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NETARSUDIL 0.02% AS A MONOTHERAPY IN PATIENTS WITH PRIMARY OPEN ANGLE GLAUCOMA AT A TERTIARY HEALTH CARE CENTRE IN CENTRAL INDIA: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Objectives: To evaluate the ocular hypotensive efficacy and safety of netarsudil 0.02% ophthalmic solution as a monotherapy in patients with primary open-angle glaucoma at a tertiary health care centre. **Methods:** In our randomized prospective interventional study, we enrolled 25 patients with primary open-angle glaucoma who presented to us in eye outpatient department. Patients were given netarsudil 0.02% ophthalmic solution at the baseline visit at the recommended once-daily dosage. Best-corrected visual acuity, fundus examination, intraocular pressure (IOP), and any adverse events were noted in follow-up visits, at day one, two weeks, four weeks, six weeks and three months. **Results:** Out of 25 patients, 24 patients were included in the study as one patient experienced conjunctival hyperemia and was excluded from the study. The mean IOP at baseline (before starting netarsudil eye drop) in the right eye was 23.66 ± 3.19 mmHg and in the left eye was 23.70 ± 3.83 mmHg. The IOP was measured after two Weeks, four weeks, six weeks and three months. The mean IOP at the three-month follow-up visit in the right eye was 18.04 ± 3.15 mmHg, and in the left eye was 18.33 ± 3.49 mmHg. In

our study, the reduction in intraocular pressure was statistically significant (p-value <0.0001). Most of the patients did not report any major adverse effects. Only a few patients were reported to have mild irritation and itching. **Conclusion:** We concluded that the use of netarsudil 0.02% ophthalmic solution as monotherapy in patients with primary open-angle glaucoma is safe and efficacious.

KEYWORDS: Netarsudil, primary open angle glaucoma, intraocular pressure, Rock inhibitor, norepinephrine transport (NET) inhibitor, monotherapy.

INTRODUCTION

Glaucoma is an optic neuropathy characterized by an acquired loss of retinal ganglion cells, resulting in a characteristic optic nerve head appearance and a corresponding progressive loss of vision.[1] The second leading cause of blindness worldwide is glaucoma affecting more than 64 million people aged 40–80 years.[2] It is estimated that the glaucoma population will increase to over 110 million by 2040, augmenting the need for new approaches to glaucoma therapy.[2] Although the pathogenesis of glaucoma remains unclear, the progressive degeneration in the retinal ganglion cells is a key cellular event that leads to glaucomatous optic disc changes with associated visual field loss.[3]

Despite the many pathways and known associations with this disease, intraocular pressure (IOP) is the most predominant and solely modifiable factor.[4] Currently, the reduction of intraocular pressure (IOP) is the only therapeutic intervention demonstrated to slow damage to the optic nerve and preserve vision.[5] Medical intervention that lowers IOP is currently the first-line therapy for preventing the progression of optic nerve damage and subsequent vision loss.[5] Beta-adrenergic antagonists, carbonic anhydrase inhibitors, prostaglandin F2α analogues and selective alpha-2 adrenergic agonists are the commonly used topical ocular hypotensive agents. Due to allergies, adverse effects or contraindications of these agents, many patients are not able to tolerate them. In a normal functioning eye, the principal drainage route for aqueous humor is through the trabecular outflow. A narrow normal range of IOP is maintained by pressure-sensitive regulation of aqueous outflow.[6] An increase in IOP occurs due to high resistance to outflow via the trabecular pathway leading to the development of glaucoma. The causes of increased outflow resistance are not understood fully. There is an increase in the contractile tone and stiffness of the trabecular meshwork (TM), changes in extracellular matrix deposition, and changes in the permeability of the inner wall of Schlemm's canal in glaucoma.[6] Currently, available therapeutic options mainly

decrease aqueous humor production (inflow drugs) and/or increase uveoscleral outflow (known as outflow drugs) to lower IOP instead of targeting the diseased TM pathway directly.[7,8]

Netarsudil is a compound of amino isoquinoline amide, a member of the class of inhibitors of Rho-associated protein kinase (ROCK) and norepinephrine transport (NET). In December 2017, netarsudil gained approval from the Food and Drug Administration (FDA) of the United States. Netarsudil lowers IOP through three mechanisms: increasing trabecular aqueous outflow, decreasing aqueous production, and decreasing episcleral venous pressure.[9-11] The reuptake of norepinephrine at noradrenergic synapses is blocked by the inhibition of NET by netarsudil, thus increasing the strength of endogenous norepinephrine signaling. This reduces aqueous humor formation and blood flow to the ciliary processes.[10] So the longer duration of action and greater efficacy of netarsudil may be due to its NET inhibitory activity. The objective of this study is to evaluate the safety and ocular hypotensive efficacy of netarsudil 0.02% ophthalmic solution as a monotherapy in patients with primary open-angle glaucoma at a tertiary health care centre.

MATERIALS AND METHODS

Design: This randomized prospective interventional study was performed at a tertiary health care centre in central India. Approval from the institutional ethical committee was obtained and this study complied with the tenets of the Declaration of Helsinki. Written informed consent was taken from the patients. The study period was six months.

Eligibility criteria: Patients between 50-80 years of age with a diagnosis of primary open-angle glaucoma based on raised intraocular pressure, optic disc changes, visual field defects, and open angles were included in the study. Both newly diagnosed and previously diagnosed cases of primary open-angle glaucoma were included in the study. Patients who were not willing to give consent or to come for frequent follow-up, patients with other types of glaucoma such as angle-closure, pseudoexfoliation or pigment dispersion, patients having a history of previous glaucoma surgery or glaucoma laser treatment were not included in the study.

Method: Demographic information was collected at the first visit, and informed consent was taken. Anterior segment examination of the eye with slit-lamp biomicroscopy, visual acuity assessment with Snellen’s chart, intraocular pressure measurement using Perkins applanation

tonometer, dilated fundus examination for optic disc evaluation, gonioscopy with Zeiss four mirror goniolens and automated perimetry for visual field examination was done on Humphrey perimeter at first visit. Patients who were using other anti-glaucoma medications were advised to stop the medications prior to the study, depending upon the type of anti-glaucoma drug used. The washout period for prostaglandin analogues and beta-adrenergic antagonists was four weeks; for adrenergic agonists, it was two weeks; and for carbonic anhydrase inhibitors, it was five days. Netarsudil ophthalmic solution of 0.02% was given to all enrolled patients at the first visit, and they were instructed to instill one drop in each eye once in the evening. Best-corrected visual acuity, fundus examination, intraocular pressure measurement and adverse event assessment were done and recorded at five follow-up visits on day one, two weeks, four weeks, six weeks, and three months. Data collection was performed, followed by inputting the information into Microsoft Excel for subsequent analysis which was performed using SPSS version 29.0.

RESULTS

Out of 25 patients who participated in the study based on inclusion criteria, one patient was excluded as he developed an adverse event. Out of 24 patients, 11 patients were newly diagnosed cases of primary open-angle glaucoma and 13 patients were previously diagnosed cases of primary open-angle glaucoma. Table 1 presents the age distribution of the study population. Of the 24 patients enrolled in the study, the most prevalent age group was that of patients aged 61-70 years (n=13, 54.16%). The mean age was 66.2 years.

Table 1: Age distribution of the study population.

Age (in years)	No. of patients	Percentage (%)
50-60	4	16.66
61-70	13	54.16
71-80	7	29.16
Total	24	100

Figure 1 shows the gender-wise distribution of subjects included in the study. Out of total 24 patients, 15 (62.50%) were males and 9 (37.50%) were females.

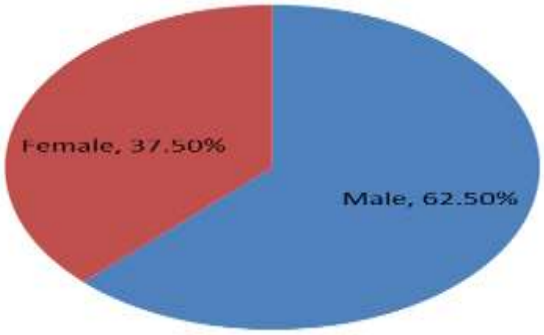

Fig. 1: Gender-wise distribution of subjects included in the study.

Table 2 shows the number of previous anti-glaucoma medications used by patients. Out of 13 patients who were previously diagnosed cases of primary open-angle glaucoma, 8 patients were on one anti-glaucoma medication and 5 patients were on two anti-glaucoma medications.

Table 2: Number of previous anti-glaucoma medications used by patients.

Total number of previous anti-glaucoma medications	Number of patients
1	8
2	5

Table 3 shows the intraocular pressure measurements at different follow-up periods in the right eye and left eye. Data from both eyes of each patient was analyzed to evaluate the difference in mean change in IOP values achieved after the treatment with netarsudil 0.02% ophthalmic solution. IOP measurements were presented as mean ± standard deviation. A one-way repeated measure ANOVA test was used for IOP measurements at different follow-up periods in the right eye and left eye. A p-value <0.05 was considered statistically significant. The mean IOP at baseline (before starting netarsudil 0.02% eye drop) in the right eye was 23.66 ± 3.19 mmHg and in the left eye was 23.70 ± 3.83 mmHg (mean ± standard deviation). The intraocular pressure (IOP) measurements were taken at two, four and six-week intervals, with the last measurement completed three months following the first dose. At the end of three months, the mean IOP in the right eye was 18.04 ± 3.15 mmHg and in the left eye was 18.33 ± 3.49 mmHg (mean ± standard deviation). There was a statistically significant reduction in IOP in patients treated with netarsudil 0.02% eye drop (p-value <0.0001).

Table 3: Intraocular pressure measurements at different follow-up periods in the right eye and left eye.

Follow-up period	Measured IOP in mmHg (Mean ± Standard deviation)		p-value		t-score	
	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
Baseline (before starting netarsudil 0.02% eye drop)	23.66 ± 3.19	23.70 ± 3.83	-------	-------	-------	-------
2 Weeks	22.58 ± 3.18	22.37 ± 3.77	<0.0001	<0.0001	8.12	9.305
4 Weeks	20.83 ± 3.17	21.12 ± 3.76	<0.0001	<0.0001	14.42	14.372
6 Weeks	19.58 ± 3.16	19.75 ± 3.70	<0.0001	<0.0001	14.490	17.91
3 Months	18.04 ± 3.15	18.33 ± 3.49	<0.0001	<0.0001	19.565	24.026

In our study, out of 24 patients, 10 (41.66%) patients had mild irritation and itching, and 4 patients (16.66%) had mild conjunctival hyperemia. In none of the patients using netarsudil 0.02% eye drop, serious adverse effects were observed.

DISCUSSION

The primary objective of this study was to evaluate the safety and ocular hypotensive efficacy of netarsudil 0.02% ophthalmic solution as a monotherapy in patients with primary open-angle glaucoma at a tertiary health care centre. Netarsudil is a Rho kinase inhibitor. Studies suggested that the IOP-lowering effect of ROCK inhibitors might be better than other first-line glaucoma medications.[12]

In our study, of the total 24 patients, the majority of subjects, n=13 (54.16%) were aged between 61 and 70 years. Age is a major risk factor for primary open-angle glaucoma, as the prevalence increases as people get older.[13,14] In our study, we found that, out of a total of 24 patients, 15 (62.50%) were males and 9 (37.50%) were females. In the study conducted by Khachatryan, N. et al. and Rudnicka, A. R. et al.; male gender is found to be a significant risk factor for primary open-angle glaucoma.[15,16]

Netarsudil 0.02% ophthalmic solution is found to lower IOP in patients of primary open-angle glaucoma who were already on multiple anti-glaucoma agents. The novel mechanism of action of netarsudil by acting on all three pathways may allow IOP-lowering efficacy in patients with suboptimal response to other available agents.[17] Phase 3 clinical trials ROCKET-1 and ROCKET-2 found monotherapy of netarsudil 0.02% to be non-inferior to timolol, in patients who had a washout of glaucoma medications prior to the protocol.[18]

In our study, the reduction in mean IOP in the right eye from baseline was 23.66 mmHg to 18.04 mmHg and in the left eye from baseline was 23.70 mmHg to 18.33 mmHg at the end of three months, and this was statistically significant (p-value <0.0001). In the pooled phase III trial, 0.02% netarsudil once daily decreased the IOP from a mean baseline of 21.9–23.7 mmHg to 17.5–19.5 mmHg and also, the efficacy of IOP reduction was stable in different subgroups of baseline IOP.[19] The results suggested that 0.02% netarsudil once daily was not inferior to 0.5% timolol twice daily in the treatment of open-angle glaucoma or ocular hypertension.[19] Serle et al. (2018), in the ROCKET 1 study found that the mean IOP decreased to 17.2–19.8 and 17.4–18.5 mmHg in netarsudil and timolol groups, respectively, over 12 weeks.[18] Kahook et al. (2019), in the ROCKET 2 study, also concluded that netarsudil 0.02% once daily as well as twice daily is non-inferior to timolol 0.5%, and netarsudil produced similar reductions in IOP at all three follow-up visits, 2 weeks, 6 weeks, and 3 months.[20] Khouri et al. (2019), in the ROCKET 4 study on 708 patients, found a statistically significant reduction in mean IOP relative to baseline in both netarsudil and timolol groups ($P < 0.001$).[4] Zaman et al. (2021), in their study of 260 patients with open-angle glaucoma and ocular hypertension who were prescribed netarsudil 0.02% as monotherapy or added with concomitant therapy, reported a statistically significant reduction in IOP in both subgroups at 6 weeks and 12 weeks.[21] In a study by Fridman et al. (2021), the efficacy and safety of netarsudil were evaluated by a retrospective chart review on 130 patients with severe glaucoma and they obtained an IOP reduction rate of 16.5%–17.5%, which was equivalent to 3.01–3.21 mmHg.[22] Bacharach et al. observed that netarsudil had similar efficacy to latanoprost when observed in a pre-specified subgroup of patients with a baseline IOP <26 mmHg.[23]

No new safety signals were observed with netarsudil 0.02% eye drop in patients with primary open-angle glaucoma. So overall, there is a good safety profile of netarsudil 0.02% ophthalmic solution. The safety and efficacy of netarsudil 0.02% ophthalmic solution over 3 months was excellent, and minimal treatment-related adverse effects were observed.[19] In two large randomized double-sided blind trials, researchers found that 0.02% netarsudil once daily was effective and well tolerated in patients with open-angle glaucoma.[18] Netarsudil maintained the efficacy of IOP reduction, regardless of baseline IOP.[18,23]

Although 14 patients experienced treatment-related adverse events in our study, none of these were serious, and only one patient had severe conjunctival hyperemia and was discontinued

from the study. In clinical trials, netarsudil application resulted in no serious systemic effects, but conjunctival hyperemia may still potentially cause patient dissatisfaction.[18,24] In the study conducted by Bacharach et al., only two of 147 patients using netarsudil 0.01% and 0.02% OD required discontinuation due to adverse events.[23] The limitations of our study were a small sample size, short duration of follow-up and the absence of a comparison group.

CONCLUSION

Netarsudil 0.02% ophthalmic solution is a safe and effective anti-glaucoma medication in patients with primary open-angle glaucoma and can be used as monotherapy. We recommend the use of this drug as a first-line treatment in the management of primary open-angle glaucoma. It is a newer drug with no or minimal side effects, and hence it is well tolerated by individuals diagnosed with primary open-angle glaucoma. Netarsudil reduces intraocular pressure by three different means: enhancing the outflow of aqueous humor through the trabecular pathway, reducing the production of aqueous humor and also augmenting the episcleral venous pressure, which enhances its efficacy compared to other anti-glaucoma medications.

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