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Efficacy of nitric-zinc complex in the treatment of genital warts

Submission date	Recruitment status	[_] Prospectively registered
19/03/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
03/04/2020	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
03/08/2020	Infections and Infestations	

Plain English summary of protocol

Background and study aims
Genital warts is a common sexually transmitted infection (STI) passed on through vaginal, anal and, rarely, oral sex.
In this study the researchers want to evaluate the effectiveness of Verrutop®, a solution based on Nitrizinc Complex, a recently marketed medical device for the painless treatment of external genital warts, by means of a comparative procedure with Cryotherapy, one of the most common methods in clinical practice with 55% efficacy data. Verrutop® performs a selective action on the wart, sparing healthy skin; this determines a low invasiveness of the treatment with a lower incidence of side effects and post-treatment outcomes; in addition, nitric oxide, which is generated during therapy with Verrutop®, performs an antiviral action thus reducing the risk of recurrence.

Who can participate?
Adults over 18 years, with more than three untreated ano genital warts.

What does the study involve?
Participants will be randomly allocated to receive treatment for warts using either cryotherapy or Verrutop®: solution based on Nitrizinc Complex®. Each patient will receive up to four applications of the treatment as deemed necessary by the doctor. Treatment will last up to one month and there will be a follow-up appointment at three months.

What are the possible benefits and risks of participating?
Benefits:
Effectiveness of both treatments in the partial and/or complete elimination of external genital warts; from the literature data Verrutop® should be more effective than Cryotherapy (75% vs 55%), the advantages in the use of Verrutop® are the non-invasiveness of the treatment as it is able to act directly on the lesion excluding the periwound skin and less risk of recurrence thanks to the antiviral action mediated by nitric oxide released during application.
Risks:
Side effects are extremely rare and, in any case, occur only locally.
Cryotherapy is often accompanied by the appearance of burning pain at the application site; in the following days a bullous lesion is formed which evolves into erosion. Complete re-

epithelialization is generally accomplished in 7-10 days. This result can leave hypopigmentary and / or cicatricial results, especially if carried out on dark phototypes. Rarely, hypertrophic scars or small horny cysts can form.
Verrutop® is a substantially painless and selective treatment on the pathological tissue; therefore the therapeutic action focuses only on the wart with the saving of healthy tissue. Thanks to its mechanism of action which causes the "mummification" of the wart, Verrutop® does not cause ulceration and, consequently, does not cause scarring or hypopigmentary outcomes.

Where is the study run from?
1. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Italy)
2. Ospedale San Lazzaro (Italy)
3. Policlinico Sant'Orsola-Malpighi (Italy)

When is the study starting and how long is it expected to run for?
December 2017 to August 2019

Who is funding the study?
ISDIN (Spain)

Who is the main contact?
Dr Marco Cusini
marco.cusini@policlinico.mi.it

Contact information

Type(s)
Scientific

Contact name
Dr Marco Cusini

ORCID ID
http://orcid.org/0000-0003-4757-6798

Contact details
Dermatology Unit
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Via Pace, 9
Milan
Italy
20122
+39 (0)2 5503 5236
marco.cusini@policlinico.mi.it

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
1850/2017

Study information

Scientific Title
Comparative efficacy study between "Nitrizinc complex®" and cryotherapy in the treatment of external genital warts

Study objectives
Nitrizinc complex® is more effective than cryotherapy in the treatment of genital warts

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/11/2017, IRCCS Ospedale Maggiore Policlinico - Ca Granda Foundation (Segreteria Comitato Etico, Ospedale Maggiore Policlinico, Milano, Area 2, Italy; +39 (0)2 5503 5832; isabella.damilano@policlinico.mi.it), ref: 1850

Study design
Multicenter prospective randomized comparative study

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Ano genital warts

Interventions
Patients are assigned to one of the two arms according to a specially prepared block randomization list of 4 patients. Only after the enrollment of each patient does the statistician

communicate to the clinicians the treatment to be assigned in order to better guarantee the randomization management.

Cryotherapy: treatment based on the application of liquid nitrogen; Nitrogen is an inert, non-flammable gas which, in the liquid state found -196 ° C, is a suitable temperature for the induction of cytolysis of the pathological tissue. Liquid nitrogen can be applied to the wart using various devices, among which the most used are those that represent the dispensing of the product in the form of a spray. The duration of the application varies according to the lesion treated and in the media lasts a few seconds.

Verrutop®: solution based on Nitrizinc Complex®. This solution applied on the warts causes a change of colour (white-yellowish) and a hardening of the treated tissue ("mummification" process) favouring the renewal of the skin cells and the detachment of the wart. The treatment must be carried out by health personnel and takes place in the extraction of the product from a vial through a capillary and in the application of the same direct on the wart by direct contact.

At the time of enrollment, patients will be treated either with Verrutop® or with Cryotherapy. They will then be re-evaluated 10 days after the first treatment session and, in case of persistence of the lesions, another application will be carried out, for a maximum of four treatments. At the end of the four sessions, the experimenter will evaluate the response to the treatment; the evaluation includes three options:
1. Complete regression
2. Partial regression (reduction = or> 50% of the number of lesions)
3. No regression (<50% reduction in the number of lesions)

The tolerability of the two treatments will be assessed by both the investigator and the patient during and at the end of the study and will be expressed as good, moderate, poor after evaluation, at each follow-up visit, of 3 parameters:
1. Pain reported by the patient and defined as: mild 1 - moderate 2 - intense 3
2. Itching reported by the patient and defined as: mild 1 - moderate 2 - intense 3
3. Inflammation (observed by the doctor) and defined as: erythema: 1 - erosion: 2 - blisters: 3 - ulcer: 4

Only patients with complete injury regression will enter follow-up (T0), while patients with partial or absent regression will be referred to another conventional treatment. Follow-up visits will be carried out after 1 month (T1) and 3 months (T2) by T0. In the event of recurrence during follow-up, the patient will be referred to another conventional treatment.

Intervention Type
Procedure/Surgery

Primary outcome measure
At the end of the four sessions and again at three months, the experimenter will evaluate the response to the treatment; the evaluation includes three options:
1. Complete regression
2. Partial regression (reduction = or> 50% of the number of lesions)
3. No regression (<50% reduction in the number of lesions)

Secondary outcome measures
The tolerability of the two treatments will be assessed by both the investigator and the patient after every treatment session and at the end of the study and will be expressed as good,

moderate, poor after evaluation, of 3 parameters:
1. Pain reported by the patient and defined as: mild 1 - moderate 2 - intense 3
2. Itching reported by the patient and defined as: mild 1 - moderate 2 - intense 3
3. Inflammation (observed by the doctor) and defined as: erythema: 1 - erosion: 2 - blisters: 3 - ulcer: 4

Overall study start date
23/01/2017

Completion date
01/11/2019

Eligibility

Key inclusion criteria
1. First episode never treated
2. Number of lesions: 3 to 10
3. Size of the single lesion: 1-5 mm
4. Location: penis/vulva/perianal region

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
120

Total final enrolment
120

Key exclusion criteria
1. Previously treated patients
2. Circumcised patients
3. Immunosuppressed patients due to pathological and/or iatrogenic causes
4. Patients with diabetes mellitus
5. Pregnant women

Date of first enrolment
01/12/2017

Date of final enrolment
01/08/2019

Locations

Countries of recruitment
Italy

Study participating centre
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Dermatology Unit
Via Pace, 9
Milano
Italy
20122

Study participating centre
Ospedale San Lazzaro
Medical Science Department
Dermatologic Clinic
University of Turin
via Cherasco, 23
Turin
Italy
10126

Study participating centre
Policlinico Sant'Orsola-Malpighi
Dermatology Unit
Via Albertoni, 15
Bologna
Italy
40138

Sponsor information

Organisation
Isdin (Spain)

Sponsor details
Provençals 33
Barcelona
Spain
08019
(+34) 932 402 020
corinne.granger@isdin.com

Sponsor type
Industry

Website
https://www.isdin.com

ROR
https://ror.org/04dg86p75

Funder(s)

Funder type
Industry

Funder Name
ISDIN (Spain)

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/04/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to privacy reasons. In particular data will be kept as hospital sensitive data in encrypted files accessible only to those who conducted the study. Maintained for 10 years and the data of each individual patient will never be made public.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version v3	08/11/2017	03/04/2020	No	No
Results article	results	01/10/2020	03/08/2020	Yes	No