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Comparing the efficacy of Xalatan and a similar latanoprost (Drenatan) in open angle glaucoma patients

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两种拉坦前列素类药物治疗开角型青光眼的疗效比较

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摘要

目的:比较适利达与类似药物 Drenatan 在原发性开角型青光眼患者中关于降低眼内压的单药治疗疗效。

方法:该回顾性研究包括 62 例患者(119 眼)。初诊时,正在使用适利达的患者转为使用类似药物拉坦前列素(Drenatan)。12wk 后的复诊阶段进行全面的眼科检查,包括裂隙灯、Goldmann 压平眼压计、立体眼底、前房角镜、超声角膜测厚仪以及自动视野检查。

结果:使用 Drenatan 之前和之后平均眼内压分别为 12.30±2.02mmHg 和 12.38±2.05mmHg($P=0.559$)。$R=0.987$ 显示两者显著相关。

结论:适利达和 Drenatan 在降低眼内压方面具有相似功效。该发现对于降低公共卫生成本,维护其药物疗效和安全性政策具有重要意义。

关键词:拉坦前列素;通用药品;开角型青光眼;药品比较

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Abstract

• AIM: To compare the monotheraphy efficacy of the brand latanoprost Xalatan and a similar latanoprost (Drenatan) regarding intraocular pressure (IOP) reduction in patients with primary open angle glaucoma (POAG).

• METHODS: Sixty two patients (119 eyes) were enrolled in this observational, retrospective study. In the first visit, the patient came in using the brand latanoprost (Xalatan) and it was changed to the similar latanoprost (Drenatan). In the second visit, 12wk later, a complete ophtalmologic exam including slit lamp examination, Goldmann applanation tonometry, stereoscopic fundus examination, gonioscopy, ultrasound pachymetry, automated visual field testing was performed.

• RESULTS: The mean IOP was 12.30±2.02mmHg and 12.38±2.05mmHg with using Xalatan and Drenatan, respectively. The $P=0.559$ demonstrates this relation. In fact, a correlation between the groups of $R=0.987$ points out the remarkable resemblance of both groups.

• CONCLUSION: Both Drenatan and Xalatan have similar efficacy in reducing IOP. Such finding is pivotal to public health to reduce cost and maintain its policies concerning drug efficacy and safety, this is especially significant in countries in which treatment cost is a barrier for patient adhesion to treatment.

• KEYWORDS: latanoprost; generic drug; open angle glaucoma; drug comparison

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INTRODUCTION

Glaucoma is one of the leading causes of irreversible blindness in the world according to the World Health

Organization. Elevated intraocular pressure (IOP) is the most important risk factor in the development of the glaucomatous optic neuropathy[1-2]. Studies have reported the value of reducing IOP in the treatment of primary open angle glaucoma (POAG)[3-5]. Currently, there are five major classes of antiglaucomatous drugs used to reduce IOP: beta-adrenergic antagonists, adrenergic agonists, parasympathomimetics, prostaglandin analogues and carbonic acid inhibitors[2-8]. Prostaglandin analogues are fast becoming the mainstay of therapy for subjects with glaucoma, they are once daily dosing and effective intraocular pressure-lowering medications that work *via* uveal and scleral collagen breakdown to increase aqueous humor outflow *via* uveoscleral pathway[5,8-9]. Latanoprost, the first prostaglandin to become commercially available, offers certain advantages over other medications for treatment of POAG and ocular hypertension (OH)[7, 10-12]. Clinical studies showed that latanoprost reduces IOP by 20-36% with minimal side effects[2, 13]. Xalatan (latanoprost 50 mcg/ml) is commercially available since 1996 and 1997 in the USA and most European countries, respectively, and it is used in many countries around the world which including Brazil. Along with Xalatan there are generic and similar latanoprost brands available in the Brazilian market, while Drenatan may be chemically equivalent to Xalatan, there is no available information on whether it has similar efficacy and safety. Generic eye drops have the same active ingredient and are becoming more common throughout the years, mainly due to lower costs to the patients and health care system, but they differ from the original product in some aspects, such as their inactive ingredients (adjuvant solution)[11]. The aim of this study is to compare efficacy in IOP reduction of similar brand latanoprost in patients with POAG. In this study, we specifically compared Xalatan with its similar formula Drenatan. According to Brazilian legislation, a similar brand has to present biopharmaceutical comparability to the brand name and relative bioequivalence, however, it has not the need to be clinically tested in order to be commercialized.

SUBJECTS AND METHODS

The study was carried out at Eye's Institute of Medical Science University Hospital, Belo Horizonte, Minas Gerais, Brazil. This was a single center, observational, retrospective study. Patient information and clinical data was collected from two different appointments (from May 2013 to March 2015). In the first visit, the patient came in using the brand latanoprost (Xalatan) when it was changed to Drenatan. The second visit happened 12wk later. Subjects were instructed to instill one drop of study medication in the affected eye(s) every evening at approximately 21:00 o'clock and to use the dropper bottles within 4wk of opening.

Due to the observational and retrospective nature of the study, for which data were obtained from review of medical charts, with no intervention or deliberate modification of biologic, physiologic, psychologic, or social variables, patient informed consent was not required.

Inclusion criteria were individuals with 16 years old or older, unilateral or bilateral primary open angle glaucoma (POAG) and under Xalatan monotherapy treatment for at least 3mo. Exclusion criteria of this study were: narrow or closed angle, history of acute angle closure glaucoma, history of argon laser trabeculoplasty or of any ocular filtering surgeries (the unoperated eye could be enrolled in the study), ocular surgery or ocular inflammation/infection in either eye within 3mo prior to screening or best corrected visual acuity ≤20/200. Patients, who had no previous glaucoma treatment, had doubtful adherence to the medication prescribed or missed appointments were also excluded from the study group.

Data concerning age, gender, time from diagnosis of glaucoma, last recorded intraocular pressure (IOP), associated comorbidities, previous glaucoma treatments, and antiglaucomatous therapy were collected from medical charts.

The Wilcoxon signed-rank test was used for non-parametric statistical hypothesis, such as checking for IOP differences in the same patient when using Xalatan or Drenatan. Demographic and clinical variables related to IOP were analyzed using Mann-Whitney non-parametric test.

The IOP was measured in the same calibrated Goldmann applanation tonometer from 7:00 to 11:00 am by three different glaucoma fellows at the glaucoma department.

Slit-lamp examinations were performed to examine conjunctiva, lids, bulbi, cornea, iris, lens for opacities or other changes, anterior vitreous/vitreous membrane and anterior chamber with special emphasis on cells and flare. Indentation gonioscopy, detailed retinal and optic disc examination were also executed. Ultrasound pachymetry (Sonomed A-Scan/Pachymeter PacScan 300AP) was performed at baseline consultation and automated visual field testing (Humphrey Perimetry, Carl Zeiss Inc. Using the Swedish interactive threshold algorithm program) in one of the two visits within the time period presented.

RESULTS

Sixty-two patients, out of 90, were enrolled. Regarding those, 39 were women (62.90%) and 23 were men (37.10%). Drenatan was administered for 107.41±24.42 d on 59 right eyes (49.58%) and on 60 (50.42%) left eyes. The total number of 119 eyes presented a mean intraocular pressure (IOP) of 12.30±2.02 and 12.38±2.05 with Xalatan and Drenatan, respectively. Table 1 presents the demographics aspects of this study.

The difference in IOP reduction between the two drugs was not statistically significant. Table 2 demonstrates this relation. In fact, a correlation between the groups of $R=0.986774$ points out the remarkable resemblance of both groups. No statistical difference was found in patients presenting diabetes and/or systemic hypertension when comparing Xalatan and Drenatan efficacy in reducing the IOP.

Table 1 Patient demographic characteristics

Demographic characteristis	Statistical data of the study sample
Gender, n(%)	
M	23 (37.10%)
F	39 (62.90%)
Age, mean±SD (range)	62.8±14.4 (16-91)
Pachimetry, mean±SD (range)	529.32±37.64 (437-612)
Disc excavation, mean±SD (range)	0.75±0.13 (0.4-subtotal)
Systemic disease	
Hypertension, n(%)	39 (62.90%)
Diabetes, n(%)	20 (32.26%)

Table 2 Two by two comparison related to IOP score

Variable	N	Mean	PD	P25	Median	P75	P
Xalatan iop od	62	12.30	2.03	11.00	12.00	14.00	0.584
Drenatan iop od	62	12.49	1.95	11.00	12.00	14.00	
Xalatan iop os	63	12.33	2.03	11.00	12.00	14.00	0.868
Drenatan iop os	63	12.27	2.15	11.00	12.00	13.00	

IOP: Intraocular pressure.

DISCUSSION

Prostaglandin analogs have become the most commonly prescribed class of medications for patients with open angle glaucoma (OAG) surpassing beta-blockers in 2001[8, 14-15]. Prostaglandin analogs often are preferable to other classes because of their greater efficacy at lowering intraocular pressure (IOP), once daily dosing regimen and relatively benign side effect profile. Latanoprost is still one of the most widely prescribed topical hypotensive eye drops in Brazil.

Previous studies have shown that, in patients with open angle glaucoma, a single drop of Xalatan 0.005% solution administered daily, reduced diurnal IOP from 22 to 39% on a 1 to 12mo period in well-controlled trials[12-13, 16-17]. Latanoprost is well tolerated and induces minimal systemic adverse events. In 6-month trials, the most commonly occurring drug-related ocular events in latanoprost recipients were mild to moderate conjunctival hyperemia[16].

It is undoubtedly important to verify the efficacy and comparability of the similar brand of latanoprost to Xalatan. A study from Slovakia showed the similarity between Unilat and Xalatan in terms of efficacy and tolerability. Seventy-seven subjects, in seven private ophthalmic outpatient departments in Slovakia, were analyzed during 2008. Results confirmed UNILAT's therapeutical indications and demonstrated non-inferiority to the original product concerning efficacy and safety in the treatment of glaucoma and ocular hypertension[18-19].

A single center, cross over, prospective study from India showed a significant difference in intraocular pressure between Latanoprost and Xalatan at week 12 but not at week 24[17]. With a number of 30 subjects recruited they concluded that the magnitude of IOP lowering in patients with primary open angle glaucoma (POAG) and ocular hypertension (OH) with Xalatan and Latoprost was different, being greater when Xalatan was used.

A larger double-masked, randomized, multicenter 12-week study with 184 patients in Italy confirmed the noninferiority of generic latanoprost in lowering IOP and concluded it was a well-tolerated eye drop[20]. Schwartz *et al*[21-22] reported differences in the amount of active ingredients and preservatives between brand and generic prostaglandin analogs, although a head to head trial reported them both to have similar efficacy and side effects.

The frequently quoted "80-125% bioavailability" rule applied to generic versions of systemic drugs does not apply to eye drops. Topically applied medication is subject to different guidelines. Bioavailability and efficacy studies are required only if there is a change in the active ingredients, with regard to specification of the physical properties, inactive ingredients or application device[8, 10, 18].

Having equivalent efficacy been established, it is pivotal to evaluate the cost of treatment. One of the few drawbacks of prostaglandin analogs relative to other medication classes is cost[18]. Normally, the brand name is pricier than the similar drug. During an online research conducted on June 23rd 2015 prices of Drenatan and Xalatan in main pharmaceutical networks in Brazil varied from R$ 42.76 to R$ 55.85 for Drenatan and from R$ 106.60 to R$ 125.95 for Xalatan representing a difference of 125.5% to 149.3%.

Such a considerable difference in cost must be assessed to benefit the patient. Can reduction in therapy cost mean an increase in patient compliance? Patient cooperation concerning chronic medical therapy is known to be a struggle and any additional hurdle, such as cost, has to be minimized[23]. Successful treatment outcomes rely on the daily use of medication to minimize disease progression. A study evaluating patient adherence to daily use of latanoprost eye drops with the introduction of generic brands in the market found an improvement of 25% or more from the period before generic latanoprost was available[18-19].

Our study has potential limitations that warrant consideration. The IOP measurements were taken in different morning hours and we could have registered the IOP values in unpaired hours, having the data collected being affected by IOP fluctuation, although this variation influenced both groups. The weakness of the study design itself, being retrospective and based on chart review, where some data could not be found or not registered accordingly for meeting the inclusion criteria. Finally, the lack of the information regarding the patient's compliance to treatment; we have not considered whether compliance was present, in what level it was present and if it changed after the drug substitution.

In the future, a prospective, randomized, controlled trial can be conducted in order to have the similar drug achieve comparability status to the original one. This is true for all topical medications, which are not evaluated for biodisponibility.

Our study concludes that both Drenatan and Xalatan have similar efficacy in reducing intraocular pressure. We believe that new drugs should have a comparability study to make sure

they are as effective as the brand eye drop that underwent clinical trials. Public health policies often target the relationship between drug's cost, efficacy and safety. Thus, this study is elucidatory, showing these drugs' efficacy is similar. These factors are especially significant in countries in which treatment cost is a barrier for patient adherence to treatment. Providing cost reduction and maintaining efficacy can improve adherence and consequently alter the disease outcomes and its effect in the patient's life.

REFERENCES

1 Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK 2nd, Wilson MR, Gordon MO. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120(6):701-713

2 Velpandian T, Kotnala A, Halder N, Ravi AK, Archunan V, Sihota R. Stability of latanoprost in generic formulations using controlled degradation and patient usage simulation studies. *Curr Eye Res* 2015;40(6):561-571

3 Magnitude and causes of visual impairment. Fact sheet no. 282, November 2004. Available from: http:// www. who. int/mediacentre/factsheets/fs282/en/

4 Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. *Arch Ophthalmol* 2002;120(10):1268-1279

5 Kim YI, Kim JH, Lee TY, Lee KW. Efficacy and safety of glaucoma patients' switch from a 2% dorzolamide/0.5% timolol fixed-combination brand-name drug to its generic counterpart. *J Ocul Pharmacol Ther* 2015;31(6):335-339

6 The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. *Am J Opthalmol* 2000;130(4):429-440

7 Medeiros FA, Weinreb RN. Medical backgrounders: glaucoma. *Drugs Today* 2002;38(8):563-570

8 Khouri AS[1], Realini T, Fechtner RD. Use of fixed-dose combination drugs for the treatment of glaucoma. *Drugs Aging* 2007;24(12):1007-1016

9 Angmo D, Wadhwani M, Velpandian T, Kotnal A, Sihota R, Dada T. Evaluation of physical properties and dose equivalency of generic versus branded latanoprost formulations. *Int Ophthalmol* 2017;37(2):423-428

10 Queen JH, Feldman RM, Lee DA. Variation in number of doses, bottle volume, and calculated yearly cost of generic and branded latanoprost for glaucoma. *Am J Ophthalmol* 2016;163:70-74.e1

11 Kolko M, Koch Jensen P. The physical properties of generic latanoprost ophthalmic solutions are not identical. *Acta Ophthalmol* 2017;95(4):370-373

12 Stjernschantz J, Alm A. Latanoprost as a new horizon in the medical management of glaucoma. *Curr Opin Ophthalmol* 1996;7(2):11-17

13 Hylton C, Robin AL. Update on prostaglandin analogues. *Curr Opin Ophthalmol* 2003;14(2):65-69

14 Stein JD, Sloan FA, Lee PP. Rates of glaucoma medication utilization among older adults with suspected glaucoma, 1992 to 2002. *Am J Ophthalmol* 2007;143(5):870-872

15 Stein JD, Ayyagari P, Sloan FA, Lee PP. Rates of glaucoma medication utilization among persons with primary open angle glaucoma, 1992 to 2002. *Ophthalmology* 2008;115(8):1315-1319

16 Camras CB. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month masked, multicenter trial in the United States. The United States Latanoprost Study Group. *Ophthalmology* 1996;103(1):138-147

17 Narayanaswamy A, Neog A, Baskaran M, George R, Lingam V, Desai C, Rajadhyaksha V. A randomized, crossover, open label pilot study to evaluate the efficacy and safety of Xalatan in comparison with generic latanoprost (latoprost) in subjects with primary open angle glaucoma or ocular hypertension. *Indian J Ophthalmol* 2007;55(2):127-131

18 Stein JD, Shekhawat N, Talwar N, Balkrishnan R. Impact of the introduction of generic latanoprost on glaucoma medication adherence. *Ophthalmology* 2015;122(4):738-747

19 Strmen P, Jancus V, Okkelová J, Tvrdonová M. Clinical trial of the generic product UNILAT following its efficiency and safety in glaucoma and intraocular hypertension. *Cesk Slov Oftalmol* 2010;66(6):258-261

20 Digiuni M, Manni G, Vetrugno M, Uva M, Milano G, Orzalesi N, Fogagnolo P, Centofanti M, Campos E, Rossetti L. An evaluation of therapeutic noninferiority of 0.005% latanoprost ophthalmic solution and Xalatan in patients with glaucoma or ocular hypertension. *J Glaucoma* 2012;22(9):707-712

21 Schwartz GF, Quigley HA. Adherence and persistence with glaucoma therapy. *Surv Ophthalmol* 2008;53(Suppl 11):S57-S68

22 Kahook MY, Fechtner RD, Katz LJ, Noecker RJ, Ammar DA. A comparison of active ingredients and preservatives between brand name and generic topical glaucoma medications using liquid chromatography tandem mass spectrometry. *Curr Eye Res* 2012;37(2):101-108

23 Kumbar SK, Mirje M, Moharir G, Bharatha A. Cost analysis of commonly used combination of drugs in primary open angle glaucoma. *J Clin Diagn Res* 2015;9(5):FC05-8