

Case Series: Rho Kinase Inhibitor for the Treatment of Corneal Edema after Cataract Surgery in Patients with Low Endothelial Count

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Abstract

Rho-kinase inhibitors promote the proliferation of corneal endothelial cells, increasing intercellular adhesion and suppressing apoptosis. Three cases of patients with low endothelial count, who underwent cataract phacoemulsification plus intraocular lens implantation and who received topical Ripasudil, a Rho kinase inhibitor, one week before and one month during the postoperative period, are described. The first case had 1,691 cells/mm², the second 1,487 cells/mm², and the third 1,359 cells/mm². Following the treatment with Ripasudil in the perioperative period, 6 months after surgery, specular microscopies were performed, obtaining the following results: 1,525 cells/mm², 1,361 cells/mm², and 1,215 cells/mm², respectively, evidencing a loss of endothelial cells between 8.47% and 10.6%, since this is not so significant despite the background pathologies, it could be postulated that Rho kinase inhibitors have a protective effect on the corneal endothelium.

Keywords: *Corneal endothelium; Rho-kinase inhibitors; Cumulative dissipated energy; Corneal endothelial cell density; Hexagonality; Coefficient of variation in corneal endothelial cells; Central corneal thickness*

1. Introduction

Rho-kinase is a serine/threonine protein kinase that is responsible for maintaining cell shape and adhesion through its action on the cell cytoskeleton. It has an effect on the Rho-A protein, which is responsible for the functioning of the cytoskeleton machinery, by facilitating its transformation between an active conformation bound to Guanosine Triphosphate (GTP) and an inactive one bound to Guanosine Diphosphate (GDP). Other factors, such as guanine nucleotide exchange (GEF), GTPase

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activating proteins (GAP), and guanine nucleotide dissociation inhibitors (GDI), also play an important role in this activation along with Rho-kinase. Through these interactions, the Rho-A protein significantly contributes to adhesion, cell proliferation, and determines morphological changes in cells through its action on actin and myosin contractility. Rho-A and its effector Rho-kinase 2 (ROCK 2) are predominantly expressed in human corneal endothelial cells; therefore, they are also involved in actomyosin contraction of corneal endothelial cells [1].

The corneal endothelium is the ocular structure that is responsible for maintaining transparency at the corneal level through a pump function, as well as a barrier, which is responsible for reducing the flow of aqueous humor to the corneal stroma. Any significant compromise at the corneal level such as Fuchs endothelial corneal dystrophies, corneal trauma, etc., promotes the migration and dissemination of constant endothelial cells. However, taking into account that there is a physiological loss of 0.6% per year of endothelial cells, when the cell density (2500-3000 cells/mm² in healthy patients) reaches values below a critical level (<1000 cells/mm²), the deterioration of endothelial function produces corneal cloudiness with decreased visual quality in our patients [2].

Rho kinase inhibitors are known to promote corneal endothelial cell proliferation, increase intercellular adhesion, and suppress apoptosis [3]. Topical management of corneal decompensation with Rho kinase inhibitors has shown potential use in Fuchs' endothelial dystrophy [4,5] corneal edema due to acute surgical trauma as well as in cataract surgery and other etiologies, as well as in tissue engineering therapy for endothelial disease. Among the options available for ophthalmic use are Ripasudil and netarsudil, which are generally very well tolerated with few mild and transient local side effects [6].

2. Case Presentation

2.1 Case 1

A 76-year-old female patient, with no significant history, attended for evaluation due to decreased visual acuity in both eyes, with a predominance of the right eye. She presented 20/400 uncorrected visual acuity (UDVA), that did not improve, with a diagnosis of senile LOCS III NO4 NC4 cataract and advanced AMD in both eyes. The case complies with the Declaration of Helsinki. The ethics committee and the institutional review board of Clínica La Luz approved the case report, obtaining the written informed consent of the patient. A normal anterior segment evaluation, auxiliary examinations specular microscopy with a CD 1691 cel/mm² CV 38 and Hex 54 CCT 591. Cataract surgery with phacoemulsification plus intraocular IOL implantation (Alcon Acrysof IQ P 22.50 D) with the Phaco Chop technique was decided without complications.

EDC 5.61 Day 1 of the postoperative period: clear cornea, anterior chamber formed, Tyndall 1+, pupillary reflex present, and the intraocular lens centered in the sac. (FIG. 1a) Treatment was started with Ripasudil (Rho-kinase Inhibitor) 1 drop every 3 h 1 week before surgery and 1 month during the postoperative period, Moxifloxacin 0.5% + Dexamethasone 1 drop every 4 h, Prednisolone 1% 1 drop every 2 h for 3 days and then every 4 h for 10 days, Nepafenac 0.1% 1 drop every 8 h for 4 weeks and. At 6 months of follow-up specular microscopy CD 1525 cells/mm² CV 40 and Hex 39 CCT 549. (FIG. 1b) UDVA of 20/200 and CDVA (corrected distance visual acuity) 20/150.

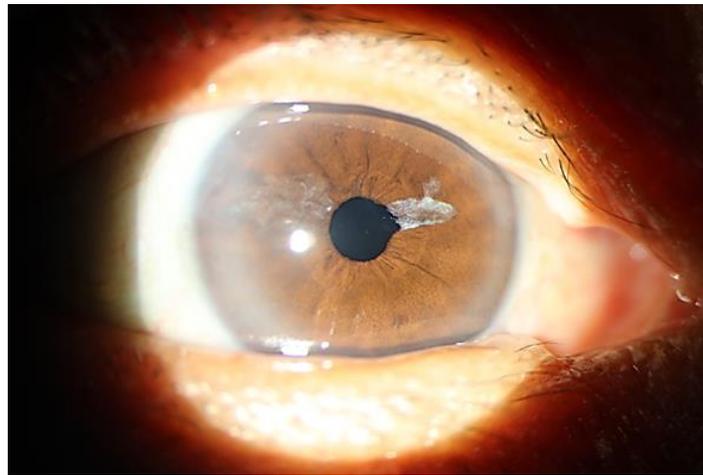


FIG. 1a. Case #1 Biomicroscopy on the first postoperative day.

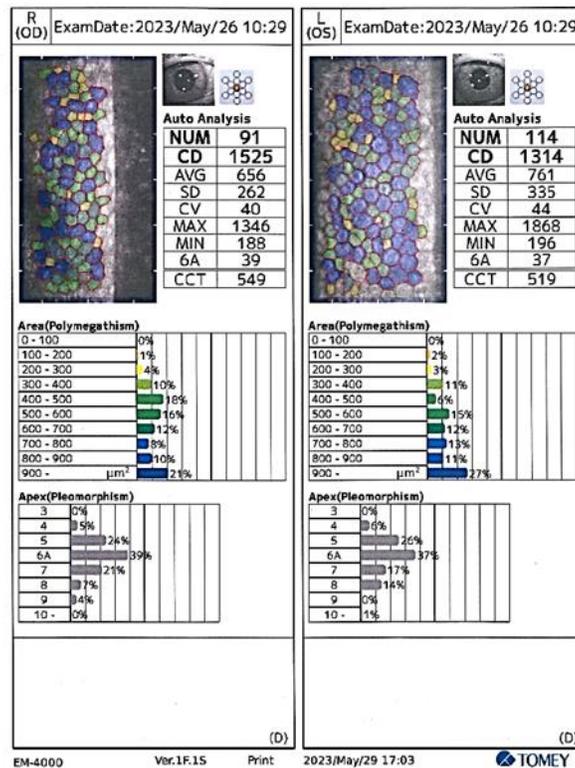


FIG. 1b. Case #1 Postoperative specular microscopy 6 months after cataract surgery plus intraocular lens implantation.

2.2 Case #2

A 66-year-old female patient, with no significant history, attended for evaluation due to decreased visual acuity with a predominance of the right eye. On examination, she presented UDVA 20/200 and CDVA 20/60, with a diagnosis of senile cataract LOCS III NO3 NC3. The case complies with the Declaration of Helsinki. The ethics committee and the institutional review board of Clínica La Luz approved the case report, obtaining the written informed consent of the patient. A normal anterior segment evaluation, auxiliary examinations specular microscopy. In the preoperative evaluation, specular microscopy

CD 1487 cells/mm² CV 30 and Hex 59 CCT 519. Cataract surgery with phacoemulsification plus intraocular IOL implant (Alcon Acrysof IQ (P 20.0 D)) is indicated.

Day 1 of the postoperative period: clear cornea, formed anterior chamber, present pupillary reflex and the intraocular lens centered in the sac. Treatment was started with Ripasudil (Rho-kinase inhibitor) 1 drop every 3 h 1 week before surgery and 1 month during the postoperative period, Moxifloxacin 0.5% + Dexamethasone 1 drop every 4 h, Prednisolone 1% 1 drop every 2 h for 3 days and then every 4 h for 10 days, Nepafenac 0.1% 1 drop every 8 h for 4 weeks and. At 6 months of follow-up specular microscopy: CD 1361 cells/mm² CV 34 and Hex 53 CCT 498. As well as UDVA 20/100 CDVA of 20/60 and anterior segment without alterations (FIG. 2a & 2b).

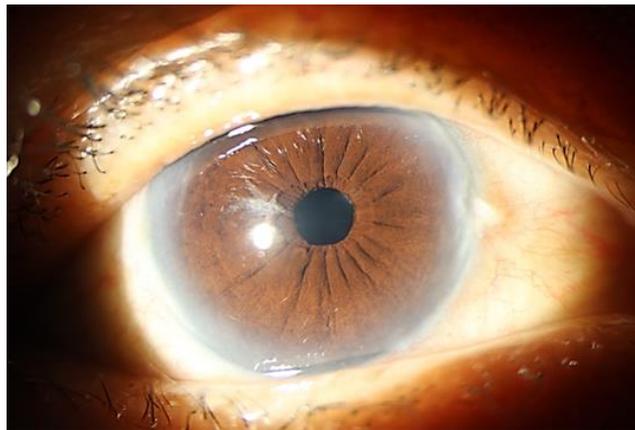


FIG. 2a. Case #2 Biomicroscopy at 6 months postoperative clear cornea.

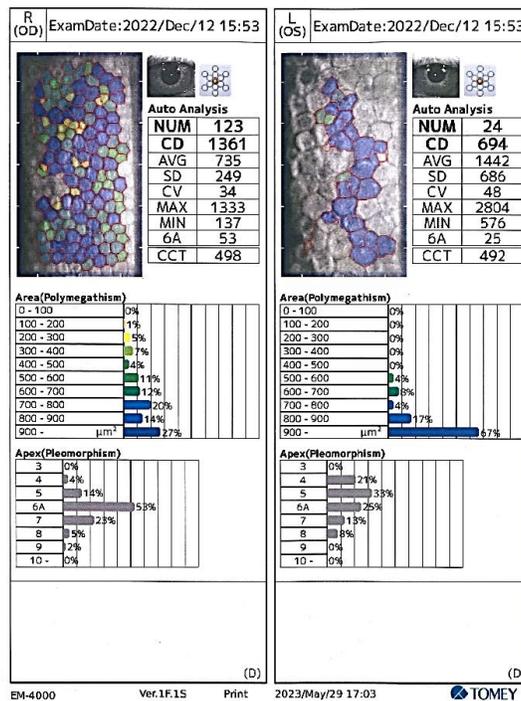


FIG. 2b. Case #2 Specular microscopy 6 months after surgery.

2.3 Case #3

An 83-year-old female patient, with a single eye with suspicion of glaucoma in the right eye with a history of perforated corneal ulcer + endophthalmitis in the left eye who came for evaluation due to decreased visual acuity in both eyes. Upon examination of the right eye UDVA 20/100 and CDVA 20/60 with a diagnosis of senile cataract LOCS III NO3 NC4. The case complies with the Declaration of Helsinki. The ethics committee and the institutional review board of Clínica La Luz approved the case report, obtaining the written informed consent of the patient. A normal anterior segment evaluation, auxiliary examinations specular microscopy. In the preoperative evaluation, specular microscopy CD 1359 cells/mm² CV 38 and Hex 38, CCT 530. Cataract surgery with phacoemulsification plus intraocular IOL implantation (Alcon Acrysof IQ P 22.5 D) was performed without complications. CODE 6.62

Day 1 of the postoperative period: clear cornea, anterior chamber formed, Tyndall 1+, pupillary reflex present, and the intraocular lens centered in the sac (FIG. 3a). Treatment was started with Ripasudil (Rho-kinase inhibitor) 1 drop every 3 h 1 week before surgery and 1 month during the postoperative period, Moxifloxacin 0.5% + Dexamethasone 1 drop every 4 h, Prednisolone 1% 1 drop every 2 h for 3 days and then every 4 h for 10 days, Nepafenac 0.1% 1 drop every 8 h for 4 weeks and. At 6 months of follow-up specular microscopy CD 1215 cel/mm² CV 48 and Hex 34 CCT 528. As well as UDVA 20/80 CDVA of 20/30 (TABLE 1).

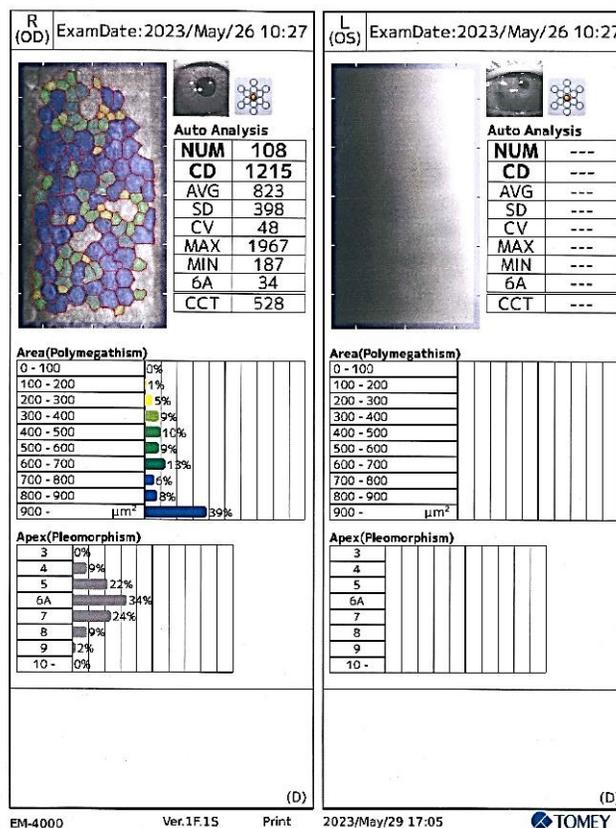


FIG. 3a. Case #3 Postoperative specular microscopy 6 months after cataract surgery plus intraocular lens implantation.

TABLE 1. Corneal endothelial cell density, CV and hexagonality, CCT before the operation and 6 months after the 3 patients, as well as the CDE used and the % endothelial variation.

	Preoperative	CDE	6 months postoperative	% Change in endothelium
1st patient	CED 1691 CV 38 HEX 54 CCT 591	5.61	CE 1525 CV 40 HEX 39 CCT 549	9.9 %
2nd patient	CED 1487 CV 30 HEX 59 CCT 519	2.95	CE 1361 CV 34 HEX 53 CCT 498	8.47 %
3rd patient	CED 1359 CV 38 Hex 38 CCT 530	6.62	CE 1215 CV 48 HEX 34 CCT 528	10.6 %

3. Discussion

The corneal endothelium is made up of a single layer of cells that generally fail to regenerate after significant damage. At birth, human beings have approximately 6,000 endothelial cells/mm², which decrease by an average of 0.6% per year. On the other hand, it is well known that an endothelial density of <1000 cells/mm² conditions a high risk of corneal decompensation and, consequently, decreased visual quality [7].

Endothelial cells play a critical role in corneal transparency through a balance between the cell barrier and the active ion pump mechanism, which maintains corneal deturgence. The corneal endothelium has a low regenerative capacity due, in part, to high concentrations of TGF-β₂ and cAMP within the aqueous humor that are thought to upregulate p27 KIP1, preventing endothelial cell proliferation. Corneal endothelial dysfunctions, due to progressive or acute cell loss, have a negative impact on the dynamic functional integrity of the endothelial cell, resulting in corneal edema, stromal scarring, and compromised visual acuity, which will eventually lead to corneal blindness [7,8].

Rho-associated protein kinase inhibitors were initially developed as intraocular pressure-lowering drugs but have been suggested to have an effect on endothelial cells. Ripasudil, RHO Kinase inhibitor, has a protective effect towards the corneal endothelium in cataract surgery for patients with low endothelial cell density. However, both preclinical and clinical studies that evaluated these drugs reported conjunctival hyperemia with high incidence rates, so the therapeutic potential in most cases is limited by adverse effects [9].

The development of ophthalmic topical uses of Rho Kinase inhibitors has led researchers to test their beneficial effects on the corneal endothelium, especially after damage caused by phacoemulsification surgery. Rho Kinase inhibitors have been proposed to promote proliferation of corneal endothelial cells, however, the mechanism by which ROCK inhibitors affect corneal endothelium is unclear.

In our study, endothelial cell loss after cataract surgery ranged from 8.47% to 10.6% when Rho kinase inhibitors topical treatment was applied to patients with low pre-surgical endothelial counts who underwent cataract phacoemulsification surgery,

who it is lower than that found in the normal population by Xing Du et al [10] (12.4%) and Walkow et al [11] (11.9%). Minimal changes in the coefficient of variation, hexagonality as well as endothelial cell counts compared to the normal population indicate that Rho kinase inhibitors have a beneficial effect on corneal endothelial cells when administered topically in the eye. Perioperative [12].

The limitations of our study are based on a small number of patients, so we suggest a larger number of studies to know the ideal dosage regimen to obtain better results, as well as to know the exact mechanism by which Rho kinase inhibitors act on the corneal endothelium promoting its healing after phacoemulsification.

Regarding our patients who used Rho kinase inhibitors in the perioperative period of their cataract surgeries with phacoemulsification plus intraocular lens implantation, it was evidenced that there was a not so significant loss of endothelial cells 6 months after cataract surgery and that the perioperative use of Rho kinase inhibitors could have a protective effect on the corneal endothelium.

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