Case Report

Headache associated with travoprost

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ABSTRACT

Background: Putative adverse effects of prostaglandin analogs in patients treated for glaucoma include periocular skin darkening, herpes simplex keratitis, cystoid macular edema, iritis, and headaches. Here, we report a case of migraine headache after a travoprost administration and discuss the role of prostaglandin analogs in migraine-like headaches.

Case Presentation: A 70-year-old man visited the hospital complaining of pain, redness, and sensitivity to light for 1 week associated with gradual loss of vision in the right eye after cataract surgery, which had been performed 2 years prior. After the examination, the patient was diagnosed with pseudophakic bullous keratopathy and advised to undergo optical penetrating keratoplasty of the right eye. On postoperative day 3, his intraocular pressure (IOP) was 30 mmHg at 10:00 AM in the right eye. A single dose of 0.004% travoprost was instilled in the right eye on the same day. His IOP decreased to 16 mmHg at 2:00 PM. The next day, he presented with migraine-like headache that had started within 1 h after the instillation the previous night. Unremarkable neurological examination and neuroimaging suggested that travoprost had caused the migraine. Although the headache gradually resolved, it reappeared after the administration of other prostaglandins. Trabeculectomy was performed on the right side. The IOP was controlled, and the headache was resolved.

Conclusions: This case indicates a potential causal relationship between topical prostaglandin analogs and migraine-like headaches, as evidenced by symptom resolution upon discontinuation. However, large-scale studies including control groups are required to prove a causal relationship between topical prostaglandin analog administrations and headache development.

KEYWORDS

migraine, headaches, prostaglandin analogues, travatan Z, xalatan, intraocular pressures

INTRODUCTION

Prostaglandin analogs are the principal monotherapy modality for primary open-angle glaucoma [1, 2]. They chiefly increase the uveoscleral outflow of aqueous tissue by remodeling the extracellular matrix of the sclera and ciliary muscles, thereby widening the connective tissue spaces. They also variably increase the aqueous outflow through the trabecular meshwork, thereby lowering the intraocular pressure (IOP). Currently, the prostaglandin analogs available in the market are travoprost, latanoprost, bimatoprost, unoprostone, and tafluprost [3].

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Travoprost is an ester prodrug of the 17-phenyl-PGF2 alpha molecule. It is converted into its free acid form by corneal hydrolases in the corneal epithelium. Esterification makes it more lipid-soluble, which enhances its corneal permeability. The free acid then binds to the PGF2 receptors in the ciliary body and trabecular meshwork, which increases the aqueous outflow. It is available as a 0.004% ophthalmic solution and administered once daily, preferably in the evening, to lower the early morning diurnal spike in IOP. The onset of action is 2–4 h after the first administration, with the peak effect attained at 8–12 h [4, 5].

The most common and well-documented local side effects of topical prostaglandin analogs include hyperemia, burning of the conjunctiva, darkening of the iris, elongation of the eyelashes, and periocular skin pigmentation. Less commonly reported side effects include iris cysts, cystoid macular edema, anterior uveitis, and reactivation of herpes simplex keratitis [6]. Retinal pigment epithelial layer detachment has also been reported [7]. Other side effects include eyelid darkening, eyelash hypertrichosis, and deepening of the superior sulcus of the eyelid [8]. Its systemic safety profile is excellent because of rapid systemic inactivation and low therapeutic concentrations [9, 10].

A few cases of latanoprost-induced migraine headaches have been reported, with discontinuation of the drop providing symptomatic relief [11]. A patient discontinued travoprost because of headaches and gastrointestinal disturbances [12]. Although both are prostaglandin analogs, their chemical components differ [13]. Here, we report a case of migraine-like headache after travoprost instillation, similar to that with latanoprost, with the difficulty faced by ophthalmologists in managing elevated IOP.

CASE PRESENTATION

A 70-year-old man visited the hospital complaining of pain, redness, and sensitivity to light for 1 week associated with gradual loss of vision in the right eye after cataract surgery, which had been performed 2 years before. He had type 2 diabetes mellitus and hypertension for the past 20 years and was under medication. He had no relevant history of systemic or ocular diseases.

The best-corrected distance visual acuity was tested using a Snellen chart (I chart HD projector; Appasamy Associates, Chennai, India) and was counting fingers at 1 m in the right eye and 6/6 in the left eye. His near visual acuity in the left eye was N6, as determined using a reduced Snellen near vision chart (N-notation). As he was severely symptomatic, the objective and subjective refractions differed. The ocular motility was normal, and a slit-lamp examination (Haag-Streit AG, Koeniz, Switzerland) revealed epithelial bullae and an edematous and hazy cornea in the right eye in the presence of a posterior-chamber intraocular lens. The IOPs were 14 and 16 mmHg at 11:30 AM in the right and left eyes, respectively, measured with a Goldmann Applanation Tonometer (AT900, Haag-Streit, Koeniz, Switzerland). The central corneal thicknesses were 780 and 570 μm with ultrasound pachymetry in the right and left eyes, respectively, performed by Appascan Max with Pachymeter (Appasamy Associates, Chennai, India). Optical coherence tomography (CIRRIUS 6000, Carl Zeiss Meditec AG, Jena, Germany) revealed chronic Descemet membrane detachment (Figure 1). Therefore, he was diagnosed with pseudophakic bullous keratopathy, for which he was fitted with a bandage contact lens (SiHy Spherical, silicone hydrogel soft contact lenses; Silver Line Laboratories, Delhi, India), which reduced the symptoms immediately [14, 15]. He was advised to undergo optical penetrating keratoplasty in the right eye [16, 17].

On postoperative day 3, his IOPs were 30 and 16 mmHg in the right and left eyes, respectively, at 10:00 AM. A single dose of 0.004% travoprost (Alcon Laboratories, Inc., Fort Worth, TX, USA) was instilled in his right eye on the same day along with the administration of an oral carbonic anhydrase inhibitor (Diamox, Sun

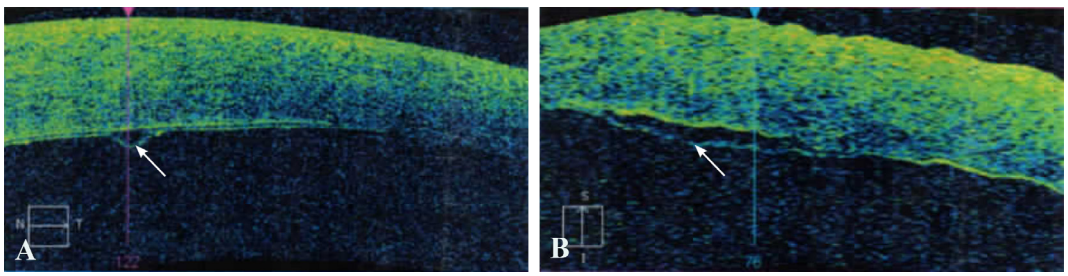

Figure 1. Cross-sectional optical coherence tomography (CIRRIUS 6000, Carl Zeiss Meditec AG, Jena, Germany) image of the cornea shows Descemet's membrane detachment of the right eye (white arrow). (A) The horizontal direction is from the nasal to the temporal direction, and (B) the vertical direction is from the inferior to the superior direction.

Pharma, Mumbai, India). His IOP decreased to 16 mmHg at 2:00 PM. Therefore, he was discharged on the same day along with the prescription of an immunosuppressant (50-mg azathioprine once daily), an oral steroid at a dosage of 40 mg/day tapered weekly to a maintenance dose of 10 mg/day, and a topical steroid (Pred Forte, prednisolone acetate; Allergan). The patient complained of mild headache on the right side at the time of discharge, for which he was prescribed with a paracetamol tablet.

The patient visited the hospital 1 day after experiencing severe unilateral throbbing headache extending from the right eye to the right cranium along with nausea within 1 h of instillation of a travoprost eye drop in the right eye the previous night. Lightheadedness and hypokalemia were associated with continuous and persistent vomiting. His IOP in the right eye was 24 mmHg at 9:00 AM. His blood pressure increased to 180/90 mmHg. Both complete neurological examination and brain computed tomography showed normal findings. After consultation with a physician, the patient's antihypertensive medications were modified. Blood pressure and potassium levels stabilized. As systemic examination and neuroimaging yielded normal results, travoprost was suspected to have caused the headache. Therefore, the travoprost treatment was discontinued.

The patient was then admitted to our hospital for observation. The following day, his headache had disappeared, but the IOP was 28 mmHg at 8:00 AM in the right eye. He was administered a trial single-dose 0.005% latanoprost (Latoprost RT, Sun Pharmaceutical Industries Ltd., India) to lower the IOP. He developed headache within 10 min of application. Therefore, latanoprost was also terminated, and the brimonidine/timolol-fixed combination brimonidine 0.2%/timolol 0.5% (Combigan Ophthalmic Solution, Allergan India Ltd., India) eye drops were prescribed. This reduced the IOP of the right eye to 18 mmHg at 1:00 PM, without headache symptoms. However, at the 1-month follow-up, he complained of persistent mild headache for 1 week. As brimonidine is an α_2 adrenergic agonist, this too releases prostaglandin endogenously [18], potentially causing his headache after prolonged use. At this visit, his IOP in the right eye was 24 mmHg at 11:00 AM. Therefore, the medication was discontinued, and trabeculectomy with mitomycin was advised for IOP control in the right eye [19].

He underwent trabeculectomy in the right eye augmented with mitomycin C (0.02% for 1 min) [20] by an ophthalmologist. On postoperative day 1, his IOP had reduced to 16 mmHg at 12:30 PM. We prescribed 0.5% topical loteprednol etabonate and 0.5% moxifloxacin (Mofloren LP, Indoco Remedies Ltd., Mumbai, India), thrice a day, tapered over 2 weeks. We also prescribed systemic steroids at 40 mg/day initially, tapered by 10 mg/week until 10 mg/day was achieved and maintained for the next 2 months. The patient experienced no symptoms of headache after trabeculectomy, and the IOP was well-controlled. This suggests that prostaglandin analogs could be the main cause of the migraine-like headache in the patient, as determined via a diagnosis of exclusion.

This case report was approved by our institutional ethics committee. The patient provided written informed consent for publication of the case report.

DISCUSSION

The findings of this case indicate a potential causal relationship between topical prostaglandin analogs and the development of migraine-like headaches based on symptom resolution upon discontinuation. Alternatives, such as trabeculectomy, should be considered when managing challenging cases similar to this one.

Migraine is a common cause of moderate-to-severe headaches. It is debilitating and can last for 4–72 h. The headache is usually of the unilateral and throbbing type. It is also associated with nausea, vomiting, and photophobia. A visual aura may precede it in one-fourth of the patients. The onset of migraines is most commonly observed in teenagers. An onset after 50 years of age is rare [21]. Migraine is caused by cortical hyperexcitability. Attacks are initiated by at least one trigger. Visual auras are caused by a depolarization wave called cortical spreading depression [22]. Without a prior episode of migraine headache, the patient developed migraine-like headache after the administration of travoprost. Headaches have been reported with other prostaglandin-analogous eye drops, such as unoprostone isopropyl and bimatoprost [23].

New theories on migraines state that the trigeminal vascular system plays a crucial role [22]. Prostaglandin receptors are present in the trigeminal nucleus caudalis and trigeminal ganglion. Prostaglandins are found in the smooth muscle of cranial arteries. This causes dilatation of the cranial vessels [24]. Travoprost may have caused the migraine-like headache by activating the trigeminal vascular system. Schnober et al. reported a case of severe headache during the follow-up of patients with primary open-angle glaucoma or ocular hypertension treated with a fixed-dose combination of 0.004% travoprost and 0.5% timolol, which resolved before the end of the study [25].

PGF2 alpha, the parent compound, is a vasoactive agent. Conjunctival hyperemia is partially mediated by the release of nitric oxide by the PGF2 alpha isopropyl ester. It also stimulates endogenous prostaglandin production

in the ciliary body, such as PGD2, E2, and F2 alpha. They are vasoactive agents. Therefore, a significant amount of vasoactive prostaglandins can be produced in the eye at a low concentration of this drug [26]. Therefore, following the withdrawal of travoprost, the activation of the trigeminal vascular system was terminated in this patient, which might have caused dilation of the cranial vessels, leading to the presentation of a migraine-like headache.

Migraine headache following the administration of prostaglandin analogs is rare but plausible [13, 27]. Earlier reports have described headaches related to latanoprost administrations [11, 28]. In Li et al.'s study involving 250 patients with primary open-angle glaucoma treated with travoprost or latanoprost once in the evening for 3 months, the frequency of headaches was higher among latanoprost-treated patients than that among travoprost-treated patients (two [2%] with travoprost and 15 [9%] with latanoprost) [29]. Travoprost contains three fluorine atoms [30], which made practitioners assume that it may yield different results. However, similar to latanoprost, travoprost causes migraine-like headaches.

In a randomized clinical trial involving patients with open-angle glaucoma or ocular hypertension treated with prostaglandin analogs, Parrish et al. identified that 23 (16.9%), 25 (18.2%), and 23 (16.7%) patients receiving latanoprost, bimatoprost, and travoprost experienced systemic adverse events, respectively. Headache was reported by 2% of patients in any treatment group, along with nasopharyngitis and upper respiratory tract infections [31]. Gandolfi et al. conducted a multicenter clinical trial comparing the efficacy and safety of bimatoprost and latanoprost in patients with glaucoma or ocular hypertension. The frequency of headaches associated with latanoprost (4.4%) was significantly higher than that associated with bimatoprost (0%). The patients discontinued latanoprost because of headache and brow ache [32]. In a prospective multicenter trial of patients with open-angle glaucoma or ocular hypertension treated with latanoprost, Zimmerman et al. found that headache was the most common systemic adverse event (n = 9, 0.2%), leading to discontinuation of latanoprost [33]. Despite the replacement of travoprost with a single dose of latanoprost, the patient developed a headache within 10 min of application. Therefore, the latanoprost treatment was discontinued.

Brimonidine affects uveoscleral outflow, similar to prostaglandin analogs [34], and has an excellent systemic safety profile [35]. It was administered to the patient because it does not induce exogenous prostaglandin release [18], implying that it does not induce prostaglandin release immediately after instillation. This prolongs the period required for endogenous prostaglandin release, as the patient reported a migraine-like headache after 1 month of everyday use. Therefore, ophthalmologists should be cautious before prescribing prostaglandin analogs as monotherapy.

The present case indicated that a possible pharmacological action of prostaglandin analogs caused vasoactive reactions, leading to migraine-like headaches. Therefore, a patient taking prostaglandin analogs complaining of headache requires careful evaluation and management. Ophthalmologists should be cautious before prescribing prostaglandin analogs as a monotherapy. However, case reports are limited by a low level of evidence verifying this causal relationship. Therefore, large-scale studies including control groups are required to confirm the causal relationship between topical prostaglandin analog administrations and the development of migraine-like headaches before generalizing this assumption.

CONCLUSIONS

By diagnosis of exclusion, the present patient developed migraine-like headaches because of prostaglandin analogs. Migraine associated with travoprost can be debilitating. Therefore, alternatives, such as trabeculectomy, should be considered when managing challenging cases similar to this patient. However, further studies are required to prove such a causal link. Moreover, even without validation of a causal relationship, caution is advised with the administration of prostaglandin analogs in patients who develop headaches with a trial dose instillation until well-designed, large-scale, controlled studies provide more conclusive findings.

ETHICAL DECLARATIONS

Ethical approval: This case report was approved by our institutional ethics committee. The patient provided written informed consent for publication of the case report.
Conflict of interests: None.

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