic clarithromycin prescription in 500 mg film-coated tablets of the trademark Clarithromycin® from the Medley laboratory, at a dose of 500 mg orally every 12 hours for 10 days. All antibiotics given reference drugs, according to the National Agency of Sanitary Surveillance (ANVISA), a survey conducted on the official website on June 2, 2018, at http://portal.anvisa.gov.br /registros-e-autorizacoes/medicines/products/medicines-reference/list.

Therapy with penicillin (amoxicillin or oral penicillin V) or with macrolides (in case of allergy to penicillin) is recommended by international medical societies.
All patients diagnosed with non-streptococcal pharyngotonsillitis (Group B) will receive only symptomatic treatment. Recalling that if there is sepsis or any evidence of local complication (Lemierre's syndrome), the patient should have been excluded and treated appropriately according to medical criteria. Depending on the clinical symptoms and medical criteria, anti-inflammatories and analgesics such as diclofenac, ibuprofeno and paracetamol may be used, also according to the Brazilian Society of Otorhinolaryngology.

Returns for clinical reassessment and antibiotic therapy will be performed after 48 hours, 10 days, 30 days and 60 days after PDT. In the return visits, clinical reassessment will be performed and the results of oropharyngeal culture will be checked. If necessary, by the presence of symptoms and/or bacterial growth in the culture, antibiotic therapy may be instituted or reviewed, according to the agent isolated in culture.

In addition to the programmed returns, the patient will record in the study journal, adequate form to be provided by the research, the possible occurrences of signs and symptoms and the evolution of the clinical picture, as well as adverse effects that may occur. You may also request

extra consultation in case of symptoms.
The following outcomes will be assessed:
1. Clinical:
1.1. Fever
1.1.1. Presence of fever in 48 hours
1.1.2. Duration of fever in days
2. Pain
2.1. Presence of pain in 48h
2.2. Duration of pain in days
3. Lemierre syndrome
4. Recurrence
2. Laboratory
2.1. Oropharynx swab culture - Pre, 5 min, after the intervention and 48h after the intervention
3. Complications:
3.1. Rheumatic fever - 2 months
3.2. GNDA post streptococcal - 1 month
3.3. Peritonsillar abscess - 14 days

The diagnosis of rheumatic fever is based on the Jones Criteria Modified (2015). The criteria are: (a) carditis, (b) arthritis (polyarthritis, polyarthralgia and / or monoarthritis), (c) chorea, (d) erythema marginate, (e) subcutaneous nodule. The following criteria are minor: a) monoarthralgia, b) fever (> 38.5°C), c) increase in erythrocyte sedimentation rate - ESR (? 60 mm in the first hour) and/or C-reactive protein - CRP mg/dL), (d) prolongation of the prolonged PR interval. The diagnosis of rheumatic fever will be based on the evidence of previous EBHGA infection (rapid test or culture) and the presence of at least two major criteria, or a major criterion and two minor criteria. Only complementary investigation (inflammatory tests, echocardiography, electrocardiogram) will be performed in case of compatible clinical symptomatology.

The diagnosis of acute diffuse post-streptococcal glomerulonephritis is clinically based on the presence of the classical triad: edema, arterial hypertension and hematuria. Confirmation is confirmed by hematuria and proteinuria in the urine sediment, by elevated serum urea and creatinine concentrations.
Any clinical complications will be diagnosed and treated under the direct responsibility of the investigating physicians within the UFSCar health network (medical outpatient clinics, University Hospital of UFSCar) and USP.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Curcumin gum

Primary outcome measure
Negativation of counting colonies of EBHGA in culture of oropharyngeal swabs, verified after five minutes and after two days of intervention

Secondary outcome measures

Fever resolution, verified by the rate of fever resolution in two days of treatment, and by the number of days until fever resolution

Overall study start date
05/02/2018

Completion date
01/07/2020

Eligibility

Key inclusion criteria
1. Age between 18 and 45
2. Signature of the Informed Consent Form
3. Presence of fever > 38ºC, oropharyngeal hyperemia, hypertrophy or presence of exudate in palatine tonsils

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
125

Key exclusion criteria
1. Use of antibiotics in the 24 hours prior to admission to the protocol
2. Clinical condition indicating the immediate use of antibiotic therapy (sepsis, peritonsillar abscess, organic insufficiency, immunodeficiency, clinical suspicion of Lemierre's syndrome)

Date of first enrolment
20/05/2019

Date of final enrolment
01/07/2019

Locations

Countries of recruitment
Brazil

Study participating centre
Santa Casa de Misericórdia de São Carlos
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Organisation
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Funder(s)

Funder type
Research organisation

Funder Name
Fundação de Amparo à Pesquisa do Estado de São Paulo

Alternative Name(s)
São Paulo Research Foundation, State of São Paulo Research Foundation, Foundation for Research Support of the State of São Paulo, FAPESP

Funding Body Type
Private sector organisation

Funding Body Subtype
Local government

Location
Brazil

Results and Publications

Publication and dissemination plan
The researchers intend to publish the research protocol before the end of the study.

Intention to publish date
01/07/2020

Individual participant data (IPD) sharing plan
The data is being kept in REDCAP and the researchers intend to make it available after publication.

IPD sharing plan summary
Stored in repository