Journal of Al-Farabi for Medical Sciences volume (3), No (1) Feb (2025)

ISSN: 2957-7675 (Print)
Journal of Al-Farabi for Medical Sciences
https://www.iasj.net/iasj/journal/439/issues
Published by Al-Farabi University College

Intraocular hypotensive effects of cinnarizine vs timolol in experimentally induced glaucoma

Luma Saad Baqir[1] , Mohammed J. Manna[1] , Haider R Mohammad[2], Murtadha S. Jabur[3]

1College of Dentistry, Mustansiriyah University, Baghdad, Iraq
2 College of Pharmacy, Mustansiriyah University, Baghdad, Iraq
3 College of Pharmacy, National University for Science and Technology, Nasiriya, Iraq

Abstract

Background: Glaucoma is progressive irreversible optic nerve degeneration in which there are optic disc cupping with loss of ganglionic axons and loss in the visual field. Cinnarizine, a calcium channel antagonist, block alpha -1S subunit of voltage-dependent L-type calcium channel.

Aim of the study: to investigate the intraocular hypotensive effects of cinnarizine as calcium ion entry blocker to prevent or treat glaucoma in comparing with the approved drug, timolol.

Methodology: The study sample that consist of thirty rabbits were divided into 3 groups. Group A: 10 rabbits represent the control group and received the vehicle into each eye. Group B: 10 rabbits received timolol 0.5% w/v into the right eye and the vehicle into the left. Group C: 10 rabbits received cinnarizine 0.5% w/v into the right eye and the vehicle into the left. Basal intraocular pressure was recorded in all rabbits for both eyes. At least 3 readings were documented for each IOP measures and the mean was obtained before instillation of drugs. One drop of cinnarizine 0.5% or timolol 0.5% was administered in the right eye; whereas the left eye considered as a control and one drop of normal saline was applicate into the eye. After 30 min of drugs administration, IOPs were measured in each eye. In addition, IOP measurements were done every 10 min for 170 minutes.

Results: Intraocular pressure for all groups remain normal till 30 minutes. Then, a significant sharp increment ($p < 0.05$) was measured at 40 minutes in the control group (group 1). Whereas in the timolol group (group 2), the increment of IOP was significantly ($p < 0.05$) less than group 1. Moreover, the cinnarizine group (group 3) also demonstrate a significantly ($p < 0.05$) less increment of IOP. Across all of the fifteen readings (except baseline) which were measured every 10 minutes, IOP was highly significant ($p < 0.01$) less in group 2 and group 3 than the control group.

Conclusion: Topical ocular administration of cinnarizine 0.5% has been showed a significant ocular-protective effect by prevention of acute rise of intraocular pressure; and by cinnarizine represent a possible promising drug for glaucoma.

KEYWORDS: Cinnarizine, timolol, intraocular pressure, glaucoma.

INTRODUCTION

Glaucoma is progressive irreversible optic nerve degeneration in which there are cupping of optic disc with loss of ganglionic axons and loss in the visual field [1]. Glaucoma is one of the major risk factors that may causes blindness worldwide [2]. Primary open-angle glaucoma which is most common type of glaucoma is usually associated with elevated intraocular pressure (IOP) [3]. Higher IOP represents the major consequence for glaucoma, but fortunately it is modifiable [2]. Thus, the goal of management of glaucoma depends on reducing IOP to the normal level (≤ 21 mmHg) [3]. Medical treatments of glaucoma are aimed to lower IOP via reducing the production of aqueous humor or improving the flow of aqueous humor through the uveoscleral outflow (pressure-independent outflow), or a combination of both [4]. Also, there is another subway by decreasing episcleral venous pressure which is related to improving in aqueous humor flowing [4].

In the late 1970s, Timolol is a non-selective β-adrenergic receptor blocker agent was introduced in both oral and topical formulations [5]. Blocking of receptors is reversible, but on the other hand the blocking is long-acting [6]. With topical administration, timolol activity occurs in about 20 to 30 min [7]. Since the late 1970s and early 1980s, timolol was the most common β-blocker used for glaucoma management topically [8]. When timolol used as eye drop, through the nasal mucosa ~80% of the ocular dose can be absorbed systemically [9]. However, some 12% to 88% of an eye drop dose may be lost into eyelid [9].

Cinnarizine, a calcium channel antagonist, block alpha -1S subunit of voltage-dependent L-type dihydropyridine calcium channel (calcium ion entry), so it used experimentally as a selective vasodilator of peripheral vessels and do not show action on myocardium [10]. By inhibiting H1 receptor moderately, cinnarizine has sedative antihistaminic activity [11]. In addition, it also has anticholinergic, antidopaminergic, and antiserotonergic activity [11]. Originally extracted from wood reed roots *Cinna arundinacea* ("riza" means "roots" of *Cenna*) [12]. In 1955, it was first synthesized by Janssen Pharmaceutica which marketed it by the brand (trade) name Stugeron® in 1958 [12].

Cinnarizine exhibits effective sedative vestibular suppressant activity due to partially its antihistaminic activity [13]. It inhibits the effect on potassium currents by acting on vascular smooth muscle cell contractions, also it depresses the labyrinth [14]. This effect on the human the vestibulo-ocular reflex making cinnarizine used in the treatment of vestibular vertigo. Cinnarizine also modulate central vestibular neurons [14].

Cinnarizine has poor aqueous solubility (lipophilic) and can cross the blood-brain barrier readily [15]. Cinnarizine promote cerebral blood flow, so it can be used in the management of cerebrovascular diseases such as post-traumatic cerebral symptoms and apoplexy [16]. Moreover, cinnarizine used successfully in the prophylaxis of migraine in clinical trials and in epilepsy as adjunctive therapy [16].

The therapeutic effect of cinnarizine on retinal vasculopathy has been clinically evaluated over a period of several months to three years [17]. Nihard revels that cinnarizine improve tissue perfusion, normalizes optic disc and improve the visual field [17].

The aim of the study was to validate the intraocular hypotensive effects of cinnarizine as calcium ion entry blocker to prevent or treat glaucoma in comparing with the approved drug, timolol.

MATERIALS AND METHODS

Ethical and scientific committees in college of pharmacy and college of dentistry, Mustansiriyah University were approved the study. A thirty New Zealand albino (white, NZW) rabbits weight 2.2–2.7 Kg and aged 5-6 months. In the animal house under optimum hygienic condition, the rabbits were adapted individually in appropriate restraint devices (cages) in comfortable ventilated environment 2 weeks prior to the experimental work. NZW Rabbits were let to drink water and fed with green leafy alfalfa ad libitum.

The study sample that consist of thirty rabbits were divided into 3 groups. Group A: 10 rabbits represent the control group and received the vehicle into each eye. Group B: 10 rabbits received timolol 0.5% w/v into the right eye and the vehicle into the left. Group C: 10 rabbits received cinnarizine 0.5% w/v into the right eye and the vehicle into the left.

Timolol ophthalmic solution USP 0.5% w/v (Timoptic®, Merck) was used in the study. Pure powder of cinnarizine was purchased from Sigma-Aldrich via special order bureau for chemicals sale, Baghdad, Iraq. Cinnarizine eye drop was freshly prepared by dissolving in phosphate buffer and diluted with normal saline in order to yield 0.5% w/v concentration.

Schiøtz tonometer was used to record intraocular pressure because it is easy-to-use, inexpensive, portable instrument. After 1 min of administrating lidocaine as ocular anesthetic, IOPs were measured precisely by Schiøtz tonometer. The indentation force that used first was 5.5 g weight. The readings were converted to mm Hg by using Schiøtz conversion table. After every use, Schiøtz tonometer was disinfected. Schiøtz tonometer was calibrated by manometric method.

Ocular hypertension was inducted in NZW rabbits by 15 ml/kg dextrose 5% in water (D5W), after shaving the hair over the marginal ear vein and cleaning the injection site, through the readily accessible marginal ear vein of rabbits with 25-gauge needle.

Basal intraocular pressure was recorded in all rabbits for both eyes. At least 3 readings were documented for each IOP measures and the mean was obtained before instillation of drugs. One drop of cinnarizine 0.5% or timolol 0.5% was administered in the right eye; whereas the left eye considered as a control and one drop of normal saline was applicate into the eye.

After 30 min of drugs administration, IOPs were measured in each eye. In addition, IOP measurements were done every 10 min for 170 minutes. Experimentation schedules were done at the same time of each experiment's day.

Statistical analysis

All data were analyzed by using the version 28.0 of SPSS (Statistical Package for the Social Sciences, SPSS Inc. Chicago, Illinois, USA). The means, standard errors, standard deviations from mean, and 95% confidence intervals were used as descriptive statistics. one-way ANOVA used to test statistical differences between groups , T-test paired for comparison between Pre and Post results within each group. A P-value < (0.05) was deemed to be significant, and a P-value < (0.01) was deemed to be highly significant.

RESULTS

Intraocular pressure for all groups remain normal till 30 minutes. Then, a significant sharp increment ($p < 0.05$) was measured at 40 minutes in the control group (group 1). Whereas in the timolol group (group 2), the increment of IOP was significantly ($p < 0.05$) less than group 1. Moreover, the cinnarizine group (group 3) also demonstrate a significantly ($p < 0.05$) less increment of IOP. Across all of the fifteen readings (except baseline) which were measured every 10 minutes, IOP was highly significant ($p < 0.01$) less in treatment groups (group 2 and 3) than the control group (group 1)

Topical cinnarizine has approximately same effect as topical timolol in lowering acute elevation of IOP. Table 1 show that both cinnarizine and timolol has a comparable effect, with very slight preference for cinnarizine. The experimental drug of this study cinnarizine show a successful decrease in IOP induced by D5W infusion when it was given before induction.

Intraocular Pressure (IOP) of Right Eye (mm Hg)	Animal Groups			P-Value [a]
	Group A	Group B	Group C	
Baseline Measurements	20.3	19.2	19.7	0.525 NS
After 30 minutes	20.3	19.2	19.7	0.525 NS
After 40 minutes	42.65	41.3	41.9	0.492 NS
After 50 minutes	42.65	40.7	41.4	0.042*
After 60 minutes	41.55	38.6	38.7	0.035*
After 70 minutes	40.7	36.5	36.45	0.021*
After 80 minutes	39.8	34.6	34.3	0.009**
After 90 minutes	38.75	32.35	32.05	0.007**
After 100 minutes	37.65	30.2	30.0	0.006**
After 110 minutes	36.55	29.1	28.85	0.003**

After 120 minutes	35.4	28.2	27.95	0.003**
After 130 minutes	34.5	27.25	26.8	0.002**
After 140 minutes	33.55	26.2	25.9	< 0.001**
After 150 minutes	32.45	25.3	24.9	< 0.001**
After 160 minutes	31.4	24.25	23.8	< 0.001**
After 170 minutes	30.5	23.2	22.75	< 0.001**
P-Value [b]	0.276 [NS]	< 0.001**	< 0.001**	

Table 1: The effect of cinnarizine 0.5% on intraocular pressure in acute ocular tension. [a] one-way ANOVA used to test statistical differences between study groups (horizontally), [b] T-test paired for comparison between Pre and Post treatment groups. NS: No significant ($p \geq 0.05$) , (*) is significant ($p < 0.05$). (**) is highly significant ($p < 0.01$).

DISCUSSION

This study was used the marginal ear vein procedure for inducting an increase in IOP in evaluating and investigating cinnarizine because it is the more dependable, fastest, and easiest technique for screening a new agent decreasing IOP [18,19]. By administration of D5W infusion, water entrapped into the eyes, and an acute raise of IOP occur [20].

The main point in treatment of glaucoma is to understand how aqueous humor formed and outflowed [21]. All of the current approved drugs for treatment of glaucoma act either by decreasing formation of aqueous humor or by increasing aqueous humor drainage through the pressure-independent uveoscleral outflow or decreasing episcleral venous pressure [22]. It is important to know the composition of aqueous humor, to target the causes of IOP. Aqueous humor has an excess of chloride and hydrogen ions, and essentially protein free [23]. In addition, it is also containing several enzymes, like carbonic anhydrase and dopamine β-hydroxylase, as well as, prostaglandins and phospholipase A_2 [24]. The process of aqueous humor formation in the ciliary body has three ways; active secretion , followed by ultrafiltration and then simple diffusion [25]. In which the ultrafiltration process depends on the balance between the hydrostatic pressure and the oncotic pressure [26]. So, this study focuses on a new agent that decreases the ultrafiltration to decrease aqueous humor formation, as well as, decreases the episcleral venous pressure to increase aqueous humor outflow.

Calcium channel antagonists decrease the calcium ion intracellularly by blocking the calcium ion entry across the cell membrane, thereby blockage calcium influx has a beneficial effect in decreasing the pressure by causing relaxation [27]. Many studies have been showed that high doses of cinnarizine decrease blood pressure [14,16,28]. Moreover, other studies have been showed that cinnarizine has an antidopaminergic effect to a degree that may cause drug-induced parkinsonism [11,15,29]. These two main properties; decreasing blood pressure by blocking calcium ion influx and the antidopaminergic effect, were the causes of success of cinnarizine in lowering IOP in this study. Actually, by blocking the calcium channels, the episcleral venous pressure were decreased by facilitating aqueous humor to drainage outflow [26]. On the other hand, the calcium channel antagonist activity of cinnarizine helped in decreasing aqueous humor formation by decreasing the hydrostatic pressure to favor the oncotic pressure resists the fluid movement [27-29]. Additionally, the antidopaminergic effect of cinnarizine may contribute in the success of this study by targeting and lowering dopamine β-hydroxylase but this point need more molecular pharmacological study to confirm it.

Moreover, from decades the studies showed that cinnarizine has even an ability to restore partially the degeneration that occur in the post-ganglionic fibers [16,17,29]. In addition, normalization of optic disc aspects was documented in patients with glaucoma partially [17]. Previous studies have been concluded that the selectivity of calcium-entry-blockers obviously enhance retinal perfusion in ischemic areas [10,26,27]. Also, cinnarizine was found to possess an improving effect on the visual function and has a prominent feature in the treatment of retinal vasculopathies [17].

CONCLUSION

Topical ocular administration of cinnarizine 0.5% has been showed a significant ocular-protective effect by prevention of acute rise of intraocular pressure; and by cinnarizine represent a possible promising drug for glaucoma may be with simple structural modification.

Financial support

There are no financial supports.

Conflicts of interest

There are no conflicts of interest.

ACKNOWLEDGMENT

The authors would like to thank Mustansiriyah University (www.uomustansiriyah.edu.iq) Baghdad/Iraq and department of pharmacology / college of medicine for providing the practical platform of this study.

REFERENCES

1- Webb, T. E. R. A review of glaucoma surgical therapy. *Vet Ophthalmol*. 2021; 24 (S1):34–38.

2- Wu, A., Khawaja, A. P., Pasquale, L. R., & Stein, J. D. A review of systemic medications that may modulate the risk of glaucoma. *Eye (Lond)*. 2020; 34 (1):12-28.

3- Morgan, W. H. & Yu, D. Surgical management of glaucoma: a review. *Clin Exp Ophthalmol*. 2012; 40 (4):388-99.

4- Pereira, I. C. F., van de Wijdeven, R., Wyss, H. M., Beckers, H. J. M., & den Toonder, J. M. J. Conventional glaucoma implants and the new MIGS devices: a comprehensive review of current options and future directions. *Eye (Lond)*. 2021; 35 (12):3202-3221.

5- Xu, J., Ge, Y., Bu, R., Zhang, A., Feng, S., Wang, J., *et al*. Co-delivery of latanoprost and timolol from micelles-laden contact lenses for the treatment of glaucoma. *J Control Release*. 2019; 10 (305):18-28.

6- Cuggino, J. C., Tártara, L. I., Gugliotta, L. M., Palma, S. D., & Alvarez Igarzabal, C. I. Mucoadhesive and responsive nanogels as carriers for sustainable delivery of timolol for glaucoma therapy. *Mater Sci Eng C Mater Biol Appl*. 2021; 118:111383.

7- Konstas, A. G., Schmetterer, L., Katsanos, A., Hutnik, C. M. L., Holló, G., Quaranta, L., *et al*. Dorzolamide/Timolol Fixed Combination: Learning from the Past and Looking Toward the Future. *Adv Ther*. 2021; 38 (1):24-51.

8- Belfort, R., Paula, J. S., Lopes Silva, M. J., Della Paolera, M., Kim, T., Chen, M. Y., & Goodkin, M. L. Fixed-combination Bimatoprost/Brimonidine/Timolol in Glaucoma: A Randomized, Masked, Controlled, Phase III Study Conducted in Brazil. *Clin Ther*. 2020; 42 (2):263-275.

9- Cimolai, N. Neuropsychiatric Adverse Events from Topical Ophthalmic Timolol. *Clin Med Res*. 2019; 17 (3-4):90-96.

10- Türkeş, C., Demir, Y., & Beydemir, Ş. Anti-diabetic Properties of Calcium Channel Blockers: Inhibition Effects on Aldose Reductase Enzyme Activity. *Appl Biochem Biotechnol*. 2019; 189 (1):318-329.

11- Baghel, S., Cathcart, H., Redington, W., & O'Reilly, N. J. An investigation into the crystallization tendency/kinetics of amorphous active pharmaceutical ingredients: A case study with dipyridamole and cinnarizine. *Eur J Pharm Biopharm*. 2016; 104:59-71.

12- Sarhan, R. M., Thabet, H. S., Nazeer, J. T., & William, S. The impact of cinnarizine and griseofulvin on juvenile and adult stages of *Schistosoma mansoni*. *J Helminthol*. 2019; 26 (94):e41.

13- Togha, M., Martami, F., Abdollahi, M., Mozafari, M., Cheraghali, H., Rafiee, P., & Shafaei, M. Cinnarizine as alternative recommendation for migraine prophylaxis: a narrative review. *Expert Rev Neurother*. 2020; 20 (9):943-951.
14- Anagnostou, E., Koutsoudaki, P., Stavropoulos, A., & Evdokimidis, I. Effect of common antivertiginous agents on the high velocity vestibulo-ocular reflex. *Clin Neurophysiol*. 2017; 128 (11):2211-2216.
15- Raghuvanshi, S., & Pathak, K. Recent Advances in Delivery Systems and Therapeutics of Cinnarizine: A Poorly Water Soluble Drug with Absorption Window in Stomach. *J Drug Deliv*. 2014; 2014:479246.
16- Nagarwal, R. C., Ridhurkar, D. N., & Pandit, J. K. In Vitro Release Kinetics and Bioavailability of Gastroretentive Cinnarizine Hydrochloride Tablet. *AAPS PharmSciTech*. 2010; 11 (1):294-303.
17- Nihard, P. Effect of Calcium-Entry-Blockers on Arterioles, Capillaries, and Venules of the Retina. *Angiology*. 1982; 33 (1):37-45.
18- Biswas, S., & Wan, K. H. Review of rodent hypertensive glaucoma models. *Acta Ophthalmol*. 2019; 97 (3):e331-e340.
19- Chen, S., & Zhang, X. The Rodent Model of Glaucoma and Its Implications. *Asia Pac J Ophthalmol (Phila)*. 2015; 4 (4), 236–241.
20- Pang, I.-H., & Clark, A. F. Inducible Rodent Models of Glaucoma. *Prog Retin Eye Res*. 2020; 75:100799.
21- Jubair, S., Al-Rubae'i, S. H. N., Al-Sharifi, A. N. M., & Suleiman, A. A. Investigation of CYP1B1 Gene Involvement in Primary Congenital Glaucoma in Iraqi Children. *Middle East Afr J Ophthalmol*. 2020; 26 (4):203-209.
22- Al-Shakarchi, F. I. Blindness in Iraq Leading Causes, Target Patients, and Barriers to Treatment. *Middle East Afr J Ophthalmol*. 2011; 18 (3):199-203.
23- Jubair, S., Muftin, N. Q., Hashim, N., Rieyadh, S., & Saad, H. Investigation of MYOC gene involvement in primary congenital glaucoma in a sample of Iraqi children. *Gene Reports*. 2019; 16:100413.
24- Weinreb, R. N., Aung, T., & Medeiros, F. A. The pathophysiology and treatment of glaucoma: a review. *JAMA*. 2014; 311 (18):1901-11.
25- Manna, M. J., Jabur, M. S., Mohammad, H. R., & Abdulamir, H. A. The potential effect of topical aminophylline on acute glaucoma model. *Res. J. Pharm. Technol*. 2022; 15 (1):197-200.
26- Jabur, M. S., Manna, M. J., Mohammad, H. R., Baqir, L. S., & Abdulamir, H. A. Ocular Hypotensive Effect for the Topical Amlodipine 0.5% Eye Drop. *Lat. Am. J. Pharm*. 2023; 42(special issue):311-314.
27- Bulsara, K. G., & Cassagnol, M. Amlodipine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
28- St-Onge, M., Dubé, P.-A., Gosselin, S., Guimont, C., Godwin, J., Archambault, P. M., *et al*. Treatment for calcium channel blocker poisoning: A systematic review. *Clin Toxicol (Phila)*. 2014; 52 (9):926-44.
29- Teive, H. A. G., Troiano, A. R., Germiniani, F. M. B., & Werneck, L. C. Flunarizine and cinnarizine-induced parkinsonism: a historical and clinical analysis. *Parkinsonism Relat Disord*. 2004; 10 (4):243-5.