International Journal of Medical and Pharmaceutical Case Reports
4(3): 72-76, 2015; Article no.IJMPCR.2015.064
ISSN: 2394-109X

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Use of Human Embryonic Stem Cells (hESCs) in the Treatment of Glaucoma

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Authors' contributions

This work was carried out in collaboration between both authors. Author GS conceived of the study, and participated in its design and coordination and helped to draft the manuscript. Authors GS and LD read and approved the final manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJMPCR/2015/18440
Editor(s):
(1) Syed A. A. Rizvi, Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, USA.
Reviewers:
(1) S. K. Prabhakar, Ophthalmology, JSS University, India.
(2) Anonymous, Department of Health Sciences Research, Mayo Clinic College of Medicine, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1101&id=38&aid=9406

Case Study

Received 21st April 2015
Accepted 6th May 2015
Published 25th May 2015

ABSTRACT

Glaucoma is a degenerative, optic neuropathy that results in damage to the optic nerve due to increased intraocular pressure (IOP). IOP can be influenced by hypertension, body mass index, atherosclerotic disease and diabetes. Cell based therapies play an important role in treating eye diseases, especially (irreversible loss of cells) due to glaucoma. We used human embryonic stem cell (hESC) therapy in two patients with glaucoma. hESCs are derived from a patented technology and are in use since the last 13 years. After the therapy, patients showed signs of improvement in their sight such as in peripheral vision, as well as in cognitive abilities like concentration and speech.

Keywords: Glaucoma; hESC; IOP.

ABBREVIATIONS

POGA (primary open angle glaucoma); AMD (age related macular degeneration); hESCs (human embryonic stem cells); OPCs (oligodendrocyte precursor cells); RGCs (retinal ganglion cells); VEP (Visual evoked potential) and ERG (electroretinogram).

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1. INTRODUCTION

Glaucoma is a degenerative, optic neuropathy [1] resulting in structural damage to the optic nerve due to intraocular pressure (IOP) followed by visual dysfunction [2]. The IOP can be influenced by hypertension, body mass index, [3] atherosclerotic disease and diabetes [4]. The most common form of glaucoma is primary open angle glaucoma (POGA), in which sudden buildup of fluid occurs within the eye.

Glaucoma is the leading cause of blindness in the United States and around the world [5]. Resnikoff and colleagues reported that about 37 million people with glaucoma worldwide became blind, of which 82% were 50 years and older [6].

There is no effective cure for glaucoma. Medicines (like prostaglandin analogs, mitotics, carbonic anhydrase inhibitors), LASER and surgeries are used to prevent further damage of the eyes by lowering the IOP [5]. Treatment with these medicines increases the risk of conjunctival hyperemia, irritation and ocular surface effects, hypertrichosis, pruritus, gastrointestinal disorders etc [7]. Treatment with laser and surgery may exacerbate the risk of bleeding, swelling in the eye, increased eye pressure and vision loss [5].

Stem cells have the potential to prevent the initial injury and increase the resistance of cells to injury (cytoprotection). Cell based therapies play an important role in treating eye diseases especially (irreversible loss of cells) due to glaucoma [8].

In our previous studies, we have shown the improvement in the patient with cerebral palsy and patients with cortical visual impairment after hESCs therapy [9,10]. Here, we present two cases of patients suffering from visual impairment as a result of glaucoma. The patients had an uneventful recovery after the treatment.

2. METHODOLOGY

The cell lines were cultured and maintained as per our proprietary in-house patented technology in a good manufacturing practices (GMP), good laboratory practices (GLP) and good tissue practices (GTP) certified laboratory (Patent-WO 2007/141657A PCT/1B 2007 published 13 December 2007).

The evidence for the use of hESCs at Nutech Mediworld has been submitted in written and accepted at House of Lords, Regenerative Medicine, Science and Technology Committee [11]. hESCs used in this study were chromosomally stable and free from animal and microbial product(s). We have established the safety and efficacy of this cell line in patients with incurable conditions [12].

The patients provided with a written and videographed informed consent before the start of the treatment. The study was approved by an independent institutional ethics committee. The institutional committee for stem cell research and therapy of Nutech Mediworld, New Delhi, India reports to the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT). Further, a detailed report of the patient regarding the therapy, its outcomes on patients and commencement of therapy was given to Government of India. We followed the guidelines of biomedical research (year 2000) on human participants in India.

Cells were administered through different routes; intramuscular (i.m) route twice daily to “prime” the body and, 1 ml hESCs (<16 million cells) were administered twice a week through intravenous (i.v) route to “home in” to the required area. The hESCs were also given as eye drops (1 mL of hESCs administered thrice with a gap of 30 minutes) twice a week and as retro-orbital injection (1mL) once in 21 days. The treatment phases were separated by a gap phase of 4-6 months. Visual evoked potentials (VEP) and electroretinogram (ERG) were performed before and after the therapy.

3. CASE PRESENTATION

3.1 Case 1

A 64 year male was admitted to our facility with chief complaints of poor vision, macular degeneration, diminished peripheral vision, increased IOP, and light sensitivity.

The patient was apparently well until 7 years of age, when he noted poor eyesight and consulted ophthalmologist. He was diagnosed with progressive myopia and was advised glasses. He underwent LASIK (bilateral) for his myopia 12-13 years back.

The patient had developed cataract 4 years ago and underwent phacotomy for the right eye 3.5 years ago and 4 months later for the left eye. At the same time, he was also diagnosed with

POGA that was worsening. He had a severe light sensitivity and was advised Timolol (1 drop OD, Merck) and Xalatan (1 drop OD, Pfizer) in the evening. He was also diagnosed with age related macular degeneration (AMD) and had loss of peripheral vision.

On examination, the patient had poor vision and macular degeneration. His flash VEP showed slightly delayed latency in the right eye as compared to the left eye and normal amplitude in both eyes. Pattern VEP showed delayed latency for all check sizes (12X16, 24X32 and 48X64) in the right eye and absent responses in the left eye. This indicated retinopathy in both eyes and posterior capsular opaqueness in the left eye. The patient was hypertensive for the last 20 years and was on medication (Coversel Plus 500mg OD, Servier Laboratories) and was a smoker. He had a family history of hypertension (both maternal and paternal side).

At our institute, hESCs therapy was started for the patient about 2.5 years back. After the therapy, peripheral vision improved significantly. He had a decreased light sensitivity and no progression was observed in the macular degeneration. His IOP is maintained. An improvement was observed in VEP and ERG after the therapy. The improvement in symptoms of the patient observed after the hESC therapy is presented in Table 1.

3.2 Case 2

A 9 yr old male child was admitted to our facility in April 2010 with complaints of aggressive behavior, poor concentration, poor balance, congenital cataract, glaucoma, phakic right eye with decreased vision, lack of speech and less social interaction.

The patient was born *via* caesarean section and had spontaneous birth cry with no obvious anomalies. Bilateral congenital cataract was operated with anterior vitrectomy and iridectomy at the age of four.

On examination, the right eye was phakic and did not respond to light and his concentration and balance was poor. The patient was diagnosed with autism, congenital cataract and glaucoma with a retinal detachment.

The patient was treated primarily with hESC and occupational therapy. After the therapy, an improvement in vision was observed. His pupil reacted to light and he could catch or throw ball. The inflammation of the eye was reduced. His speech and concentration also improved. He had reduced aggression and interacted well with others. The improvement in symptoms of the patient observed after the hESC therapy is presented in Table 1.

4. DISCUSSION

Our study reported the use of in-house cultured hESC therapy in the treatment of two patients with visual impairment due to glaucoma. Patients showed signs of improvement in their health after the treatment; such as improvement in peripheral vision, as well as in concentration and speech. No adverse events were seen in patients following the treatment with hESC.

A study by Sowmya et al. stated that mouse fibroblast induced pluripotent stem cells have the ability in generating an ample range of retinal cell types. These cells include retinal ganglion cells, cone and photoreceptors. This potency of stem cells manifest target specificity and accommodate in the outer nuclear layer of the host retina [13].

Another study by Natalie and colleagues concluded that oligodendrocyte precursor cells (OPCs), a type of neural stem cells incomparably embellishes the survival of retinal ganglion cells (RGCs) in the glaucotomous eye in a rat model. Thus, cell based therapies should be explored further as a potential treatment for retinal degenerative diseases including glaucoma, AMD, and retinitis pigmentosa (RP) [14]. The first clinical trial in Florida has just started in August 2013 using bone marrow-derived MSCs on glaucoma and will be completed in 2017 [15].

hESCs act by repairing and regenerating the injured tissue. Early analysis demonstrated that stem cells communicate with injured cells, and home at the site of injury. Homing signals, including cytokines, chemokines and growth factors released at the injured site attracts systemically or locally administered stem cells to the site. These signals function by inducing upregulation of selectins and activation of integrins, present on the surface of the stem cells [16-18]. Liu and colleagues showed tha t progenitor stem cells arrive at the optic nerve injury site and repair the injured tissue by enhancing angiogenesis [19]. Previous studies have also reported migration and differentiation of hESCs after intraocular injection [20]. The eye drops and retro-orbital injection help in delivering the hESCs to the local area of action.

Table 1. Symptoms of the patients before and after the hESC therapy

Case 1		Case 2	
Before hESC therapy	**After hESC therapy**	**Before hESC therapy**	**After hESC therapy**
Poor vision	Improved vision	No speech	Speech improved with loud voice
Macular degeneration	No progress in macular degeneration	No social interaction	Interacts well with others
Diminished peripheral vision	Peripheral vision improved	Aggressive behavior	Aggression reduced- no more hand flapping
Light sensitive	Not more light sensitive	Poor concentration	Improved concentration
Increased IOP	IOP maintained	Poor balance	Good balance - can climb stairs
		Right eye redness with decreased vision	Vision improved with reduced inflammation

We possibly assume that the hESCs used in our study also rely on the same mechanism of action. hESCs used in our study have a very small size (<1 μm) and can thus permeate across parenchyma and migrate to the damaged zone and replace the damaged cell. We have previously reported an improvement in vision with hESC therapy in 40 patients with cortico-visual impairment. After the therapy, 27 patients gained normal vision; 10 patients could see objects up to 25 cm from the eye; 2 patients could see blurred images; and 1 had perception of light [21].

5. CONCLUSION

Therefore, it is summarized that hESCs showed good therapeutic potential in the treatment of patients with visual impairment due to glaucoma. We have been using hESCs for patients with various incurable conditions since last 13 years and have not observed any AE. However, more clinical trials and follow-up studies are needed to prove the long term efficacy and safety of hESCs in the treatment of patients with glaucoma.

ACKNOWLEDGEMENTS

The author acknowledges all the doctors, staff and patients of the Nutech Mediworld. The author also acknowledges Knowledge Isotopes Pvt. Ltd. (http://www.knowledgeisotopes.com) for the writing support.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=1101&id=38&aid=9406