

Fixed combination of dorzolamide / timolol eye drops versus fixed combination of brinzolamide / timolol eye drops in the treatment of primary open angle glaucoma and ocular hypertension

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المزيج الثابت من قطرات العين (دورزولوميد / تيمولول) مقابل المزيج الثابت من قطرات العين (برنزولوميد / تيمولول) في علاج داء الزرقاء مفتوح الزاوية الأولي وارتفاع ضغط العين

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طبيب اختصاصي طب و جراحة العيون في مستشفى الزهراء التعليمي في الكوت – واسط

المستخلص

خلفية : داء الزرقاء هو مرض عيني واسع الانتشار في جميع أنحاء العالم و يعد احد المسببات الرئيسية للعمى. يهدف العلاج الطبي الى خفض ضغط العين لمنع حدوث المزيد من الضرر في العصب البصري. تعتبر كل من (دورزولوميد 2% مع تيمولول 0.5%) (كوزويت®) و (برنزولوميد 1% مع تيمولول 0.5%) (ازارگا®) عبارة عن مزيج جرعة ثابتة متوفر تجاريا من قطرات العين التي تستخدم لعلاج داء الزرقاء مفتوح الزاوية الأولي و ارتفاع ضغط العين. دورزولوميد و برنزولوميد هما من مثبطات الكربونيك الأنهيداز الموضعية ممزوجة جنباً إلى جنب مع تيمولول احد موانع مستقبلات بيتا. تعمل مثبطات الكربونيك الانهيداز و موانع مستقبلات بيتا على خفض ضغط العين من خلال تثبيط إنتاج الخلط المائي من قبل الظهارة الهدبية .

الهدف : كان الهدف من هذه الدراسة السريرية العلاجية المستقبلية هو مقارنة الفعالية والآثار الجانبية لكل من المزيجين في علاج حالات الزرقاء و ارتفاع ضغط العين.

المرضى و الأساليب : تم تسجيل 50 حالة زرقاء و ارتفاع ضغط العين في هذه الدراسة قسم المرضى عشوائيا إلى مجموعتين من 25 مريضا. تلقت مجموعة الأولى المزيج الاول من قطرات العين مرتين يوميا بينما تلقت المجموعة الثانية المزيج الثاني من قطرات العين مرتين يوميا. تم قياس و تسجيل ضغط العين الأساسي و من ثم متابعته على فترات منتظمة من 2 أسابيع لمدة شهر ثم شهريا لمدة 6 أشهر و بعد ذلك تم تحديد نسبة الانخفاض. سجلت الآثار الجانبية التي أبلغ عنها المرضى.

النتائج : سجلت كلتا المجموعتين انخفاضا كبيرا إحصائيا في ضغط العين الأساسي ($P = 0.0001$) . في المجموعة الأولى تراوح الانخفاض من 7,0 الى 12,0 ملم زئبقي (9-21,5 ٪) في حين تراوح الانخفاض في المجموعة الثانية من 6,5 الى 11,0 ملم زئبقي (7-20,9 ٪) . لم يكن هناك اختلاف كبير بين المجموعتين ($P = 0.6075$) . سجلت المجموعة الثانية اثارا سلبية أقل من المجموعة الأولى ($P = 0.0412$) .

الاستنتاج : كلا المزيجين فعال على قدم المساواة في خفض ضغط العين في مرضى داء الزرقاء و ارتفاع ضغط العين ولكن كان المزيج الثاني أكثر احتمالا.

الكلمات الرئيسية : الزرقاء ، دورزولوميد ، برنزولوميد ، تيمولول ، كوزويت ، ازارگا

Abstract

Background: Glaucoma is a worldwide major blinding eye disease. Medical treatment aims at reduction of intraocular pressure (IOP) to prevent further damage to the optic nerve. Dorzolamide 2.0% + timolol 0.5% (D / T - FC) (Cosopt®) and brinzolamide 1.0% + timolol 0.5% (B / T - FC) (Azarga®) are both types of commercially available fixed dose combination eye drops that are used to treat primary open angle glaucoma (POAG) and ocular hypertension (OHT). Dorzolamide and brinzolamide are topical carbonic anhydrase inhibitors (CAIs) fixed combined with timolol a beta-adrenoceptor blocker. CAIs and beta blockers reduce IOP through inhibiting the production of aqueous humor by the ciliary epithelium.

Aim: The aim of this prospective clinical therapeutic study was to compare the efficacy and side effects of both combinations in POAG and OHT.

Patients & methods: 50 cases of POAG / OHT were enrolled in this study. The patients were randomly assigned to 2 groups with 25 patients in each group. Group 1 received D / T - FC eye drops twice daily while group 2 received B / T - FC eye drops twice daily. Baseline IOP was measured and recorded and then followed up at regular intervals of 2 weeks for one month then monthly for 6 months and then the percentage of reduction was determined. The side effects questioned and reported by the patients were recorded.

Results: Both groups had a statistically significant reduction in IOP from baseline ($P=0.0001$). In the first group IOP reduction ranged from 7.0 to 12.0 mmHg (21.9 – 37.5 %) while in group 2 IOP reduction ranged from 6.5 to 11.0 mm Hg (20.7 – 37.9 %). No significant difference existed between the 2 groups ($P=0.6075$). Group 2 reported less adverse effects than group 1 ($P=0.0412$).

Conclusion: Both combinations were equally effective in reducing IOP in glaucoma and OHT patients, however B / T - FC was more tolerated.

Keywords: glaucoma, brinzolamide, dorzolamide, timolol, Cosopt, Azarga

Introduction

Glaucoma is a major eye disease. It is the second leading cause of preventable blindness globally and in most regions of the world (1, 2).

Glaucoma is a heterogeneous group of disorders. All forms of the disease have in common a potentially progressive and characteristic optic neuropathy which is associated with visual field loss as damage progresses, and in which intraocular pressure (IOP) is usually a key modifying factor (3).

Primary open angle glaucoma (POAG), the most common type of glaucoma, is a chronic progressive disease often, though not always, accompanied by elevated IOP. In this disorder, retinal ganglion cell loss and excavation of the optic nerve head produce characteristic peripheral visual field deficits. Patients with normal-tension glaucoma present with typical visual field and optic nerve head changes, without a documented history of elevated IOP. A variety of secondary causes, such as pigment dispersion syndrome and ocular trauma can result in glaucoma as well. Ocular hypertension (OHT) is IOP higher than normal (>21 mmHg) in the absence of optic nerve damage or visual field loss (4).

Reduction of elevated IOP is the only established modifiable risk factor shown to reduce the risk of glaucoma-associated optic neuropathy (5, 6) Treatment options for glaucoma includes medications, laser and surgery.

Medications lower IOP either by decreasing production of aqueous humor by the ciliary epithelium or by increasing aqueous outflow through the trabecular meshwork (conventional) pathway or uveoscleral (unconventional) pathway (7, 8). Currently, there are five major classes of drugs used for the treatment of glaucoma: (a) cholinergics (acetylcholine receptor agonists); (b) adrenoceptor agonists; (c) carbonic anhydrase inhibitors (CAIs); (d) beta-adrenoceptor antagonists; and (e) prostaglandin analogues (PGAs) (9, 10).

Treatment typically begins with the selection of an agent for IOP reduction. The use single medication to reach the target IOP is preferable, but when this is not possible then the concomitant use of two or more medications is necessary. In fact the Ocular Hypertension Treatment Study showed that almost 40% of patients will require a combination of two or more medications to achieve a 20% reduction in intraocular pressure (5).

When a combination of medications is used the co-administration of each medication from a separate eye drop bottle can reduce the therapeutic effect through adversely affecting patient compliance (11-13), the wash-out effect of the first medication if inadequate time spacing kept between the first and second medication (14), and increasing cost. The use of a fixed dose combination eye drops will address some of these problems. The aim of this study was to compare the efficacy (in terms of reduction of IOP) and side effects of both fixed dose combinations in cases of POAG and OH.

Patients & methods

This hospital based study was performed at our ophthalmology department in Al-Zahra' Teaching Hospital in Al-Kut - Wasit governorate, Iraq from January to November 2013. It was conducted in accordance with the ethical principles described by the Declaration of Helsinki. Informed consent was obtained from all participants. The study design was a comparative prospective clinical therapeutic randomized case series in which 50 cases age ≥ 20 years recently diagnosed with unilateral or bilateral POAG or OHT were enrolled. Patients on other medical treatment or who had surgery were not included.

A detailed history was acquired including history of systemic condition that might be adversely affected by the medications and comprehensive ophthalmic examination was performed. The ophthalmological assessment included measuring visual acuity (unaided and corrected), measuring baseline IOP by Goldmann applanation tonometer., examination of the eye anterior segment by a slit-lamp biomicroscope, examination of drainage angle by gonioscopy and examination of the posterior segment by dilated funduscopy and observing the optic nerve head. The visual field was tested using an automated static perimeter glaucoma program. The 50 patients were randomly assigned into 2 groups each with 25 patients. Group 1 received dorzolamide 2.0% + timolol 0.5% eye drops (D / T - FC) (Cosopt, Merck & Co Inc., USA) twice daily while group 2 received brinzolamide 1.0% + timolol 0.5% eye drops (B / T - FC) (Azarga, Alcon, USA) twice daily. Baseline IOP was measured and recorded before commencing treatment and then followed at regular intervals of 2 weeks for 1 month then monthly for 6 months. Measurement time was at morning between 9 and 12 am. The percentage of reduction was determined. Side effects questioned and reported by the patients were recorded.

Statistical analysis of data to determine patients characteristics. Chi square test was used to determine significance level.

Results

The patients' characteristics are shown in Table (1). Their age range was 23-70 years (mean 52 ± 8 years). Of the 50 patients, 24 (48%) were males and 26 (52%) were females. Patients were randomly assigned to 2 groups each group with 25 patients.

Average baseline IOP was 32 mmHg in group 1 and 29 mmHg in group 2. After 6 month there was 7.0 to 12.0 mmHg (21.9 – 37.5 %) and 6.5 to 11.0 mmHg (20.7 – 37.9 %) reduction in baseline IOP in group 1 and group 2 respectively. The IOP reduction in both groups was statistically significant ($P=0.0001$). No significant difference was found between the 2 groups ($P=0.6075$). IOP reductions are shown in Table (2).

Ocular adverse effects reported included burning, stinging, and irritation. The number of cases was higher (3) (12 %) in group 1 compared to 1 (4 %) in group 2 ($P=0.0412$). No serious adverse effects occurred.

Table (1): Demographics of patients

No. of cases	50 case
Age range	23-70 years
Mean age $\pm$ SD	52 $\pm$ 8 years
Sex M / F (ratio)	24 / 26 (1.5:1)

Table (2): IOP reduction

	Baseline IOP	Minimum reduction	Maximum reduction
Group 1 (n=25)	32 mmHg	7 mmHg (21.9%)	12 mmHg (37.5%)
Group 2 (n=25)	29 mmHg	6.5 mmHg (20.7%)	11 mmHg (37.9%)

$P=0.6075$

Discussion

Carbonic anhydrases (CAs) are metalloenzymes that catalyze the reversible hydration of carbon dioxide and bicarbonate. Their pivotal role in metabolism, ubiquitous nature and multiple isoforms (CA I-XIV) has made CAs an attractive drug target in clinical applications (15). Carbonic anhydrase inhibitors (CAIs) are sulfonamides. Both dorzolamide and brinzolamide are second generation topical CAIs (16). Dorzolamide was released as an alternative to acetazolamide, a first generation oral CAI, in the treatment of chronic open angle glaucoma and ocular hypertension to eliminate most of the systemic side effects associated with its use. However, dorzolamide still has several side effects such as dysgeusia (altered taste), eye pain, stinging and

conjunctival hyperemia (17). Dorzolamide lowers IOP by decreasing the production of aqueous humor from the ciliary epithelium. Furthermore, topically applied dorzolamide penetrates directly to the posterior segment of the eye and its presence is consistent with the initial report that dorzolamide increases retinal blood flow velocity in patients with normal tension glaucoma (18). Brinzolamide is a newer selective CA II inhibitor. It is a more potent inhibitor among the other catalytically active CA isoforms compared to dorzolamide (15).

When it is used as monotherapy dorzolamide 2.0% eye drops and brinzolamide 1.0% eye drops are administered 3 times daily. Timolol 0.5% eye drops is administered 2 times daily. Relative IOP reduction from baseline is peak -22% (-24% to -20%) and trough -17% (-19% to -15%) for 2.0% dorzolamide; peak -17% (-19% to -15%) and trough -17% (-19% to -15%) for 1.0% brinzolamide; and peak -27% (-29% to -25%) and trough -26% (-28% to -25%) for 0.5% timolol (19). Fixed dose combinations have become a popular choice for topical treatment of glaucoma. The fixed combination of dorzolamide 2.0% or brinzolamide 1.0% with timolol 0.5% was shown to be superior to individual components and noninferior to the concomitant use of both agents in lowering IOP (20-22).

In this study we compared the fixed combination of dorzolamide 2.0% + timolol 0.5% eye drops (D / T – FC) with the fixed combination of brinzolamide 1.0% + timolol 0.5% eye drops (B / T – FC) in terms of ocular hypotensive effect and adverse effects. The results of this study were consistent with those reported in previous studies comparing the 2 FCs of antiglaucoma medications (23, 24). The ocular hypotensive effects of both FCs were similar. Both produced a significant reduction in baseline IOP.

The lower ocular irritation of B / T – FC eye drops over D / T – FC eye drops is because B / T – FC eye drops has a neutral pH of 7.2 compared to 5.6 of D / T – FC eye drops (25). Furthermore, eye drops containing dorzolamide use sodium citrate as a buffer whereas none is present in the eye drops containing brinzolamide. On the other hand blurred vision may be a problem with B / T – FC eye drops because of its suspension form. Despite that Mundorf et al. reported that 79.2 % of patients preferred Azarga over Cosopt. The differences in preference, discomfort, and adverse events are likely attributable to formulation differences given the similarities of the active ingredients. Stronger patient preference for B / T – FC eye drops may lead to better therapeutic compliance (26). Rossi et al reported that B / T – FC eye drops is associated with reduced topical discomfort and improved signs of ocular surface disease. The good tolerability and comfort of this FC might contribute to good patient adherence (27).

Auger et al in a study aimed to determine the impact of switching patients requiring multiple drug treatment from the D / T – FC to the B / T – FC and potential effects on tolerability and compliance reported a reduction in stinging but an increase in blurred vision. They concluded that the advantage of one eye drop over the other then becomes patient-specific, depending on which side effect they find most tolerable and suggest that both eye drops are acceptable choices in treating patients with glaucoma, and are interchangeable if compliance becomes an issue because of a specific side effect of one eye drop or the other (28).

Conclusion

Both combinations were equally effective in reducing IOP in glaucoma and OHT patients, however the B + T FC was more tolerated.

Disclosure

The author reports no conflicts of interest in this work.

References

1-Thylefors B, Négrel A-D, Pararajasegaram R and Dadzie KY. (1995). Global data on blindness. Bulletin of the World Health Organization;73(1):115-21.

2-World Health Organization.(2000). Prevention of blindness and deafness. Global initiative for the elimination of avoidable blindness. Geneva: WHO; WHO document WHO/PBL/97.61 Rev2

3-Kanski JJ.(2011). Clinical Ophthalmology A Systematic Approach. 6th edition. Butterworth Heinemann Elsevier: 374.

4-American Academy of Ophthalmology text books. Glaucoma

5-Kass MA, Heuer DK, Higginbotham EJ, et al. (2002). 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; 120:701–713.

6-Heijl A, Leske MC, Bengtsson B, et al. (2002).The Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: Results from the Early Manifest Glaucoma Trial.Arch Ophthalmol; 120:1268–1279.

7-Shaarawy TM, Sherwood MB, Hitchings RA, et al. (2009). Glaucoma: Medical Diagnosis and Therapy. Vol 1. Philadelphia, PA: Elsevier Limited.

8-Brubaker RF. (1991).Flow of aqueous humor in humans [The Friedenwald Lecture]. Invest Ophthalmol Vis Sci.32:3145-3166.

9-Marquis RE and Whitson JT. (2005). Management of glaucoma: focus on pharmacological therapy. Drugs Aging. 22(1):1-21.

10-Whitson JT. (2007).Glaucoma: a review of adjunctive therapy and new management strategies. Expert Opin Pharmacother. 8(18):3237-49.

11-Tsai JC, McClure CA, Ramos SE, et al. (2003).Compliance barriers in glaucoma: a systematic classification. J Glaucoma.12:393–398.

12-Robin AL and Covert D. (2005).Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? Ophthalmology.112:863–868.

13-Robin AL, Novack GD, Covert DW, et al. (2007).Adherence in glaucoma: objective measurements of once daily and adjunctive medication use. *Am J Ophthalmology*.144:533–540.

14-Fechtner RD and Realini T.(2004).Fixed combinations of topical glaucoma medications. *Curr Opin Ophthalmol*. 2004;15:132–135.

15-Pinard MA¹, Boone CD, Rife BD, Supuran CT and McKenna R. (2013). Structural study of interaction between brinzolamide and dorzolamide inhibition of human carbonic anhydrases. *Bioorg Med Chem*.Nov 15;21(22):7210-5.

16-Scozzafava A1 and Supuran CT.(2014). Glaucoma and the applications of carbonic anhydrase inhibitors. *Subcell Biochem*.75:349-59.

17-Sanseau A, Sampaolesi J, Suzuki E, Lopes J, Borel H. (2013). Preference for a fixed combination of brinzolamide / timolol versus dorzolamide / timolol among patients with open angle glaucoma and ocular hypertension. *Clin Ophthalmol*. 7: 357–362.

18-Sugrue MF. (2000).Pharmacological and ocular hypotensive properties of topical carbonic anhydrase inhibitors. *Prog Retin Eye Res*. 19(1):87-112.

19-Van der Valk R1, Webers CA, Schouten JS, Zeegers MP, Hendrikse F and Prins MH. (2005).Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. *Ophthalmology*. 112(7):1177-85.

20-Kaback M, Scoper SV, Arzeno G, James JE, Hua SY, Salem C, Dickerson JE, Landry TA and Bergamini MV. (2008).Intraocular pressure-lowering efficacy of brinzolamide 1%/timolol 0.5% fixed combination compared with brinzolamide 1% and timolol 0.5%. *Ophthalmology*. 115 (10):1728-34, 1734.e1-2.

21-Nagayama M, Nakajima T and Ono J. (2014).Safety and efficacy of a fixed versus unfixed brinzolamide/timolol combination in Japanese patients with open-angle glaucoma or ocular hypertension. *Clinical Ophthalmology*, 8 219-228.

22-Strohmaier K, Snyder E, DuBiner H and Adamsons I. (1998).The efficacy and safety of the dorzolamide-timolol combination versus the concomitant administration of its components. *Dorzolamide-Timolol Study Group. Ophthalmology*, 105(10):1936-44.

23-Manni G1, Denis P, Chew P, Sharpe ED, Orengo-Nania S, Coote MA, Laganovska G, Volksone L, Zeyen T, Filatori I, James J and Aung T. (2009). The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma*. 18(4):293-300.

24-Sezgin Akçay Bİ1, Güney E, Bozkurt KT, Unlü C and Akçali G. (2013).The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus

dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. J Ocul Pharmacol Ther. 29(10):882-6.

25-Silver LH. (2000). Ocular comfort of brinzolamide 1.0% ophthalmic suspension compared with dorzolamide 2.0% ophthalmic solution: results from two multicenter comfort studies. Brinzolamide Comfort Study Group. Surv Ophthalmol;44S141–5.

26-Mundorf TK, Rauchman SH, Williams RD and Notivol R. (2008). Brinzolamide/Timolol Preference Study Group A patient preference comparison of Azarga (brinzolamide/timolol fixed combination) vs Cosopt (dorzolamide/timolol fixed combination) in patients with open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2(3):623–628.

27-Rossi GC1, Pasinetti GM, Sandolo F, Bordin M and Bianchi PE. (2011). From dorzolamide 2%/timolol 0.5% to brinzolamide 1%/timolol 0.5% fixed combination: a 6-month, multicenter, open-label tolerability switch study. Expert Opin Pharmacother. 12(16):2425-31.

28-Graham Anthony Auger, Mathew Raynor, and Simon Longstaff. (2012). Patient perspectives when switching from Cosopt® (dorzolamide-timolol) to Azarga™ (brinzolamide-timolol) for glaucoma requiring multiple drug therapy. Clin Ophthalmol. 6: 2059–2062.