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EFFECT OF TOPICAL RIPASUDIL ON CORNEAL ENDOTHELIAL CELL LOSS FOLLOWING CATARACT SURGERY: A PROSPECTIVE COMPARATIVE STUDY

Ophthalomology

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ABSTRACT

Background: Corneal endothelial damage and postoperative corneal edema remain important concerns following cataract surgery. Rho-associated protein kinase (ROCK) inhibitors such as ripasudil have shown potential protective effects on cornel endothelial function and wound healing. This study evaluates the effect of topical ripasudil on corneal endothelial cell density (ECD), Central cornel thickness (CCT), and intraocular pressure (IOP) following cataract surgery. **Methods:** In this prospective comparative study, 40 eyes undergoing cataract surgery were divided into two groups; a ripasudil group and a control group, with 20 eyes each. Baseline and 3-month postoperative ECD, CCT and IOP were assessed. Percentage endothelial cell loss and postoperative/preoperative change ratios for CCT and IOP were calculated and compared between the groups. **Results:** Baseline ECD was comparable between the ripasudil and control groups (1180±85 vs 1170±90 cells/mm2). At 3 months, the ripasudil group showed significantly better endothelial cell preservation, with lower percentage endothelial cell loss (5.3±1.8%) compared with controls (10.3±2.7%) (p= 0.001). CCT decreased in both groups, with a greater reduction in the ripasudil group. The CCT change ratio was 0.973±0.010 in the ripasudil group and 0.989±0.012 in the control group, and the difference between the groups was statistically significant (p=0.002). **Conclusion:** These results suggest that ripasudil may preserve corneal endothelial integrity and reduce postoperative endothelial cell loss after cataract surgery, indicating potential broader utility in protecting the corneal endothelium in intraocular procedures, especially in eyes with reduced endothelial reserve.

KEYWORDS

Ripasudil, Corneal Endothelium, Endothelial Cell Density, Cataract Surgery, Central Corneal Thickness, ROCK Inhibitor

INTRODUCTION

The cornea is a transparent avascular tissue that acts as a structural barrier and protects the eye against infections. The corneal layers include epithelium, Bowman's layer, stroma, pre-Descemet's layer, Descemet's membrane and endothelium.[1]

The endothelial layer of the cornea maintains corneal clarity by ensuring it remains in a relatively dehydrated state. The dehydration is mediated by a pump-leak process, as fluid egresses from a relatively hypo-osmotic stroma towards a relatively hypertonic aqueous humor. This osmotic gradient is maintained by the Na^+/K^+/ATPase pump present on the basolateral surface of the endothelial cells and the intracellular carbonic anhydrase pathway.[2]

The endothelial cell density is approximately 3500-4000 cells/mm^2 and decreases by about 0.6% per year, reaching around 2000-2500 cell/mm^2 in adulthood. An endothelial cell density of lower than 500 cells/mm^2results in corneal dysfunction.[3]

The cells get arrested in the G1 phase of the cell cycle and do not typically proliferate and regenerate in vivo. Therefore, the loss of corneal endothelial cells results in compensatory enlargement and migration of the residual cells.[4]

Cataract surgery is one of the well-known factors that cause endothelial cell loss and corneal decompensation. Studies done in the normal population to assess the response of the endothelium to cataract surgery have shown a decrease in the endothelial density over a 3-month period postoperatively.[5]

The mean percentage endothelial cell loss with SICS, is reported to be about 11.2% at 1 month and 17.66% at 3 months after SICS.[6,7]

Multiple factors like corneal distortion, irrigation, solution turbulence, mechanical trauma by instruments, nuclear fragments, intraocular lens contact, and free oxygen radicals, all have been implicated in causing corneal damage in cataract surgery.[8]

Excessive endothelial cell loss can impair endothelial pump function, leading to postoperative corneal edema, delayed visual rehabilitation and in severe cases, pseudophakic bullous keratopathy.[8,9,10] Therefore, preservation of corneal endothelial integrity is essential in the postoperative period to promote rapid recovery of corneal clarity and optimize visual outcomes.

Rho is a small GTPase that is activated by guanine nucleotide exchange factors (GEFs).[11] ROCK signaling regulates a wide spectrum of fundamental cellular events such as cell adhesion, motility, proliferation, differentiation and apoptosis.[12,13]

Rho-A and it's effector Rho-kinase 2 (ROCK 2) are predominantly expressed in human corneal endothelial cells, thereby mediating the actomyosin contraction of the cells.[14]

Two ROCK inhibitors have been approved for use in the clinical setting. Fasudil was approved in 1995 in Japan, where it is used to suppress cerebral vasospasm by inhibition of actomyosin contraction.[15] Ripasudil was approved in Japan in 2014 in an eye drop form to increase the outflow of the aqueous humor as a treatment for glaucoma.[16]

Koizumi and colleagues demonstrated that inhibition of the ROCK signaling pathway with ROCK inhibitor Y-27632 resulted in inhibition of apoptosis and increased proliferation of corneal endothelial cells from the cynomolgus monkey.[17] Okumura et al, further characterized the effects of ROCK inhibitors on corneal endothelial wound healing by showing that topical administration of ROCK inhibitor Y-27632 augmented cell proliferation in vitro and in vivo.[18,19]

Contact inhibition and transforming growth factor (TGF)- β1, an anti-proliferative regulator present in the aqueous humor, cause arrest of corneal endothelial cells in G1 phase of the cell cycle. ROCK inhibitors facilitate progression of these cells from G1 to S phase by increasing cyclin D levels and suppressed phosphorylation of p27 by activation of phosphatidylinositol 3- kinase signalling. Cyclin D and p27 are regulators of the G1/S progression, so this explained how ROCK inhibition promoted the proliferation of corneal endothelial cells.[20,21]

In the present study, we aimed to evaluate the effect of the effect of topical ripasudil on corneal endothelial cells following manual SICS; to determine wether it offers a protective benefit to the corneal endothelium in the postoperative period.

METHODS

This prospective comparative study was conducted at the Department of Ophthalmology, Smt. M.T. Agarwal Municipal General Hospital, Mumbai to evaluate the effect of topical Ripasudil on postoperative endothelial cell loss following manual small incision cataract surgery (MSICS) in patients with low endothelial cell density.

Patients with age-related cataract of nuclear sclerosis grade 2-3 scheduled for uncomplicated MSICS were screened for eligibility. Patients with corneal endothelial disorders such as Fuchs endothelial

dystrophy, prior ocular surgery or trauma, glaucoma, pre-existing corneal pathology affecting endothelial assessment, ocular surface disorders, intraoperative complications including posterior capsule rupture or vitreous loss, or active ocular inflammation were excluded.

A total of 40 eligible eyes were enrolled and randomly assigned into two equal groups of 20 eyes each. A written informed consent was obtained from all participants prior to enrollment, according to the Declaration of Helsinki. All surgeries were performed using a standardized manual small incision cataract surgery technique by a single surgeon to minimize surgical variability.

The postoperative regimen was standardized for all patients and consisted of topical moxifloxacin 0.5% eye drops administered four times daily for one week, along with topical prednisolone acetate 1% eye drops administered six to eight times daily in the early postoperative period with gradual tapering over four to six weeks based on clinical response. A cycloplegic agent, homatropine 2%, was used twice daily for the first postoperative week. Lubricating eye drops were prescribed as needed.

In addition to standard therapy, patients in the intervention group received topical ripasudil 0.4% eye drops, administered twice daily, starting from the first postoperative day and continued for a duration of three months. The control group received only standard postoperative therapy without ripasudil.

Outcome measures included endothelial cell density (ECD), central corneal thickness (CCT), and intraocular pressure (IOP), which were recorded preoperatively, seven days after the surgery and at 3 months postoperatively. ECD was measured using a (Topcon Corporation, Tokyo, Japan) non- contact specular microscope. CCT was measured using an ultrasonic pachymeter, and intraocular pressure was measured using a Tono-pen tonometer.

Patients were followed postoperatively on day one, at one week, at one month, and at three months. Specular microscopy, ultrasonic pachymetry and Tono-pen tonometry were performed preoperatively and repeated at three postoperatively.

Surgical Procedure

Manual small-incision cataract surgery (MSICS) was performed under peribulbar anesthesia. A superior fornix-based conjunctival flap was fashioned, followed by cautery of the scleral bed. A 6-7 mm frown-shaped partial-thickness scleral incision was made 1.5-2 mm posterior to the limbus and extended into a self-sealing sclerocorneal tunnel. A side-port incision was created, and the anterior chamber was filled with viscoelastic. A continuous curvilinear capsulorhexis was performed, followed by hydrodissection and hydrodelineation. The nucleus was prolapsed into the anterior chamber and delivered through the scleral tunnel using a wire vectis. Residual cortical matter was removed using a Simcoe irrigation-aspiration cannula. A posterior chamber intraocular lens was implanted in the capsular bag, viscoelastic was aspirated, the anterior chamber was reformed and wound integrity was confirmed.

Statistical Analysis

Data distributions were assessed for normality using the Shapiro–Wilk test. Following confirmation of a parametric distribution, the independent t-test was used to compare ECD, CCT and IOP before and after surgery in both ripasudil and control groups. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA)

RESULTS

A total of 40 eyes of 40 patients were enrolled in the study. 20 patients received 0.4% topical ripasudil following surgery, while 20 patients received only standard postoperative care. The mean age of patients was 74.3±5.8 years in the ripasudil group and 73.6±6.1 years in the control group.

The mean preoperative endothelial cell density was comparable between the two groups, measuring 1180±85 cells/mm^2 in the ripasudil group and 1170±90 cells/mm^2 in the control group, with no statistically significant difference. At 3 months postoperatively, mean endothelial cell density decreased in both groups. However, the reduction was less pronounced in the ripasudil group, which showed a mean ECD of 1118±84 cells/mm^2 compared with 1050±95 cells/mm^2 in the control group. The mean percentage endothelial cell loss [(ECD before surgery-ECD after surgery)/ECD before surgery x100] at 3 months was 5.3±1.8% in the ripasudil group and 10.3±2.7% in the control group. The endothelial cell loss was significantly lower in the ripasudil group than in the control group (p = 0.001), suggesting a protective effect of ripasudil on the corneal endothelium following surgery.

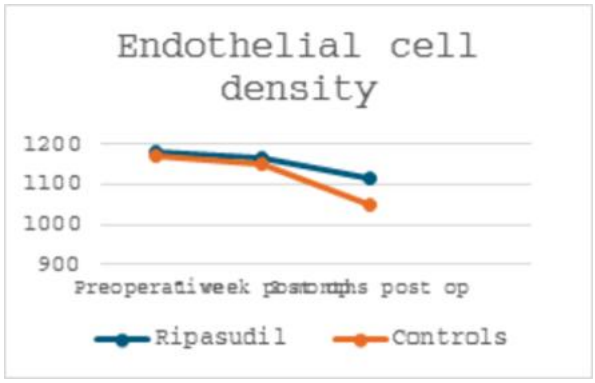

Figure 1: Depicts the Endothelial Cell Density Loss After Surgery In The Ripasudil and the Control Groups. The ECD Decreased Progressively in Both Groups During Follow-up. However, the Decline was Less Pronounced in the Ripasudil Group, Indicating Better Preservation of Corneal Endothelial Cells Compared with Controls.

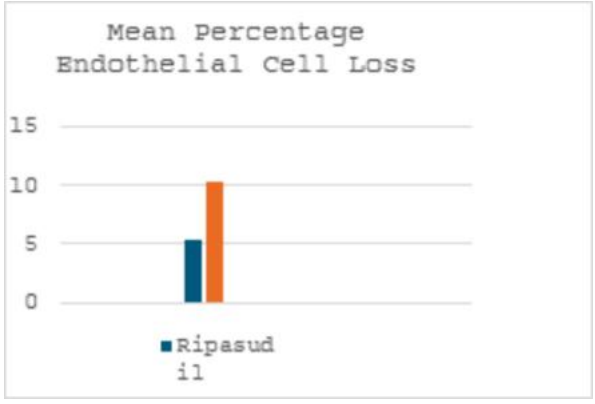

Figure 2: Depicts the Mean Percentage Endothelial Cell Loss After Surgery in the Ripasudil and Control Groups. The Percentage ECD Loss is Presented as (ECD Before Surgery – ECD After Surgery)/ECD Before Surgery X100%. The Mean Percentage Endothelial Cell Loss, 3 Months After the Surgery, was Lower in the Ripasudil Group Than in the Control Group, Suggesting a Protective Effect of Ripasudil on the Corneal Endothelium.

Central corneal thickness showed a similar trend. Preoperative values were comparable between groups, with 534.0±18.2 µm in the ripasudil group and 532.6±17.9 µm in the control group. At 3 months postoperatively, CCT decreased in both groups with a greater reduction observed in the ripasudil group, which showed a mean value of 519±17.5 µm compared with 526.8±17.8 µm in the control group. The CCT change ratio [CCT after surgery/CCT before surgery] was 0.973±0.010 in the ripasudil group and 0.989±0.012 in the control group. The difference in the CCT change ratio between the two groups was statistically significant (p=0.002).

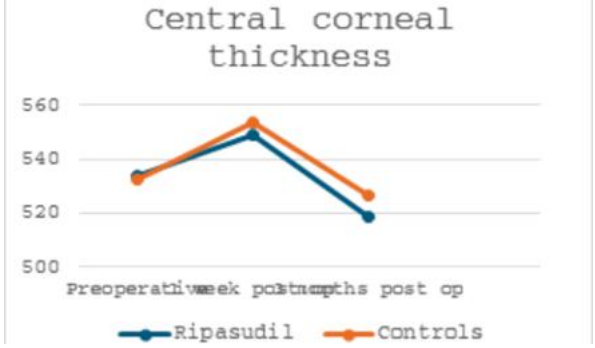

Figure 3: Depicts Changes in the Central Corneal Thickness After

Surgery in the Ripasudil and Control Groups. CCT Increased Transiently at 1 Week Postoperatively in Both Groups, Followed by a Reduction at 3 Months. The Reduction was More Pronounced in the Ripasudil Group, Resulting in a Lower Mean CCT at the Final Follow up Compared with the Control Group.

Intraocular pressure remained stable throughout the follow-up period. Baseline IOP was similar in both the groups, measuring 13.6±1.8mm Hg in the ripasudil group and 13.4±1.7mm Hg in controls. At 3 months, only a mild reduction was noted in both the groups, with values of 12.9±1.6mm Hg and 13.0±1.5mm Hg, respectively. The IOP change ratio was 0.949±0.045 in the ripasudil group and 0.971±0.052 in the control group, with no statistically significant difference between the two groups (p=0.18).

DISCUSSION

In our study, the endothelial cell density decreased in both groups following surgery. However, the percentage endothelial cell loss at 3 months was significantly lower in the ripasudil group, suggesting a protective effect on the corneal endothelium. A similar trend was observed for the central corneal thickness, with a significantly greater reduction in the ripasudil group. No significant reduction in intraocular pressure was observed in both the groups.

Antonini et al reported a case series involving three patients with pre-existing endothelial compromise (Fuchs endothelial corneal dystrophy) undergoing cataract surgery, treated with topical ripasudil 0.4% four times daily. In one case that developed PBK postoperatively, topical ripasudil effectively resolved stromal oedema, improved visual acuity and delayed the necessity for keratoplasty. Two additional patients received ripasudil prophylactically before and after cataract extraction successfully maintaining clear corneas postoperatively, with no evidence of endothelial failure concluding that topical ripasudil could serve as an effective adjuvant therapy to reduce the incidence of postoperative pseudophakic bullous keratopathy in patients with compromised ECD.[22]

Similarly, a randomised controlled trial in Fuchs patients by Keeratidamkerngsakul et al, reported that 1 month of postoperative ripasudil drops led to ~0% endothelial cell loss vs ~7% loss in controls. Although central corneal thickness increased slightly in both groups over 3 months, ripasudil treated eyes showed overall better endothelial function.[23]

Alkharashi et al. conducted a prospective comparative trial in cataract surgery patients. In this study, patients receiving ripasudil three times daily for five postoperatively showed significantly less endothelial cell loss at 12 months (4.5%) compared to untreated controls (12.8%, p = 0.001). Correspondingly, central corneal thickness measurements indicated less persistent corneal oedema in treated patients.[24]

In another study conducted by Lavy e al. to evaluate the efficacy of ripasudil in managing various corneal oedema conditions, topical ripasudil was administered to 16 patients with corneal edema due to various conditions such as post cataract surgery, post penetrating keratoplasty, post DMEK, FECD, post Ahmed glaucoma valve and post trabeculectomy. It was observed that CCT showed a significant reduction, from 619.50±56.36 µm pretreatment to 572.5±75.48 µm in a duration of approximately 4.9±2.2 months, while endothelial cell count showed a marginal but not statistically significant increase from 849.00±570 cells/mm^2 pretreatment to 874.75±625.59 cells/mm^2 post treatment.[25]

The present study has certain limitations, including the relatively small sample size, which may limit the generalisability of the findings. Further studies with a larger sample size and longer follow-up are called for to confirm the endothelial protective effect of topical ripasudil following cataract surgery and to prove its long-term efficacy and safety.

In conclusion, the findings of the present study suggest that topical ripasudil may have a beneficial role in preserving corneal endothelial cell function following cataract surgery. The observed reduction in endothelial cell loss indicates that topical ripasudil could serve as a promising adjunctive therapy for endothelial protection in the postoperative period. However, larger prospective studies are needed to confirm these findings and further define its role in routine clinical practice.

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