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ORIGINAL PAPER

Intraocular pressure-lowering effects of ripasudil, a rho-kinase inhibitor, and selective laser trabeculoplasty as adjuvant therapy in patients with uncontrolled glaucoma

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Abstract

Objectives To compare the intraocular pressure (IOP)-lowering effects of ripasudil, a rho-kinase inhibitor, and selective laser trabeculoplasty (SLT) as adjuvant therapy in Japanese glaucoma patients and to identify the factors associated with treatment success.

Methods We performed a retrospective medical chart review of patients with glaucoma who received ripasudil or SLT as an adjuvant therapy. We collected data on 65 eyes (65 patients) with primary open-angle glaucoma, normal-tension glaucoma, or exfoliation glaucoma with at least 12 months of follow-up. IOP and number of glaucoma medications at 0, 1, 3, 6, 9, and 12 months were compared between and within groups. A repeated-measures mixed model was used to perform statistical analysis. We also investigated factors associated with treatment success, which was defined as $\geq$ 20% reduction in IOP at all follow-up periods, using univariate and multivariate logistic regression analysis.

Results Significant IOP reduction was observed at all time-points after treatment in the ripasudil group (n = 33) and in the SLT group (n = 32), with no statistically significant difference between the groups before or after treatment. Patients in the SLT group used more anti-glaucoma medications before treatment, but fewer during follow-up, than those in the ripasudil group. Regardless of treatment, higher baseline IOP was associated with treatment success [crude odds ratio: 1.21 (95% confidence interval: 1.06–1.38), adjusted odds ratio: 1.37 (95% confidence interval: 1.06–1.77)].

Conclusions Adjuvant SLT or ripasudil in patients with inadequately controlled glaucoma both reduced IOP to a similar degree, but SLT contributed to reducing the number of medications used.

Keywords Glaucoma · A rho-kinase inhibitor · Selective laser trabeculoplasty · Intraocular pressure

Background

Glaucoma is the third leading cause of blindness and distance visual impairment worldwide, after refractive errors and cataracts [1], and the leading contributor to newly certified visual impairments in Japan [2]. Owing to a super-aging society, the number of glaucoma patients is expected to increase

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substantially. According to a population-based survey in Japan [3, 4], primary open-angle glaucoma (POAG) is the most common type of glaucoma. Elevated intraocular pressure (IOP) due to impaired aqueous humor outflow is strongly associated with the onset and progression of glaucoma. Therefore, lowering IOP using prescription eyedrops, oral medications, laser treatment, surgery, or a combination of any of these reduces the speed of glaucomatous damage and visual field loss.

Glaucoma treatment often starts with prescription eyedrops. The first-line medical treatment is prostaglandin analogues, followed by beta-blockers, carbonic anhydrase inhibitors, and alpha-adrenergic agonists. Ripasudil (Glanatec® ophthalmic solution 0.4%; Kowa company, Ltd., Japan), a rho-associated protein kinase (ROCK) inhibitor ophthalmic solution, was approved by the Japanese government in 2014 and is reported to reduce IOP [5–9]. The mechanism by which ROCK inhibitors lower IOP involves changing the status of the trabecular meshwork and Schlemm's canal endothelial cells, resulting in an elevation of the conventional aqueous outflow.

Selective laser trabeculoplasty (SLT) also enhances conventional aqueous outflow [10] without damaging the tissues adjacent to the trabecular meshwork. Several randomized clinical trials of SLT [11–13] have already reported IOP-lowering effects equivalent to medical therapy in POAG and ocular hypertension. Here, we compare the additive IOP-lowering effects of ripasudil and SLT, both of which increase conventional aqueous outflow, in Japanese patients with glaucoma.

Materials and methods

This study was a retrospective chart review of patients with glaucoma who had received ripasudil or SLT as adjuvant therapies at Juntendo Tokyo-Koto Geriatric Medical Center and Marumoto Eye Clinic between June 2017 and December 2017. The study protocol was approved by the Institutional Review Board of Juntendo Tokyo-Koto Geriatric Medical Center. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

This investigation included 65 eyes of 65 consecutive Japanese glaucoma patients who had been diagnosed with normal-tension glaucoma (NTG), POAG, or exfoliation glaucoma (EXG), and whose IOP was inadequately controlled by anti-glaucoma medications. Subjects who had at least 12-months of follow-up for ripasudil or SLT were enrolled in this analysis. In the ripasudil group, one drop was instilled into the eye twice daily. In the SLT arm, all patients received approximately 100 adjacent but non-overlapping laser spots (0.70–1.0 mJ) over 360° of the trabecular meshwork. Exclusion criteria were a history of uveitis or trauma, previous laser or surgical glaucoma intervention, silicone oil-induced glaucoma, neovascular glaucoma, any corneal abnormality, intraocular surgery within 6 months before or after enrollment, inadequate charting, and loss of follow-up. Patients who received both SLT and ripasudil were also excluded.

Data collected included age, sex, type of glaucoma (NTG, POAG, or EXG), lens status (phakia, or pseudophakia), IOP measured at baseline and 1, 3, 6, 9, and 12 months after treatment using Goldmann applanation at 9–11 AM, and number of anti-glaucoma medications at the same time-points. For patients who underwent treatment in both eyes, only one was chosen for our analysis using a random number generator. To examine safety, we reviewed patients' complaints of blepharitis and conjunctival hyperemia, and the existence of anterior segment inflammation or transient post-SLT IOP spike.

Baseline data were analyzed statistically using a 2-tailed unpaired t test for continuous variables, and Chi-square test for categorical variables. IOP and the number of anti-glaucoma medications were analyzed using a repeated-measures mixed model. Treatment success was defined as a $\geq$ 20% reduction in IOP from baseline without any additional medication during post-treatment periods. To identify the difference in treatment success between ripasudil and SLT, we used logistic regression analysis to calculate crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). Age, sex, lens status, baseline IOP, baseline number of anti-glaucoma medications, and type of glaucoma were considered potential confounders.

The level of significance was set as ≤ 0.05. All statistical analyses were performed with STATA/SE15.1 for Windows (StataCorp LLC, TX, USA).

Results

Thirty-three consecutive patients were included in the ripasudil treatment group, and 32 were included in the SLT group. Table 1 shows the baseline characteristics of participants in both groups. There were no significant differences between the two groups in terms of age, sex, type of glaucoma, lens status, or baseline IOP. However, a significant difference in the number of anti-glaucoma medications was observed ($p = 0.027$) at the baseline.

Figure 1 shows the very similar IOP changes in the two groups of patients between baseline and follow-up. When comparing baseline IOP with all follow-up time periods for each treatment, there was a statistically significant reduction in IOP, with no statistically significant differences between the two groups. There were no significant differences in the mean IOP percentage reduction at any time point between the two groups (Table 2). At baseline, the ripasudil group used 0.6 (95%CI: 0.05–1.1) more medications than the SLT group, but there were significant differences in the number of medications between the two groups at 1, 3, and 9 months (Table 3).

Treatment success defined as a 20% or greater IOP reduction at every post-treatment time point was observed for 7 (21.9%) patients in the SLT group and 4 (12.1%) in the ripasudil group. Table 4 shows the results of the logistic regression analysis. There was no statistically significant association between treatment and success in univariate or multivariate models [crude OR for ripasudil (vs. SLT): 0.49 (95%CI: 0.13–1.88), adjusted OR: 0.18 (95% CI: 0.02–1.34)]. The only factor that predicted treatment success was higher baseline IOP [crude OR: 1.21 (95%CI: 1.06–1.38), adjusted OR: 1.37 (95% CI: 1.06–1.77)].

A transient IOP spike, defined as > 10% IOP elevation at 1 month after SLT, was observed for three patients in the SLT group (9.4%); the greatest spike was 4 mmHg. None of these patients required additional treatment to control SLT-induced increase in IOP. There were no cases of serious anterior segment inflammation. In the ripasudil group, 18 patients (54.5%) had conjunctival hyperemia and 2 (6.1%) had blepharitis. These ocular complications were temporary and recovered with eye drops or ointment. There were no systemic side effects in either group.

Discussion

Systematic reviews [14, 15] have compared the IOP-lowering effects of SLT and prostaglandin analogues or beta-blockers. Because prostaglandin analogues and beta-blockers are first-line treatments for glaucoma, most patients with glaucoma who have inadequate IOP control have already used one or both medications. Therefore, we felt it would be more realistic and interesting to compare IOP in patients taking ripasudil or SLT as adjuvant therapies that both reduce IOP by increasing conventional outflow.

To the best of our knowledge, this was the first study to examine IOP reduction in patients with inadequately managed glaucoma treated with adjuvant ripasudil vs. SLT. Our results revealed no differences

Table 1 Baseline characteristics of patients included in this study

		Ripasudil ($n = 33$)	SLT ($n = 32$)	p-values
Age	Mean ± SD	71.7 ± 1.7	70.4 ± 1.8	0.598
Gender	Males	19	16	0.540
	Females	14	16	
Lens status	Phakia	19	19	0.883
	IOL	14	13	
At baseline				
IOP	Mean (± SD)	18.4 ± 5.8	18.8 ± 5.3	0.763
Number of medications	Mean (± SD)	2.0 ± 1.0	2.6 ± 1.2	0.027
Type of glaucoma	NTG	9	7	0.789
	OAG	20	22	
	PEG	4	3	

SLT selective laser trabeculoplasty

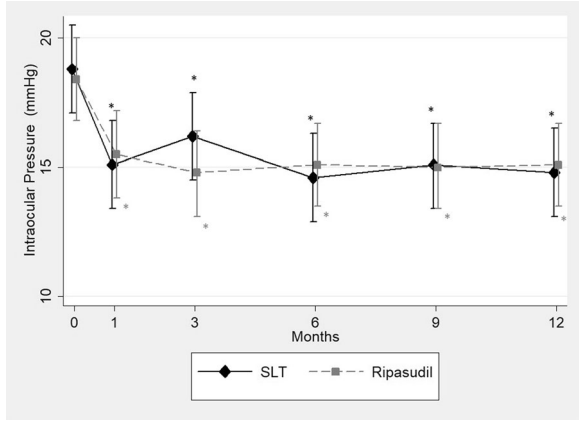

Fig. 1 Intraocular pressure changes in the ripasudil and the SLT groups of Japanese glaucoma patients between baseline and follow-up. *$p < 0.05$ compare to the baseline intraocular pressure

Table 2 Intraocular pressure percentage reduction from baseline in SLT versus Ripasudil groups

Months	Ripasudil			SLT			*p*-values**
	% Decrease	95% Confidence intervals		% Decrease	95% Confidence intervals		
		Lower limit	Upper limit		Lower limit	Upper limit	
1	15.1	8.6	21.6	16.9	10.3	23.6	0.702
3	16.3	10.0	22.7	13.4	6.9	19.9	0.533
6	15.9	9.6	22.2	21.0	14.6	27.4	0.266
9	16.2	9.9	22.5	18.7	12.3	25.1	0.583
12	14.7	8.4	21.0	18.5	12.1	24.9	0.409

SLT selective laser trabeculoplasty

** A *p*-value less than 0.05 is statistically significant

Table 3 Mean number of medication in Ripasudil Vs. SLT groups

Months	Ripasudil			SLT			*p*-values*
	Number of medications	95% Confidence intervals		Number of medications	95% Confidence intervals		
		Lower limit	Upper limit		Lower limit	Upper limit	
1	2.81	2.44	3.18	2.09	1.72	2.47	0.008
3	2.91	2.54	3.28	2.38	2.00	2.75	0.047
6	2.91	2.54	3.28	2.44	2.06	2.81	0.079
9	2.88	2.51	3.25	2.34	1.97	2.72	0.046
12	2.88	2.51	3.25	2.38	2.00	2.75	0.061

SLT selective laser trabeculoplasty

* A *p*-value less than 0.05 is statistically significant

in longitudinal data between the two groups. IOP significantly decreased from baseline in both groups, and the success rate for ripasudil was similar to that for SLT for up to 12 months of follow-up. However, patients who underwent SLT required significantly fewer medications at 1, 3, and 9 months than those who took ripasudil.

Chun et al. [16] reported a progressive reduction in IOP after SLT therapy for up to 3 months, but our results showed that although IOP declined

Table 4 Odds ratios for complete success in univariate and multivariate model

	Univariate model				Multivariate model			
	Odds ratios	95% Confidence intervals			Odds ratios	95% Confidence intervals		
		Lower limit	Upper limit	*p*-values		Lower limit	Upper limit	*p*-values
Age	1.01	0.94	1.08	0.88	1.03	0.94	1.14	0.50
Gender								
Males	1	–	–	–	1	–	–	–
Females	0.97	0.26	3.55	0.96	1.29	0.25	6.65	0.76
Lens status								
Phakia	1	–	–	–	1	–	–	–
Pseudophakia	0.77	0.20	2.95	0.70	0.26	0.03	2.26	0.22
Baseline IOP	1.21	1.06	1.38	0.004	1.37	1.06	1.77	0.02
Number of baseline medications	0.70	0.36	1.35	0.28	0.50	0.19	1.36	0.17
Type of Glaucoma								
NTG	1	–	–	–	1	–	–	–
POAG	3.39	0.38	30.09	0.27	1.01	0.06	15.89	0.99
EXG	5.63	0.50	63.28	0.16	0.71	0.01	55.19	0.88
Treatment								
SLT	1	–	–	–	1	–	–	–
Ripasudil	0.49	0.13	1.88	0.30	0.18	0.02	1.34	0.09

NTG normal-tension glaucoma

POAG primary open-angle glaucoma

EXG exfoliation glaucoma

IOP intraocular pressure

SLT selective laser trabeculoplasty

significantly 1 month after SLT treatment, it rebounded at 3 months. This was because SLT contributed to reaching the target IOP level or lower, and the need for medication was reduced. Treatment success is widely defined as a $\geq$ 20% reduction in IOP, but this can change with different medication regimens. Consistent with this, the success rate of SLT performed by resident ophthalmologists was reported to be 41%, 50%, and 36% at 3, 6, and 12 months, respectively [16]. Our success rate for SLT (21.9%) seems low in comparison, but this is likely due to the stricter definition of treatment success, which we defined as a 20% reduction without any additional medications at all post-treatment visits.

Fluctuations in IOP were smaller in the ripasudil group than in the SLT group. This was probably due to the stable number of medications during follow-up periods. Matsumura et al. [17] reported that the effect of ripasudil was time-dependent, but our longitudinal data did not show this. In our study, the mean IOP reduction after 12 months was 3.3 mmHg (95%CI: 2.0–4.6 mmHg) and mean reduction percentage was 14.7% (95%CI: 8.3–21.1%). Inazaki et al. [18] reported that IOP at 12 months was 2.6 mmHg (95%CI: 1.1–3.9 mmHg). A higher baseline IOP resulted in better outcomes in our study. Consistent with this, a post-marketing survey [19] showed greater IOP reduction for greater IOP at baseline.

The other objective of this study was to investigate predictors of treatment success, and the only predictor we identified was higher IOP at baseline, with a crude OR of 1.21 (95% CI: 1.06–1.38) and adjusted OR 1.37 (95%CI: 1.06–1.77) in univariate and multivariate analysis, respectively. Our observation that a higher

baseline IOP predicts a greater IOP reduction regardless of treatment confirms previous findings [19, 20].

In terms of adverse events, a transient IOP spike, anterior chamber inflammation, conjunctival hyperemia, transient corneal haze and cystoid macular edema have been reported for SLT [21]. Conjunctival hyperemia, conjunctivitis, blepharitis, and eye pruritus have been reported for ripasudil [19]. But our results revealed that post-treatment complications were not severe, and were reversible without additional medication.

There were several limitations to this study. First, the IOP-lowering effect might have been overestimated by excluding patients who did not follow up for at least 12 months. In fact, we excluded two patients in the SLT group and three in the ripasudil group who required glaucoma surgery or laser treatment during follow-up period. Second, we did not account for the variability in drug adherence. Approximately half of all glaucoma patients discontinued glaucoma medications within 6 months [22]. But this bias would be small, because we included only patients who visited ophthalmologists on schedule for over 12 months, who might be more inclined to comply with treatment than the general population. Third, the non-randomized nature of this study might produce a difference in an unknown baseline character between the two groups. To avoid this, we enrolled consecutive patients from both groups. Fourth, the number of patients in our study was small. There was a borderline association in treatment success and number of medications (at 6 and 12 months). A significant relationship might be observed if more patients were included. In addition, the study could not examine reported side effects because rare diseases were overlooked due to the small sample size.

Overall, our results suggest that in patients with inadequately controlled glaucoma, adjuvant ripasudil or SLT both reduce IOP in a similar manner without severe complications, but that SLT may contribute to reducing the number of glaucoma medications used.

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Compliance with ethical standards

Conflict of interest All authors (KO, FS, and TM) declare that we have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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