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Comparison of techniques of stem cell transplantation in patients with bilateral ocular surface disease

Submission date
13/07/2024

Recruitment status
No longer recruiting

Registration date
17/07/2024

Overall study status
Completed

Last Edited
21/10/2024

Condition category
Eye Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Bilateral ocular surface disease resulting from Stevens-Johnson Syndrome and chemical injuries are visually debilitating and difficult to treat. Ocular surface reconstruction by various means has been reported with variable results. This study addresses an unmet need for a prospective clinical trial comparing the outcomes of transplanting autologous oral and conjunctival epithelial cell constructs on human amniotic membranes by ex vivo tissue engineering.

Who can participate?
Patients aged between 5-90 years old with ocular surface diseases

What does the study involve?
The study included a total of 50 patients of bilateral limbal stem cell deficiency (LSCD) with limbal affected area at least 6-9clock hours with Schirmer test value less than 5mm and with no systematic disorder contraindication surgical intervention. Autologous regenerative transplantation procedure, randomized into two treatment groups, i.e. COMET and CCET. There were 25 patients in the COMET group and 25 patients in the CCET group. The sample size was calculated in the study by using a clinical superiority design. Statistical Package for Social Sciences (SPSS) version 15.0 is used to generate the random number sequences and participants were randomized to two study groups. All patients underwent comprehensive ophthalmic examination at baseline and every follow-up visit. All patients underwent surgery in one eye only. The study is an open-label design.

What are the possible benefits and risks of participating?
The possible benefit of the autologous treatment is to help reconstruct the ocular surface. No serious or other adverse events are expected during the follow-up of studies.

Where is the study run from?
Dr Rajendra Prasad Centre for Ophthalmic Sciences, Eye Bank Clinic, New Delhi, India

When is the study starting and how long is it expected to run for?
December 2013 to March 2023

Who is funding the study?
Supported by a research grant-in-aid from the Department of Biotechnology, Ministry of Science and Technology, Government of India

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
BT-1829/CSP-01, BT/01/COE/07/03

Study information

Scientific Title
Comparative evaluation of the efficacy of conjunctival stem cell transplantation with cultivated oral mucosal epithelial transplantation in patients with bilateral cicatrizing ocular surface diseases

Acronym
RCTCOMETCCET-2017

Study objectives
The corneal epithelial stem cell resides in the basal layer of the limbus, the transitional zone between the cornea and the bulbar conjunctiva. These cells govern the renewal of the corneal epithelium by generating progeny (transient amplifying cells, which are cells committed to epithelial differentiation) with limited renewal capabilities that migrate from the limbus into the basal layer of the cornea. If corneal epithelial stem cells are completely absent owing to limbal

disorders such as severe thermal or chemical burns, the source of corneal epithelial cells has been exhausted, the peripheral conjunctival epithelium invades inwardly, and the corneal surface becomes enveloped by vascularized conjunctival scar tissues, resulting in corneal opacification leading to severe visual impairment. Such pathological characteristics are considered to represent limbal stem cell deficiencies. Limbal Allograft transplantation can be performed in patients with unilateral or bilateral deficiencies, but it requires long-term immunosuppression that involves a high risk of serious eye and systematic complications. In patients with Stevens-Johnson syndrome or ocular pemphigoid, graft failure is common, even with immunosuppression, owing to serious preoperative conditions such as persistent inflammation of the ocular surface, abnormal epithelial differentiation of the ocular surface, severe dry eye and lid-related abnormalities. To avoid allograft rejection and improve surgical outcomes, some patients with unilateral stem cell deficiencies have had limbal autografts taken from the healthy eye as well as corneal epithelial grafts constructed ex-vivo by the expansion of autologous limbal stem cells harvested from healthy contralateral eyes and cultivated on cell carries such as amniotic membranes and fibrin gel with encouraging results. This process, however, cannot be used for bilateral ocular surface diseases or bilateral total limbal stem cell deficiencies.

Such patients can be helped by ex-vivo cultivated oral mucosal stem cell transplantation & conjunctival stem cell transplantation. The oral epithelium has attracted attention as a cell source, and favourable results have been obtained in animal and human studies. This study is a comparative study of conjunctival epithelial stem cell transplantation with cultivated oral mucosal epithelial transplantation in patients with bilateral ocular surface diseases i.e. Steven's Johnson syndrome & Chemical burns. A study by Leonard P. K. Ang and his co-workers showed that ex vivo cultivation of conjunctiva to form transplantable epithelial sheets for corneal replacement is a promising new treatment modality in patients with limbal stem cell deficiency (LSCD). The role of cultivation of oral mucosal stem cells and transplantation onto the ocular surface for bilateral stem cell deficiencies has been well established. However, studies evaluating the role of conjunctival epithelial stem cell transplantation in bilateral cicatrizing ocular surface diseases are needed. The present study intends to evaluate the same and compare the results with cultivated oral mucosal epithelial transplantation as initial surgical therapy in bilateral ocular surface diseases and also to compare direct limbal lenticular, simple limbal epithelial and cultivated limbal epithelial transplantation in patients with unilateral LSCD.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 17/01/2017, Institutional Commitee for Stem Cell Research (All India Institute of Medical Sciences, Ansari Nagar, New Delhi, 110029, India; +911126594579; stemcellcommittee@gmail.com), ref: IC-SCR/07/14/(R1)

2. approved 28/04/2014, Institue Ethics Committee, All India Institute of Medical Sciences (Room No. 102, 1st Floor Old OT Block, Ansari Nagar, New Delhi, 110029, India; +91 011-26594579; ethicscommitteeaiims@gmail.com), ref: IEC/NP-99/11.04.2014

Study design
Randomized parallel-group multiple-arm trial

Primary study design
Interventional

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Reconstruction of ocular surface by using stem cell therapy in patients with ocular surface disease

Interventions
Cultivated Oral Mucosal Epithelial Transplantation (COMET) and Conjunctival Cultivated Epithelial Transplantation (CCET) for ocular surface reconstruction in patients with bilateral ocular surface disease due to Stevens-Johnson Syndrome.

A. Cultivated Oral Mucosal Epithelial Transplantation (COMET):
1. Preparation:
Sterilize the oral cavity with a povidone-iodine 5% solution
Harvest a 4 mm x 4 mm tissue strip from the buccal mucosa under local anaesthesia
Collect the tissue in a transport medium (DMEM with antibiotics)

2. Cultivation:
Wash the harvested tissue with sterile phosphate-buffered saline
Culture the tissue over a denuded amniotic membrane with DMEM/F12, 10% autologous serum, and antibiotics
Incubate at 37°C in a 5% CO_2 incubator, changing the media daily
Observe cell growth at 24 hours, day 3, day 5, day 7, and day 11

3. Transplantation:
After two weeks, when a confluent cell sheet forms, transplant it in the recipient's eye
Dissect the fibrovascular pannus and spread the cell sheet over the cornea and limbus
Secure the membrane with fibrin glue and place a bandage contact lens

B. Conjunctival Cultivated Epithelial Transplantation (CCET):
1. Preparation:
4 mm x 2 mm tissue strip harvested from the conjunctival fornix
Transport media and cultivation procedures were the same as for COMET

2. Cultivation:
Culture the tissue over a denuded amniotic membrane using the same method as COMET

3. Transplantation:
After two weeks, transplant the confluent cell sheet in the recipient's eye
Followed the same transplantation steps as in COMET

C. Post-Operative Management and Follow-Up
1. COMET and CCET Recipient Eyes:
Moxifloxacin 0.5% eye drops thrice daily for four weeks
Carboxymethylcellulose 0.5% eye drops six times daily for two months, then four times daily
Prednisolone phosphate 1% eye drops four times daily for two weeks, tapering once daily over three months.
Fluorometholone 0.1% eye drops four times daily for two weeks, tapering once daily over three months.

2. Donor Eyes in CCET Group:
Moxifloxacin 0.5% eye drops thrice daily and gatifloxacin 0.3% ointment at bedtime for one week.
Carboxymethylcellulose 0.5% eye drops four times daily for three months

3. Oral Mucosa in COMET Group:
Povidone-iodine 5% rinse and gargle for four days
Mild painkiller twice daily for three days

Patients will be reviewed at baseline and on the first postoperative day, at one week, two weeks, four weeks, two months, three months, and six months. Comprehensive ophthalmic examinations were conducted at each visit.

Randomization process: Randomization was done using SPSS version 15.0.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Cultivated oral mucosal epithelial transplantation (COMET), Conjunctival cultivated epithelial transplantation (CCET)

Primary outcome(s)
The following primary outcome measures were assessed at baseline, post-op weeks 1, 2 and 4, and months 2, 3 and 6:
1. Surgical success, defined as complete epithelization and a clinically stable corneal surface, evaluated through slit lamp biomicroscopy and clinical photographs measured using ImageJ software
2. Vascularization, defined as a complete success if the cornea is avascular and partial success if there is mild vascularization not reaching up to the centre of the cornea which is completely epithelized, assessed by using slit lamp biomicroscopy and clinical photographs measured using ImageJ software
3. Conjunctivalization, defined as a complete success if there is an absence of conjunctivalization and a partial success if there is mild conjunctivalization, examined by using slit-lamp biomicroscopy and clinical photographs measured using ImageJ software

Key secondary outcome(s))
The following secondary outcome measures were assessed at baseline, post-op weeks 1, 2 and 4, and months 2, 3 and 6:
1. Improvement in best corrected visual acuity (BCVA) measured using a Snellen Visual acuity Chart
2. Improvement in corneal transparency evaluated by using slit-lamp biomicroscopy and measured using a clinical photograph and corneal grading system

Completion date
31/03/2023

Eligibility

Key inclusion criteria
1. Pediatric patients from the age group 5-18 years old
2. Adult patients from the age group above 18 years old
3. Unilateral and bilateral ocular burns i.e. Steven Johnson syndrome and chemical burns
4. In unilateral affected patients limbal area affected should be 6 - 9 clock hours
5. Schirmer test value of at least 5 mm
6. Willing to follow-up for at least 6 months
7. No systematic disorder contradicting surgical intervention
8. Patients in whom primary insult occurred at least >4 months ago

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
5 years

Upper age limit
90 years

Sex
All

Total final enrolment
50

Key exclusion criteria
Untreated concurrent problems, such as adnexal problems, glaucoma and infection

Date of first enrolment
10/01/2018

Date of final enrolment
05/11/2022

Locations

Countries of recruitment
India

Study participating centre
Dr. Rajendra Prasad Centre for Ophthalmic Sciences
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Sponsor information

Organisation
Department of Biotechnology

ROR
https://ror.org/03tjsyq23

Funder(s)

Funder type
Government

Funder Name
Department of Biotechnology, Ministry of Science and Technology, India

Alternative Name(s)
Dept. of Biotechnology, Govt of India, , , Department of Biotechnology, Department of Biotechnology, Ministry of Science & Technology, India, Department of Biotechnology, GOI, Dept. of Biotechnology, Govt. of India, Department of Biotechnology, Ministry of Sc & Tech, Govt of India, DBT

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
India

Results and Publications

Individual participant data (IPD) sharing plan
The dataset generated during and analysed during the current study will be available upon request from Prof Radhika Tandon, radhikatandon@aiims.edu

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		18/10/2024	21/10/2024	Yes	No
Protocol file			17/07/2024	No	No