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Research Article

Effect of Ripasudil on Visual Outcomes in Pseudophakic Corneal Edema: A Prospective Interventional Study

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Abstract

Purpose: To evaluate the efficacy of Ripasudil, a Rho-kinase inhibitor, in managing pseudophakic corneal edema following cataract surgery and comparison with the conventional treatment.

Methods: In this prospective interventional study, 104 patients with pseudophakic corneal edema were divided into two groups end were administered either 0.4% Ripasudil ophthalmic solution (Group A) or 5% hypertonic saline (Group B). Visual acuity, central corneal thickness (CCT), and intraocular pressure (IOP) were evaluated along with time taken for resolution of corneal edema over a period of six months.

Results: Significant improvements in BCVA, corneal clarity and CCT were observed in both groups, with slightly earlier improvements in Group A which was not statistically significant. No serious adverse effects were reported.

Conclusion: Ripasudil 0.4% ophthalmic solution is not inferior to 5% hypertonic saline drops in improving visual outcomes and reducing corneal edema in patients with pseudophakic corneal edema following cataract surgery and that it is safe, effective, and potentially offers endothelial benefits. It may serve as a non-invasive therapeutic alternative in pseudophakic corneal edema.

Keywords: Cornea; Central Corneal Thickness (CCT)

Introduction

Cornea is a transparent, avascular tissue that consists of 6 layers- epithelium, bowman's layer, stroma, Dua's membrane, Descemet's membrane and endothelium. Corneal transparency is vital for visual acuity and depends on precise regulation of stromal hydration. The Cornea maintains clarity via epithelial tight junctions, the endothelium's Na^+/K^+ ATPase pump, even and regular distribution of keratocytes, fibres & the extracellular matrix in the corneal stroma [1]. Disruption in these barriers causes fluid accumulation, resulting in corneal edema and vision loss [2]. Corneal edema is defined as the increase in the thickness of cornea due to the disturbance in hydration of stroma and accumulation of extracellular fluid in epithelium and stroma. A damaged endothelium or a disturbed stromal hydration, can cause fluid to build up in the cornea leading to corneal edema which causes loss of transparency of cornea.

Pseudophakic corneal edema is commonly seen after cataract surgery, especially phacoemulsification It may occur due to significant surgical trauma which may be due to ultrasound energy, direct mechanical trauma or toxicity of irrigating solutions, all leading to endothelial cell damage & endothelial pump failure.

Risk factors include advanced age, increased nuclear density, shallow anterior chambers, pseudoexfoliation, and surgical trauma [3,4]. Postoperative endothelial damage leads to stromal swelling, haze, and decreased visual acuity [5].

Conventional therapy includes hypertonic saline drops, corticosteroids, and bandage contact lenses [6]. Hypertonic saline acts by increasing the tear film osmolarity and thus form an osmotic gradient that extracts water out of the cornea and decreases corneal edema. Topical corticosteroids should be considered in cases of associated intraocular inflammation. Dexamethasone have shown to increase the endothelium Na+/K+ ATPase pump activity and function. A bandage contact lens may be used if necessary. Recently, Rho-associated kinase (ROCK) inhibitors like Ripasudil have shown promise in accelerating endothelial healing, enhancing pump function, and reducing corneal edema [7,8].Ripasudil is a Rho-kinase inhibitor, derived from Fasudil a drug used in the treatment of glaucoma and ocular hypertension. It is world's first Rho-associated coiled coil containing protein kinase-1 (ROCK-1) inhibitor that lowers IOP by increasing aqueous flow through Trabecular meshwork & Schlemm's canal. It is safer than prostaglandin analogues and other anti glaucoma drugs. The most common ADR of it is conjunctival hyperaemia (mild) and others being allergic conjunctivitis, punctuate keratitis, blepharitis.

This study evaluates Ripasudil's efficacy compared to hypertonic saline in pseudophakic corneal edema in terms of visual outcomes.

Materials and Methods

This prospective, comparative, open-label study was conducted at Government Medical College and Rajindra Hospital, Patiala. The study included 104 patients who developed pseudophakic corneal edema post-phacoemulsification.

Patients aged more than 25 years who had developed postoperative pseudophakic corneal edema and who showed willingness for follow-up were included in the study. Patients who developed corneal edema due to other causes or were left aphakic were excluded along with those who had other active ocular disease or had an incomplete follow up.

The patients were divided into two groups as Group A (n = 52): those who received Ripasudil 0.4% eye drops twice daily and Group B (n = 52) received hypertonic saline 5% eye drops4 times a day. The Visual Acuity was assessed by the Snellen chart, the IOP was measured by Non-contact Tonometry, CCT was measured with Nidek NT-530P. Slit Lamp Examination was done to look for corneal edema and was graded as per Oxford Cataract Treatment and Evaluation Team (OCTET) [9]. All these assessments were made on POD 1, 7, 14, 28, 90, and 120 and the data was analysed statistically.

Results

Demographics

The mean age was 65.08 ± 9.49 years (Group A) and 62.42 ± 8.74 years (Group B). Gender distribution was nearly equal. No significant differences in baseline CCT or IOP were observed. Any other systemic or ocular diseases were evaluated again with no significant difference between the two groups.

Visual acuity

Post operatively, the UCVA and BCVA were recorded at the various follow up visits and significant improvement was observed in both the groups following surgery. At six months, 92.31% of group A and 82.69% of group B achieved BCVA of 6/6 or 6/9, reflecting substantial recovery of visual function. While group A showed slightly higher proportions of patients with optimal visual outcomes, the difference between the groups were not statistically significant (p = 0.138).

Near visual acuity

At 6 months, 65.38% of Group A and 73.08% of Group B had N6 acuity. No statistical significance was observed (p = 0.080).

Corneal edema

Post operatively, the slit lamp examination was performed to look for the presence of corneal edema and its resolution on the following visits. Resolution occurred within first 2 weeks in majority of patients (Group A: 57.69%, Group B:50%), although a small

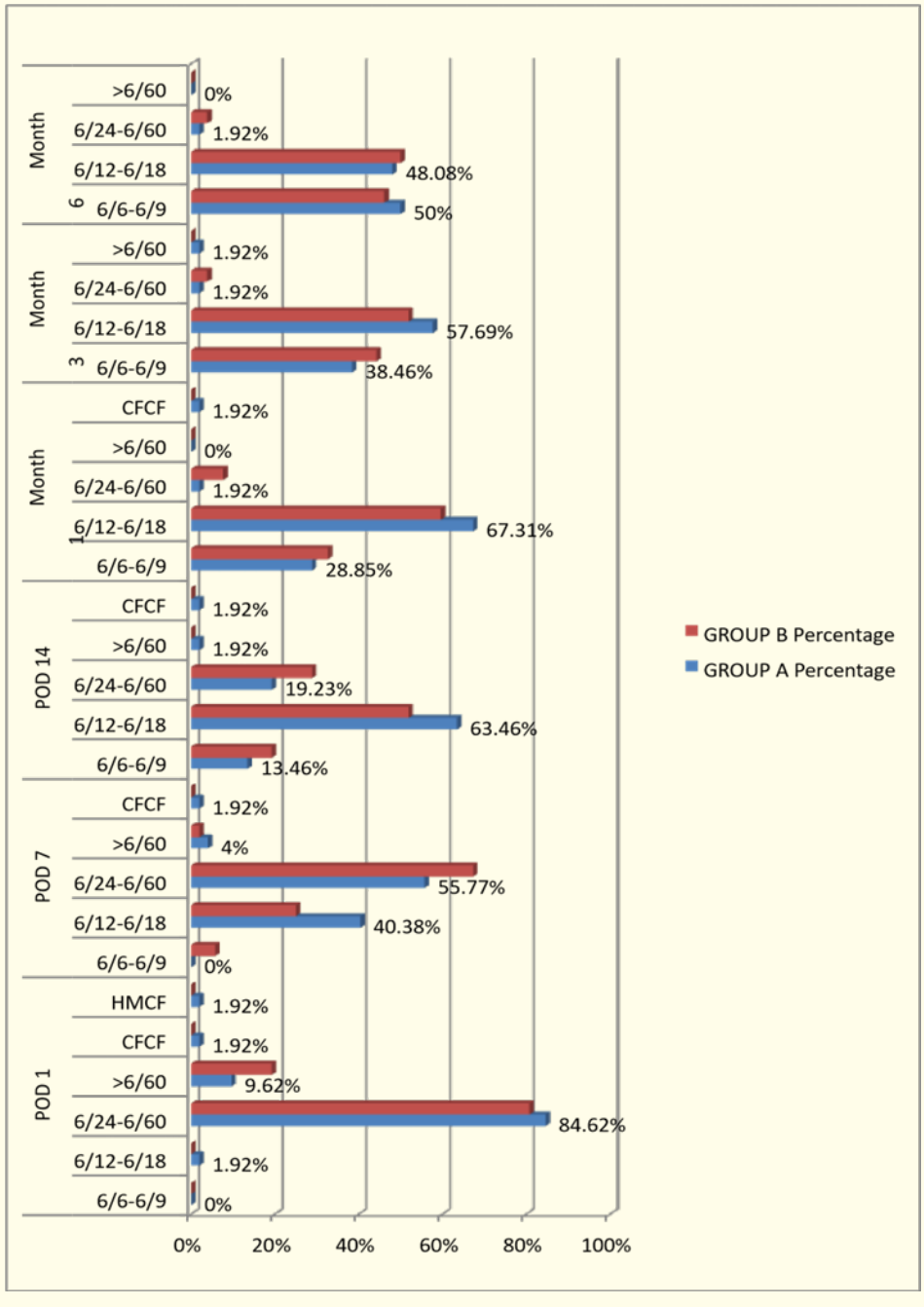

Figure 1: Post-operative BCVA in the two groups.

Post-Operative of BCVA		Group A		Group B		χ^2	p value
		Patients	Percentage	Patients	Percentage		
POD 1	6/6-6/9	0	0%	0	0%	1.341	0.511 (NS)
	6/12-6/18	3	5.77%	6	11.54%		
	6/24-6/60	48	92.31%	44	84.62%		
	>6/60	1	1.92%	2	3.85%		
POD 7	6/6-6/9	13	25%	10	19.23%	3.515	0.319 (NS)
	6/12-6/18	29	55.77%	26	50%		
	6/24-6/60	9	17.31%	16	30.77%		
	>6/60	1	1.92%	0	0%		
POD 14	6/6-6/9	26	50%	26	50%	1.021	0.796 (NS)
	6/12-6/18	23	44.23%	24	46.15%		
	6/24-6/60	2	3.85%	2	3.85%		
	>6/60	1	1.92%	0	0%		
1 Month	6/6-6/9	37	71.15%	41	78.85%	1.596	0.660 (NS)
	6/12-6/18	13	25%	10	19.23%		
	6/24-6/60	1	1.92%	1	1.92%		
	>6/60	1	1.92%	0	0%		
3	6/6-6/9	46	88.46%	43	82.69%	0.793	0.673
Month	6/12-6/18	5	9.62%	8	15.38%		(NS)
	6/24-6/60	1	1.92%	1	1.92%		
	>6/60	0	0%	0	0%		
6 Month	6/6-6/9	48	92.31%	43	82.69%	2.198	0.138 (NS)
	6/12-6/18	4	7.69%	9	17.31%		
	6/24-6/60	0	0%	0	0%		
	>6/60	0	0%	0	0%		

Table 1: Post-operative BCVA.

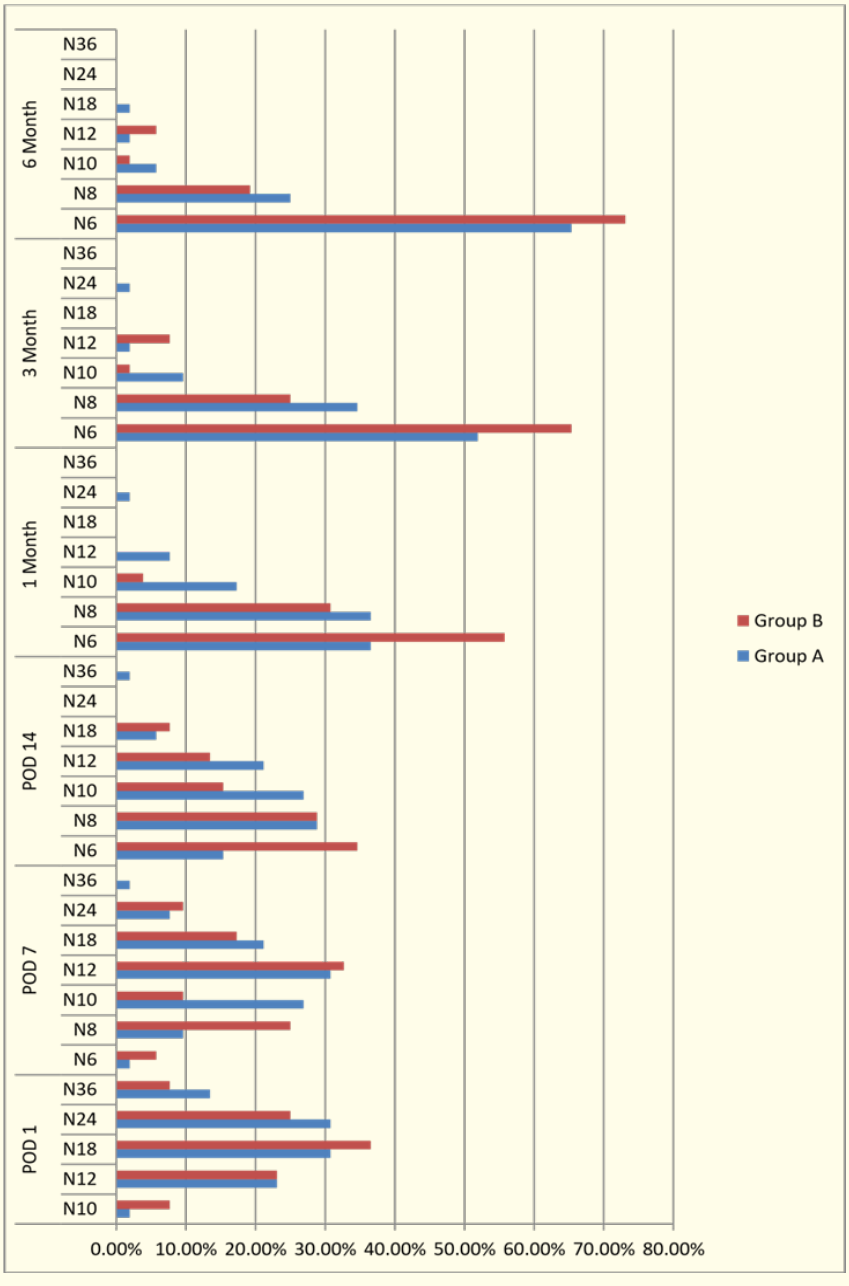

Figure 2: Post-operative BCNVA.

Post-Operative of BCVA		Group A		Group B		χ^2	p value
		Percentage	Percentage	Patients	Percentage		
POD 1	N10	1	1.92%	4	7.69%	2.456	0.129 (NS)
	N12	12	23.08%	12	23.08%		
	N18	16	30.77%	19	36.54%		
	N24	16	30.77%	13	25%		
	N36	7	13.46%	4	7.69%		
POD 7	N6	1	1.92%	3	5.77%	4.398	0.698 (NS)
	N8	5	9.62%	13	25%		
	N10	14	26.92%	5	9.62%		
	N12	16	30.77%	17	32.69%		
	N18	11	21.15%	9	17.31%		
	N24	4	7.69%	5	9.62%		
	N36	1	1.92%	0	0%		
POD 14	N6	8	15.38%	18	34.62%	4.741	0.775 (NS)
	N8	15	28.85%	15	28.85%		
	N10	14	26.92%	8	15.38%		
	N12	11	21.15%	7	13.46%		
	N18	3	5.77%	4	7.69%		
	N24	0	0%	0	0%		
	N36	1	1.92%	0	0%		
1 Month	N6	19	36.54%	29	55.77%	4.046	0.298 (NS)
	N8	19	36.54%	16	30.77%		
	N10	9	17.31%	2	3.85%		
	N12	4	7.69%	5	9.62%%		
	N18	0	0%	0	0%		
	N24	1	1.92%	0	0%		
	N36	0	0%	0	0%		
3 Month	N6	27	51.92%	34	65.38%	6.886	0.154 (NS)
	N8	18	34.62%	13	25%		
	N10	5	9.62%	1	1.92%		
	N12	1	1.92%	4	7.69%		
	N18	0	0%	0	0%		
	N24	1	1.92%	0	0%		
	N36	0	0%	0	0%		
6 Month	N6	34	65.38%	38	73.08%	9.353	0.080
	N8	13	25%	10	19.23%		(NS)
	N10	3	5.77%	1	1.92%		
	N12	1	1.92%	3	5.77%		
	N18	1	1.92%	0	0%		
	N24	0	0%	0	0%		
	N36	0	0%	0	0%		

Table 2: Post-operative BCNVA.

number required longer durations. By three months, complete resolution was achieved in all the patients. Edema (CE) grading followed OCTET criteria: CE+, CE++, and CE+++ [9].

- CE+: Transient Corneal Edema without DM folds.
- CE++: Transient Corneal Edema with less than 10 DM folds.
- CE+++: Transient Corneal Edema with more than 10 DM folds

Post-Operative of SLIT Lamp Examination		Group A		Group B		χ^2	p value
		Patients	Percentage	Patients	Percentage		
POD 1	CE-	1	1.92%	0	0%	0.402	0.940 (NS)
	CE+	41	78.85%	45	86.54%		
	CE++	9	17.31%	7	13.46%		
	CE+++	1	1.92%	0	0%		
POD 7	CE-	29	55.77%	25	48.08%	3.401	0.757 (NS)
	CE+	20	38.46%	26	50%		
	CE++	2	3.85%	1	1.92%		
	CE+++	1	1.92%	0	0%		
POD 14	CE-	48	92.31%	45	86.54%	4.966	0.083 (NS)
	CE+	2	3.85%	7	13.46%		
	CE++	2	3.85%	0	0%		
	CE+++	0	0%	0	0%		
1 Month	CE-	50	96.15%	52	100%	1.539	0.463 (NS)
	CE+	1	1.92%	0	0%		
	CE++	1	1.92%	0	0%		
	CE+++	0	0%	0	0%		
3 Months	CE-	52	100%	52	100%	--	--
	CE+	0	0%	0	0%		
	CE++	0	0%	0	0%		
	CE+++	0	0%	0	0%		
6 Months	CE-	52	100%	52	100%	--	--
	CE+	0	0%	0	0%		
	CE++	0	0%	0	0%		
	CE+++	0	0%	0	0%		

Table 3: Corneal edema on post-operative slit lamp examination.

Corneal Edema	Duration	Group A		Group B		χ^2	p value
		Patients	Percentage	Patients	Percentage		
Day of Detection of Corneal Edema	POD 1	52	100%	52	100%	3.089	0.079 (NS)
Day of Resolution of Corneal Edema	POD1-POD7	27	51.92%	25	48.08%	9.262	0.066 (NS)
	POD8-POD14	21	40.38%	20	38.46%		
	POD15-POD21	1	1.92%	3	5.77%		
	POD22-POD28	1	1.92%	4	7.69%		
	> POD28	2	3.85%	0	0%		

Table 4: Day of detection and resolution of corneal edema.

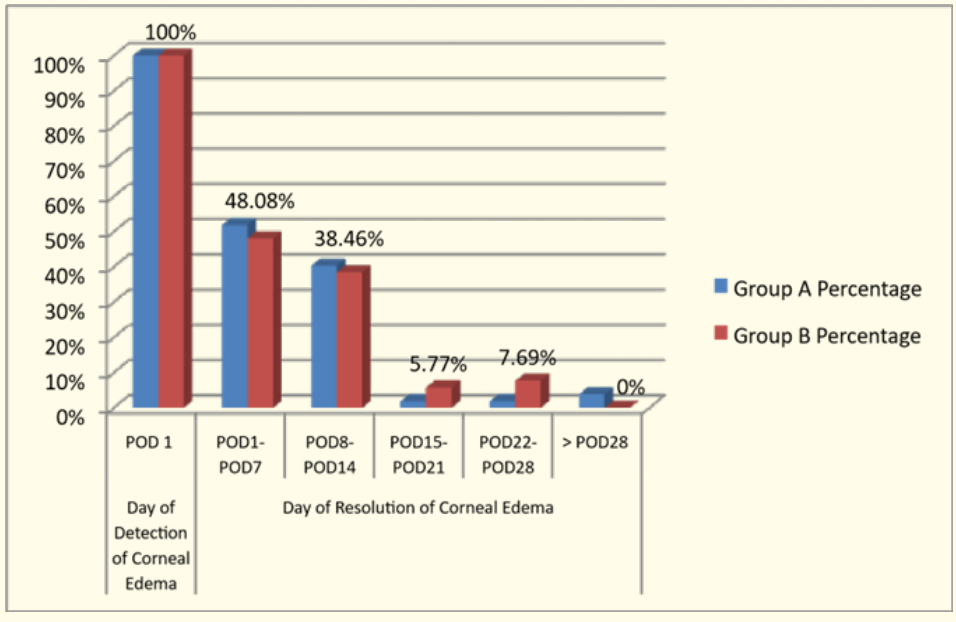

Figure 3: Resolution of corneal edema in the two groups.

Time Taken for Resolution (Days)	Group A		Group B	
	Patients	Percentage	Patients	Percentage
1-7 Days	29	55.77%	25	48.08%
8-14 Days	20	38.46%	20	38.46%
15-21 Days	0	0%	3	5.77%
22-28 Days	3	5.77%	4	7.69%
Total	52	100%	52	100%
Mean ± SD	8.90 ± 5.10		9.90 ± 5.52	
Median	6.00		8.50	
Range	4-28		3-24	
Mean Rank	50.15		54.85	
Mann-Whitney U	0.827			
p value	0.408 (NS)			

Table 5: Time taken for resolution.

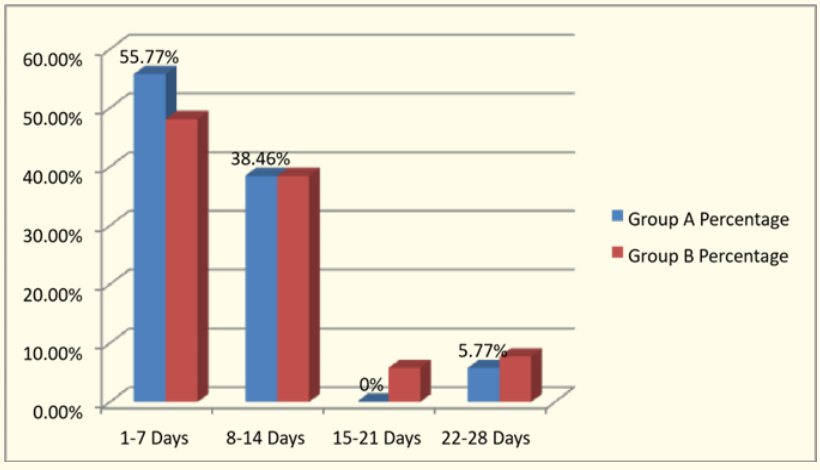

Figure 4: Time taken for resolution.

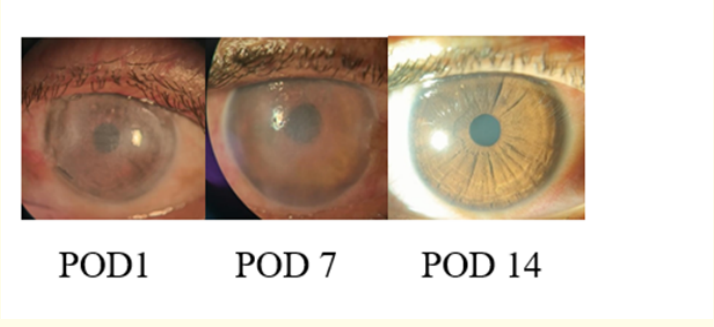

Image 1: Resolution of corneal edema in group A.

Central corneal thickness

Preoperatively a mean CCT of 505.88±11.20 µm was documented in group A and a mean CCT of 509.13 ± 13.30 µm in group B with no significant difference between the two groups.

Post operatively, a significant increase in CCT was noticed on the day of detection of corneal edema (POD 1) with mean CCT of 603.60 ± 23.10 micrometers in group A & 606.04 ± 13.98 micrometers and a significant decrease of CCT on administration of topical medication was seen with gradual resolution of corneal edema in both the groups with no significant differences observed on comparison of the two groups at any time.

Intraocular pressure

The mean pre operative IOP in both the groups were comparable with no significant difference between the two groups (p value = 0.352).

Post operatively, the mean IOP was found to be decreased due to the presence of corneal edema on POD 1 (group A 12.13 ± 2.15 mm Hg & group B 11.33 ± 2.03 mm Hg) which stabilised gradually with the resolution of corneal edema and were comparable to preoperative levels. The post operative changes of IOP shows no statistically significant difference between group A & B.

Cost-effectiveness

A cost-effectiveness analysis was conducted to compare Group A and Group B based on the cost incurred and effectiveness in terms of resolution time. The following parameters were assessed:

- **Cost incurred:** Group A had a significantly higher mean cost of Rs. 307.00, while Group B incurred Rs. 85.00, resulting in a cost difference of Rs. 222.00.
- **Effectiveness (measured as Time Taken for Resolution on a 1–14 day scale):** Group A demonstrated slightly better effectiveness, with an average score of 49, compared to 45 in Group B. The difference in effectiveness was 4 units.
- **Incremental Cost-Effectiveness Ratio (ICER):** The ICER, calculated as the difference in cost divided by the difference in effectiveness, was Rs.55.50.

This indicates that an additional unit of effectiveness (improvement in resolution score) in Group A costs Rs. 55.50 more compared to Group B.

Across all parameters analysed, there were no statistically significant differences between group A & group B. Both groups demonstrated comparable improvements in visual and structural outcomes, indicating that the treatment with Ripasudil was not found to be inferior to conventional hypertonic eye drops treatment for corneal edema.

Discussion

The importance of the corneal edema to the ocular structure and visual system is often due to the transparent nature of the cornea. Without it's clarity, the eye would not be able to perform it's necessary functions. The maintenance of stromal hydration is essential for maintaining the transparency of cornea and carrying out these functions adequately. Anteriorly, the epithelial layer and posteriorly, the Descemet's layer and endothelium through its tight junctions and endothelial pumps, maintain the stromal dehydration [10]. Corneal edema from an inadequate endothelial pump function is one of the most common complications of cataract surgery [11].

Pseudophakic corneal edema remains a common postoperative complication following phacoemulsification cataract surgery, often leading to patient discomfort, delayed visual recovery, and, in severe cases, permanent visual impairment [12]. The current study was undertaken to evaluate the therapeutic efficacy of Ripasudil, a Rho kinase inhibitor, in comparison with hypertonic saline drops, which are conventionally used in the management of corneal edema [13]. Our findings revealed that Ripasudil was as effective as hypertonic saline in improving visual outcomes and reducing corneal edema, suggesting that it may serve as a promising alternative or adjunct in the treatment regimen of this condition.

Both treatment groups showed significant improvement in visual acuity and corneal transparency over the observation period. The reduction in central corneal thickness (CCT) and improvement in best corrected visual acuity (BCVA) were comparable between the two groups, indicating that Ripasudil can match the clinical efficacy of hypertonic saline. Notably, patients in the Ripasudil group showed slightly faster early-phase recovery in some cases, although this difference was not statistically significant. This early response may suggest a more active role of Ripasudil at the cellular level in enhancing endothelial pump function and reducing fluid accumulation in the corneal stroma [14,15].

Ripasudil exerts its action through Rho-associated kinase (ROCK) inhibition, a mechanism known to promote cytoskeletal rearrangement, enhance endothelial cell adhesion, reduce apoptosis, and stimulate regenerative pathways in the corneal endothelium [16,17]. This is in contrast to hypertonic saline, which functions purely through osmotic mechanisms, drawing fluid out of the corneal stroma to temporarily relieve edema without influencing the underlying endothelial health or function. The mechanism of Ripasudil allows for a more physiological recovery process, potentially benefiting patients with borderline endothelial reserve or chronic low-grade endothelial dysfunction.

Moreover, recent studies suggest that Ripasudil may stimulate endothelial cell migration and proliferation [18,19], which could have long-term reparative effects beyond just symptomatic relief. This biological activity could explain the promising results seen in chronic corneal endothelial disorders such as Fuchs' endothelial dystrophy and bullous keratopathy [20,21], and may also contribute to its efficacy in pseudophakic corneal edema as observed in our study.

The analysis reveals a notable difference in cost between the two groups, with Group A being significantly more expensive than Group B. While Group A does demonstrate marginally improved effectiveness, the cost associated with this improvement is substantial. An ICER of Rs.55.50 suggests that for each additional unit of effectiveness gained by using Group A's approach, there is an extra expenditure of Rs. 55.50.

From a health economics standpoint, this raises critical questions about the value for money offered by Group A's intervention. If resources are constrained, stakeholders may prefer the more economical approach of Group B, especially if the marginal gain in effectiveness is not clinically or operationally significant.

Additionally, the relatively small difference in effectiveness (only 4 units) may not justify the significant cost difference unless Group A's method has other non-quantifiable benefits such as higher patient satisfaction or long-term outcomes that were not captured in this study.

While multiple studies have established the benefit of hypertonic saline in postoperative corneal edema, fewer have explored the role of Ripasudil in this specific clinical context. Our results are consistent with preliminary studies that report favourable outcomes with Ripasudil in managing endothelial dysfunction and postoperative edema. Notably, unlike most previous research which has focused on chronic corneal decompensation, this study highlights Ripasudil's role in the acute setting of pseudophakic edema, thus expanding its potential clinical application. The fact that Ripasudil performed comparably to hypertonic saline—despite their differing mechanisms of action—adds value to its potential inclusion in treatment protocols.

The findings from this study have important clinical implications. None of the patients in this study experienced any side effect due to the drugs. For patients who are intolerant to hypertonic saline due to stinging [22] ocular surface irritation, or compliance issues with frequent dosing, Ripasudil may serve as a more tolerable alternative. Its use could also be particularly valuable in patients at higher risk for persistent corneal edema—such as those with pre-existing endothelial cell compromise, shallow anterior chambers, or complicated surgeries. In addition, given the trend toward faster visual recovery observed in some Ripasudil-treated patients, it may also be advantageous in individuals requiring early visual rehabilitation, such as monocular patients, professionals reliant on vision, or those undergoing second-eye surgery shortly after the first.

The strengths of this study include its prospective, comparative design, use of standardized surgical and assessment protocols, and objective parameters such as BCVA (both distant and near), IOP, CCT to evaluate outcomes. However, the study is not without limitations. Firstly, the follow-up duration was relatively short, limiting our ability to assess long term effects, recurrence, or endothelial cell loss. Secondly, the sample size, though adequate for preliminary conclusions, was limited to a single-center population, which may affect the generalizability of results. Moreover, specular microscopy was not employed to evaluate endothelial cell density [23] or morphology pre- and post-treatment, which could have added a deeper understanding of the cellular effects of Ripasudil. Including this parameter in future studies would allow for better evaluation of Ripasudil's regenerative potential.

Further research is warranted to evaluate Ripasudil's role in a broader patient population and over a longer period. Randomized controlled trials with larger sample sizes and multicenter participation would help confirm these findings. Additionally, studies employing specular microscopy and *in vivo* confocal microscopy could provide insight into Ripasudil's impact on endothelial cell morphology and function [24].

Investigating patient-reported outcomes, such as comfort, satisfaction, and quality of vision, would further enhance understanding of Ripasudil's place, if any, in postoperative care. The potential of Ripasudil to prevent chronic corneal edema or delay the need for endothelial keratoplasty in borderline cases also merits further exploration.

Conclusion

Ripasudil 0.4% ophthalmic solution is not inferior to 5% hypertonic saline drops in improving visual outcomes and reducing corneal edema in patients with pseudophakic corneal edema following cataract surgery.

Ripasudil may offer additional biological benefits by promoting endothelial cell health and enhancing cellular recovery mechanisms, unlike hypertonic saline which acts only via osmotic mechanisms.

The use of Ripasudil may be particularly beneficial in patients with compromised endothelial function, specially in those who are intolerant to hypertonic saline, or when faster recovery is desired (e.g. one eyed).

This study demonstrates the clinical equivalence of Ripasudil to hypertonic saline in the short term, and its potential superiority in long-term endothelial support should be further explored.

Future research with larger sample sizes, longer follow-up periods, and detailed endothelial assessments using sophisticated tools is needed to validate these findings and to define the precise role of Ripasudil in the postoperative management of corneal edema.

Based on the current findings, Ripasudil can be considered a safe, effective, and well-tolerated adjunct to traditional therapy in the management of pseudophakic corneal edema.

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