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# Evaluating the efficacy of Rho kinase inhibitor eye drops in the management of corneal edema: A single-center retrospective cohort study

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**Abstract:**

**PURPOSE:** This study aimed to evaluate the efficacy of ripasudil in managing various corneal edema conditions.

**MATERIALS AND METHODS:** This single-center retrospective analysis was conducted at Hadassah Medical Center and involved 16 patients with 17 eyes. Patients were selected based on diagnostic criteria, primarily corneal edema. The conditions were as follows, listed by frequency: postcataract surgery (31.25%), postpenetrating keratoplasty (25%), post-Descemet's membrane endothelial keratoplasty (18.75%), Fuchs' endothelial corneal dystrophy (12.5%), status post-Ahmed glaucoma valve (6.25%), and status posttrabeculectomy (6.25%). The treatment regimen involved topical administration of ripasudil hydrochloride hydrate (Glanatec® 0.4%), administered three times a day or tailored to condition severity. Efficacy was assessed using pre- and posttreatment measurements of best-corrected visual acuity (BCVA), central corneal thickness (CCT), and endothelial cell count (ECC), along with slit-lamp and optical coherence tomography examinations.

**RESULTS:** The average duration of ripasudil treatment was approximately 4.9 ± 2.2 months. Significant improvements were observed in BCVA, changing from a pretreatment value of 1.106 ± 0.817 logMAR to a posttreatment value of 0.56 ± 0.57 logMAR ($P = 0.0308$). CCT also showed a significant reduction, from 619.50 ± 56.36 μm pretreatment to 572.5 ± 75.48 μm posttreatment ($P = 0.0479$). ECC showed a marginal but not statistically significant increase, from 849.00 ± 570.72 cells/mm² pretreatment to 874.75 ± 625.59 cells/mm² posttreatment ($P = 0.9010$).

**CONCLUSION:** The study provides robust evidence supporting the use of ripasudil in managing corneal edema. Significant improvements in key ocular metrics such as BCVA and CCT were observed, enhancing the overall quality of life for patients suffering from various forms of corneal edema.

**Keywords:**

Corneal edema, Rho kinase inhibitor, ripasudil

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## Introduction

Corneal edema, characterized by fluid accumulation in the corneal stroma,[1,2] leads to significant visual impairment due to loss of transparency. It is primarily caused by conditions such as Fuchs' endothelial corneal dystrophy (FECD),[1,2] postoperative complications, and ocular trauma. The condition's severity varies, affecting vision to differing extents. The corneal endothelium plays a crucial role in maintaining stromal hydration and transparency.[1,3] When endothelial cell density falls below a critical threshold, typically around 400–700 cells/mm², corneal edema and opacification occur.[1,3] While corneal transplantation remains the standard treatment, therapeutic contact lenses,[4] pharmacological interventions,[1,5,6]



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and less invasive alternatives like collagen cross-linking are increasingly utilized.[7,8] Therapeutic strategies have evolved, with a focus on maintaining optimal corneal hydration through interventions like topical hypertonic saline, although its efficacy is variably documented. Cataract surgery, a transformative ophthalmic procedure, has seen reduced incidences of corneal edema due to advancements in surgical techniques and postoperative care.[9-11] However, risks persist, including mechanical trauma, inflammation, chemical injuries, and exacerbation from preexisting conditions.[9-11] The incidence of corneal edema postsurgery varies, highlighting the need for careful patient selection and management.[10,12-14] Ripasudil, a rho kinase (ROCK) inhibitor, is recognized for its role in treating glaucoma and ocular hypertension by enhancing aqueous outflow and improving endothelial cell function.[15,16] Its application extends to managing corneal edema, although real-world clinical evidence is still emerging.[17,18] Other ROCK inhibitors such as netarsudil and fasudil offer alternative therapeutic options, each with unique profiles and approved uses in various regions. Ongoing clinical trials continue to explore the potential of new ROCK inhibitors in treating a range of ocular conditions.

Ripasudil, a Rho-associated kinase (ROCK) inhibitor, was developed by Kowa Company for treating glaucoma and ocular hypertension. It enhances aqueous outflow through the trabecular meshwork and is approved in Japan for cases unresponsive to other treatments. The main goal in managing glaucoma and ocular hypertension is to lower intraocular pressure (IOP). Ripasudil recently attracted attention for its potential to treat ocular conditions like corneal edema. Its mechanism of action involves the modulation of cellular contractility and enhancement of endothelial cell function, thereby facilitating edema resolution.[15,16] Despite its promising pharmacological profile, there is limited evidence to substantiate its efficacy in managing various forms of corneal edema, particularly in a real-world clinical setting.[15,16] It requires twice-daily dosing and can cause side effects like blepharitis. Currently, there are two other ROCK inhibitors that are commercially available, netarsudil in the US and Europe and fasudil in Japan for different indications.[17,18] This study aimed to evaluate the effectiveness of ripasudil in managing various corneal edema conditions through a single-center retrospective analysis. Since endothelial keratoplasty is currently the standard therapeutic approach, this study also addresses the pressing need for alternative, nonsurgical interventions to manage corneal edema.

**Table 1: Clinical demographics of study participants**

| Patients | Eyes (*n*) | RE/LE (%) | Age | Gender, *n* (%) |
|---|---|---|---|---|
| 16 | 17 eyes | 58.82 - RE | 69.63±10.84 | Male - 11 (68.75) |
| | | 41.18 - LE | | Female - 5 (31.25) |

Patients: Number of patients included in the study, Eyes (*n*): Total number of eyes examined, Age: Average age of the patients with SD, followed by the standard deviation, Gender: Distribution of gender among patients, with the number of individuals the percentage for the eye involved (RE, LE) and the percentage for each gender (male, female). SD=Standard deviation, RE=Right eye, LE=Left eye

## Materials and Methods

### Ethical considerations

The Medical Center Institutional Review Board (IRB) approval was obtained for this study (0418-22HMO, December 2022), and all procedures were carried out as per their guidelines. This study was conducted strictly with the Clinical Practice Guidelines and ethical guidelines outlined in the Declaration of Helsinki and received approval from the IRB. All participants provided informed consent before their inclusion in the study.

### Study design and participants

This study was a single-center, retrospective analysis conducted at Hadassah Medical Center, focusing primarily on evaluating the efficacy of ripasudil treatment in various ophthalmic conditions. Sixteen patients, 17 eyes, were enrolled in the study.

### Data collection and sources

Clinical data were systematically extracted from Hadassah Medical Center's "Mahar" electronic medical records (EMR) system. Patients were meticulously identified using targeted searches in the EMR system at Hadassah Medical Center, facilitated by the center's business intelligence unit. Supplementary imaging data were obtained from the Optical Coherence Tomography (OCT) SPECTRALIS and Picture Archiving and Communication System databases, which are integral components of Hadassah's ophthalmic care infrastructure.

**Table 2: Comparative analysis of ophthalmic parameters before and after ripasudil treatment**

| Parameter | Pre-Tx (AVG and SD) | Post-Tx (AVG) | Statistical test | *P* | Significance | *t* | Df |
|---|---|---|---|---|---|---|---|
| BCVA logMAR | 1.106±0.817 | 0.56±0.57 | Unpaired *t*-test | 0.0308 | Significant | 2.260 | 32 |
| CCT | 619.50±56.36 | 572.5±75.48 | Unpaired *t*-test | 0.0479 | Significant | 2.057 | 32 |
| ECC before TX | 849.00±570.72 | 874.75±625.59 | Unpaired *t*-test | 0.9010 | Not significant | 0.1254 | 32 |
| Tx (months) | | 4.875±2.217 | | | | | |

AVG=Average value, SD=Standard deviation, Tx (months)=Duration of ripasudil treatment in months, BCVA=Best-corrected visual acuity, LogMAR=Logarithm of the minimum angle of resolution, CCT=Central corneal thickness (μm), ECC=Endothelial cell count (cells/mm²), Df=Degrees of freedom

### Study variables
The study included pretreatment and posttreatment assessments. Pretreatment assessments included measurements of visual acuity (VA), central corneal thickness (CCT), and endothelial cell count (ECC), along with the duration of treatment (Tx in months), and the total number of Descemet's membrane endothelial keratoplasty (DMEK) procedures performed after ripasudil treatment.

### Demographics
The cohort had an average age of 69.63 ± 10.84 years, ranging between 53 and 89 years, 68.75% of males [Table 1].

### Diagnostic categories and indications for ripasudil treatment
Patients were enrolled based on diagnostic conditions that indicated the need for ripasudil treatment, with the decision to initiate ripasudil as the first-line treatment following the diagnosis of corneal edema. The most frequent condition was edema postcataract surgery ($n$ = 6, 35.29%), followed by corneal edema after penetrating keratoplasty, DMEK, and FECD, each observed three eyes of cases ($n$ = 3, 17.65%). Less frequent conditions included edema status post-Ahmed glaucoma valve and edema status posttrabeculectomy, each accounting for one eye ($n$ = 1, 5.88%) of the cases.

### Duration of corneal edema before ripasudil treatment
In this study, the duration of corneal edema before initiating treatment with ripasudil was examined. The duration varied significantly among patients, ranging from 1 to 12 weeks. The average duration of corneal edema before treatment was 3.25 ± 3.59 weeks.

### Treatment protocol
The treatment regimen involved the topical administration of ripasudil hydrochloride hydrate (Glanatec® ophthalmic solution 0.4%; Kowa Company, Ltd., Nagoya, Japan). The eye drops were administered three times a day, with the frequency tailored if the condition's severity required, as per the manufacturer's guidelines.

### Assessment parameters
Treatment efficacy evaluation included assessments both before and after the ripasudil treatment. Pretreatment assessments included best-corrected VA (BCVA) using the logMAR Scale, CCT was obtained utilizing Pentacam HR (Oculus, Wetzlar, Germany), and ECC was obtained using specular microscopy (Konan Noncon-ROBO specular microscope; Konan Medical, Irvine, CA). Slit-lamp examinations were conducted using Haag-Streit Photo-Slit Lamp BX 900 (Haag-Streit AG, Koeniz, Switzerland) and with anterior segment spectral-domain OCT (OCT, Optovue RTVue-100, Optovue Inc., Fremont, CA) was performed using Optovue technology.

Posttreatment assessments were carried out to gauge the impact. These assessments mirrored the pretreatment evaluations, including the BCVA, CCT, and ECC re-measurement. The duration of the treatment, measured in months, was recorded. Slit-lamp and OCT analyses were repeated and compared to pretreatment conditions. The number of cases requiring DMEK after ripasudil treatment was noted.

### Statistical analysis
Statistical analysis was conducted using the Statistical Package for the Social Sciences software 25.0 (SPSS Inc., Chicago, Illinois, USA). An unpaired $t$-test with a two-tailed was employed to compare pre- and posttreatment measures for each parameter: BCVA, CCT, and ECC.

In all analyses, variances were considered. A two-tailed hypothesis test was applied, and $P < 0.05$ was deemed statistically significant. A continuous model with two independent study groups was utilized for the sample size calculation. A confidence interval of 0.95 was used, and the statistical power was set at 80%. The total sample size required to detect a significant association was 16 patients, corresponding to 17 eyes.

## Results

### Treatment duration and Descemet's membrane endothelial keratoplasty incidence
The average duration of ripasudil treatment was 4.875 ± 2.2 months. After this period, a 29% incidence rate of DMEK was observed posttreatment.

### Best-corrected visual acuity
The average VA improved significantly from a pretreatment (pre-Tx) value of 1.106 ± 0.817 logMAR to a posttreatment (post-Tx) value of 0.56 ± 0.57 logMAR, respectively ($P$ = 0.0308, $t$ = 2.260 with 32 degrees of freedom).

### Central corneal thickness
CCT decreased, with average pre-Tx and post-Tx values of 619.50 ± 56.36 μm and 572.5 ± 75.48 μm, respectively ($P$ = 0.0479, $t$ = 2.057 with 32 degrees of freedom).

### Endothelial cell count
Interestingly, ECC increased slightly from an average pre-Tx value of 849.00 ± 570.72 cells/mm² to a post-Tx average of 874.75 ± 625.59 cells/mm², respectively ($P$ = 0.9010, $t$ = 0.1254 with 32 degrees of

freedom). The summary of the findings is delineated in [Table 2].

A visual comparison of the LE of a single study patient before and after 5.5 months of ripasudil treatment is provided, with slit-lamp images and OCT scans illustrating the pre- and posttreatment conditions, as shown in Figure 1.

## Discussion

The results suggest that ripasudil treatment significantly impacts BCVA and CCT, with a marginal increase in ECC.

Corneal edema management has evolved over the years with therapeutic contact lens,[4] pharmacological interventions increasingly pivotal alongside surgical options like corneal transplantation, topical hypertonic saline has been a longstanding but empirically under-validated treatment, functioning by increasing tear film osmolality to facilitate fluid removal from the cornea.[1,6] Multiple factors, including endothelial function and IOP, contribute to maintaining optimal corneal hydration, which, when disrupted, leads to edema.[5]

Cataract surgery has long been considered an intrinsic ophthalmic medical procedure, globally improving the quality of life for millions.[9] Recent advancements in surgical techniques and postoperative care have improved VA and corneal health.[10] The incidence of corneal edema or decompensation following cataract surgery has been reported for 0.2%–2.4%.[10] The incidence of corneal edema after intracapsular cataract extraction (ICCE) accompanied by anterior chamber or iris-fixated intraocular lens (IOL) implantation is markedly elevated in comparison to the incidence following ICCE without IOL implantation.[10] Corneal edema after cataract surgery arises from four leading causes. First, mechanical trauma during surgery is a leading factor, often due to ultrasound energy or instrument contact.[10,11] This highlights the inherent risks of the surgical procedure itself. Second, inflammation or infections can also contribute, often triggered by residual nuclear fragments or untreated infections. Prompt medical intervention is essential in these cases. Third, chemical injuries can occur from substances used during surgery, emphasizing the need for careful surgical preparation. Finally, preexisting conditions like Fuchs' endothelial dystrophy can exacerbate postoperative edema, making a thorough medical history vital for patient care.[10,12-14]

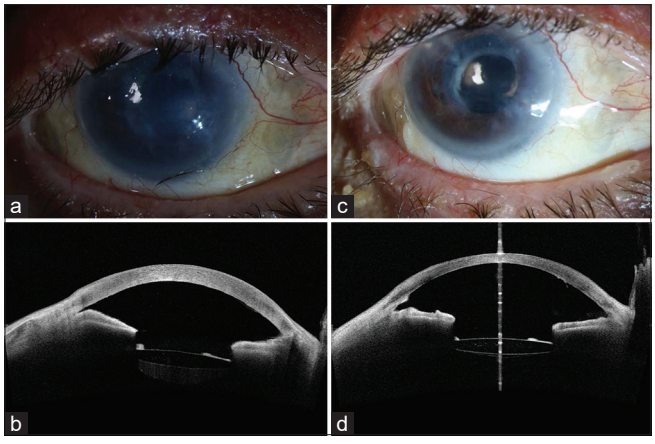


**Figure 1:** Pre- and posttreatment images of the left eye in a single study patient undergoing 5.5 months of ripasudil treatment: Slit-lamp images (a and c) and optical coherence tomography scans (b and d), with (a and b) representing pretreatment and (c and d) representing posttreatment

Ripasudil, a Rho-associated kinase (ROCK) inhibitor, was developed by Kowa Company for treating glaucoma and ocular hypertension. It enhances aqueous outflow through the trabecular meshwork and is approved in Japan for cases unresponsive to other treatments. The main goal in managing glaucoma and ocular hypertension is to lower IOP. Ripasudil recently attracted attention for its potential to treat ocular conditions like corneal edema. Its mechanism of action involves the modulation of cellular contractility and enhancement of endothelial cell function, thereby facilitating edema resolution.[15,16] Despite its promising pharmacological profile, there is limited evidence to substantiate its efficacy in managing various forms of corneal edema, particularly in a real-world clinical setting.[15,16] It requires twice-daily dosing and can cause side effects like blepharitis. Currently, there are two other ROCK inhibitors that are commercially available, netarsudil in the US and Europe and fasudil in Japan for different indications.[17,18]

Netarsudil targets both ROCK1 and ROCK2, enhancing trabecular meshwork outflow and reducing episcleral venous pressure. In addition, it has shown axonal protection in rat models. Approved in the US in 2017 and Europe in 2019 for reducing elevated IOP in primary open-angle glaucoma or ocular hypertension, it is administered once daily.[19,20] The drug has demonstrated consistent IOP reduction throughout the day and night and has been well-tolerated in multiple studies.[18,21,22]

Neither ripasudil nor netarsudil is approved in the UK, Canada, or Australia. Fasudil, available since 1995 in Japan, is mainly used for cerebral vasospasms and has been studied for diabetic macular edema.[23] Other ROCK inhibitors such as SNJ-1656 and Y-27632 are in various stages of clinical trials but are not yet commercially available.[18,19,21,22]

The observed qualitative improvement in BCVA is corroborated by previous studies, which reported

significant improvements in vision for patients with FECD when treated with ripasudil.[16,24,25] Regarding CCT, our findings align with a case series of ripasudil used to treat segmental corneal edema, which reported partial or complete resolution of the edema in most cases.[26] This is further supported by an article that discussed the rates of persistent corneal edema following cataract surgery, thereby highlighting the potential role of ripasudil in managing this condition.[15,27] Regarding ECC, the slight increase is not statistically significant. However, it is clinically significant. Ripasudil has been shown to increase the expression of genes and proteins related to cell cycle progression, cell–matrix adhesion, and migration.[15,27] As part of another study, ROCK inhibitors were also strongly endorsed as adjuvant therapy in cataract surgery, particularly in challenging cases, such as when associated with FECD.[15,27] Finally, this study's average duration of ripasudil treatment was approximately 4.9 months, with a 29% incidence rate of DMEK observed posttreatment. This suggests that ripasudil may temporarily delay more invasive procedures like DMEK, a notion further supported by existing literature.

A case series highlights the successful treatment of persistent corneal edema with topical ripasudil in four cases following anterior segment surgeries.[26] The causes included FECD, pseudophakic bullous keratopathy, and endothelial cell loss postkeratoplasty. Applied twice daily, ripasudil led to vision improvement and edema resolution without adverse effects.[26] The results suggest ripasudil's efficacy and safety for treating corneal edema, warranting further research for dosage and treatment duration optimization.[26]

A study investigation examines the regenerative potential of ripasudil on corneal endothelial cells in patients afflicted with FECD. Employing both *ex vivo* tissue samples and *in vitro* cellular models, the study elucidates the impact of ripasudil on endothelial cell dynamics.[25] The findings reveal that ripasudil favorably modulates cell cycle progression, cellular adhesion, and migration without adversely affecting the cellular phenotype in both FECD and healthy endothelial cells. In addition, the ROCK inhibitor augments the expression of proteins crucial for endothelial pump and barrier functionalities across both experimental models. These outcomes substantiate the potential of ROCK inhibitors like ripasudil as a regenerative therapeutic strategy for targeted endothelial repair in FECD patients.[25]

A clinical study aimed to assess the safety and efficacy of Descemet stripping only when augmented with ripasudil for treating FECD.[24] A total of 23 eyes were enrolled in the study. Each underwent Descemet stripping-only surgery, followed by postoperative administration of ripasudil. Notably, 22 of the 23 eyes achieved corneal clearance within an average of 4.1 weeks, significantly improving BCVA. The study's methodology was rigorous. Patients were included based on stringent criteria, such as a minimum superior ECC of 1000 cells/mm$^2$ and central guttata as the primary cause of visual impairment.[24] The protocol included adverse event reporting, periodic blood pressure monitoring, and scheduled blood tests to ensure safety. None of the adverse events reported were severe; the most common side effects were ocular surface discomfort and gastrointestinal disturbances. Regarding clinical outcomes, the trial demonstrated notable improvements in VA.[24] The mean logMAR for uncorrected VA improved from 0.43 preoperatively to 0.24 at 9 months postoperatively.

Similarly, the mean LogMAR for best spectacle-corrected BCVA improved significantly, from 0.15 preoperatively to 0.002 at 12 months postoperatively. ECC was also assessed both before and after surgery. While a decline in superior ECC was observed postsurgery, the difference between the study groups, those with and without ripasudil, was not statistically significant.[24]

Another study evaluated ripasudil's efficacy in improving BCVA in FECD patients.[16] Thirty eyes from 15 patients were randomly assigned to a ripasudil-treated or control group. The treated group received 0.4% ripasudil eye drops twice daily for 18 months.[16] Results showed significant improvements in BCVA and corneal edema in the ripasudil group.[16] Specular microscopy revealed a mean endothelial cell density of 727 ± 142 cells/mm$^2$ in this group. Multiple diagnostic tools, including anterior segment OCT, were utilized. The study concluded that ripasudil is a promising treatment for FECD.[16]

A case series examining ripasudil therapy and femtosecond laser-assisted cataract surgery on corneal endothelial morphology.[27] The first case showed improved cell shape and size in the operated eye, suggesting ripasudil's potential as a supportive therapy during surgery. The second case indicated reduced corneal decompensation, as topographical and confocal assessments confirmed. Both cases highlighted ripasudil's utility in improving endothelial cell morphology and reducing edema. These findings contribute to existing evidence supporting Rho-associated kinase inhibitors for endothelial dysfunctions and call for further research.[27]

A study evaluated ripasudil's efficacy in preserving corneal endothelial cells postcataract surgery. Involving 40 eyes from 40 patients, 20 treated with ripasudil and 20 as controls, the study found less endothelial cell loss in the ripasudil group.[15] No significant differences were observed in age, sex, or preoperative corneal thickness between the

groups.[15] The results indicate ripasudil's potential as a treatment for low endothelial cell density postcataract surgery, warranting further research for validation.[15]

In the study, it was observed that ripasudil did not increase the number of endothelial cells, suggesting its primary role in enhancing cell function rather than inducing cell proliferation. These findings are in alignment with previous studies.[24,28,29] The resolution of edema could be attributed to one of two mechanisms: either the primary effects of ripasudil on cytoskeletal reorganization and cell migration lead to morphological changes and the subsequent reopening of a previously closed endothelial defect on drug withdrawal, or the addition of ripasudil enhances cell function within an established monolayer.[24,28,29]

### Limitations and future directions

While this study offers valuable qualitative insights, it is limited by a small sample size and a relatively short duration of treatment. Further long-term studies are required to better understand the etiology, safety, and efficacy of ripasudil in the treatment of postsurgical corneal edema.

## Conclusion

In summary, while endothelial keratoplasty remains the conventional therapeutic approach, there is a pressing need for alternative, nonsurgical interventions. The study adds robust evidence supporting the use of ripasudil in managing corneal edema. The qualitative improvements observed in key ocular metrics are consistent with existing literature, underscoring the potential utility of ripasudil as an effective treatment option. Furthermore, our findings suggest that ripasudil treatment significantly enhances the overall quality of life for patients suffering from various forms of corneal edema, thereby solidifying its role in contemporary ophthalmic care.

### Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.


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### Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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