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Ocular Hypotensive Effects of Nesiritide 0.005% Eye Drops on Ocular Normotensive and Betamethasone-Induced Ocular Hypertensive Rabbits

Maimona A. Abdul-Jabbar[1] *MSc*, **Adeeb A. Al-Zubaidy**[2] *PhD*

[1]Al-Fallujah Teaching Hospital, Fallujah District, Al Anbar, Iraq,[2]Dept. of Pharmacology, College of Medicine, Warith Al-Anbiyaa University, Karbala, Iraq

Abstract

Background The only method to stop the progression of glaucoma is to decrease intraocular pressure (IOP). Nesiritide is a natriuretic peptide that is effective in reducing blood pressure via his vasodilator action, which may be effective in reducing IOP.

Objective To evaluate the efficacy of nesiritide 0.005% eye drops on IOP of ocular normotensive and betamethasone-induced ocular hypertensive rabbits in comparison with that of latanoprost 0.005% eye drops; besides, to study the safety profile of nesiritide eye drops.

Methods This study included 36 male rabbits; 18 rabbits represented the ocular normotensive groups (control, latanoprost, and nesiritide) and the other 18 rabbits represented betamethasone-induced ocular hypertension groups (vehicle, latanoprost, and nesiritide). Tested drugs instilled as one drop twice daily for 7 days in normotensive and hypertensive left eye. The IOP was measured with the aid of Schiötz tonometer. Other examined parameters were pupil diameter, light pupillary reflex, corneal sensation reflex, and conjunctival redness which were recorded before starting the experiment and then daily before and after drug application for one week.

Results This study revealed that nesiritide eye drops significantly reduced IOP since the 3rd day in both normotensive and steroid-induced ocular hypertensive model; yet, this effect was less potent than that of latanoprost eye drops. Nesiritde eye drops did not induce significant changes in the other examined parameters.

Conclusion This study revealed the efficacy and apparent safety of nesiritide 0.005% eye drops in lowering IOP in both ocular normotensive and betamethasone-induced ocular hypertensive rabbits.

Keywords Nesiritide, Latanoprost, intraocular pressure, glaucoma

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List of abbreviations: ANP = Atrial natriuretic peptide, BNP = Brain natriuretic peptide, CNP = C-type natriuretic peptide, IOP = Intraocular pressure, POAG = Primary open-angle glaucoma

Introduction

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Glaucoma is a collection of diseases with various pathophysiology, risk factors, symptoms, prognosis, and therapies. The deficit of retinal ganglion cells, weakening of the retinal nerve fiber loops, also progressive excavation of the optic disc are all common symptoms of their reforming deterioration of the optic nerve [1,2].

Eye is a unique organ in that it contains several different structures with specific physiological functions. The anterior segment of the eye contains the cornea, conjunctiva, iris, ciliary body and the lens [3].

The ciliary body's epithelial cells produce the slightly alkaline ocular fluid known as aqueous humor at a rate of 2 to 3 µl per minute [4].

Intraocular pressure (IOP) creation is based on the constancy of aqueous humor synthesis, while IOP also fluctuates according on the outflow facility. The outflow facility is determined by the aqueous humor drainage system's inherent resistance [5].

The obstruction of the drainage pathway and whether it is primary or related with detectable comorbidity, i.e., secondary glaucoma are the two ways by which the classification of glaucoma depends on [6]. Primary open-angle glaucoma (POAG) along with primary angle-closure glaucoma are the couple classes of glaucoma that are most prevalent. The position of aqueous humor drainage is at the angle formed by the iris and the cornea, which is referred to as the "angle". Progressive loss of peripheral vision fields is a hallmark of POAG, which is then followed by collapse of the central ocular field [7]. The objective is to reach a personally target point pressure by that development of glaucoma development of glaucoma is not expected [8].

Topical medicines may work in one of three ways: by boosting aqueous discharge through the trabecular meshwork, by expansion drainage through the uveoscleral pathway, or reducing aqueous humour generation. Prostaglandin analogues, beta-blockers, diuretics (carbonic anhydrase inhibitors), cholinergic agonists, and alpha-agonists are the main types of topical treatments [9].

Although the greatest cure selection for reducing the danger of advancement is currently topical hypotensive therapy, there are still several problems with relying on this approach, containing diurnal alterations in IOP, changes in optical blood derive, and neuropreservation. Also, difficulties with patient compliance as well as ineffective topical medication distribution methods make this therapy technique more challenging [10].

Additionally, immunohistochemical analysis of the neural retina and the retinal pigment epithelium revealed the presence of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). The presence of ANP and BNP in the retinal pigment epithelium raises the possibility that these peptides may have an impact on the balance of ocular fluid at the blood-retinal barrier by altering pigment epithelial function [11].

The C-type natriuretic peptide (CNP) analog TAK-639, which has recently been demonstrated to have considerable IOP reducing efficacy, belongs to the class of natriuretic peptide analogs. The drug is currently undergoing phase I clinical studies [12].

For the aforementioned reasons, it was suggested that this study compare the usual medicine latanoprost 0.005% eye drops to nesiritide 0.005% eye drops in order to test the IOP-lowering impact of nesiritide eye drops using a betamethasone-induced ocular hypertension model in rabbits.

Methods

Drugs, chemicals, and instrument

The chemicals and drugs that are used in this study are highly purified and include latanoprost eye drop (Pfizer, USA), nesiritide powder (Baoji Guokang-Technology Co., Ltd., China), betamathasone injection (Clint pharmaceuticals. United states), benzalkonium chloride (MyLeaNatural and isotonic phosphate buffer solution (Alfa, India).

Experimental animals

The study included 36 adult male rabbits that appeared healthy and weighed between 1.5 and 2 kg. According to ophthalmology and general evaluations, they were found to be normal. Water and fresh food were freely available to animals. They were kept in a typical laboratory setting along a 12-hour light period and 12-hour dark period.

Preparation of nesiritide 0.005% eye drops

The needed quantity of the tested medication powder was dissolved in the appropriate volume of phosphate buffer solution to create an isotonic solution for the ophthalmic solution. Next, benzalkonium chloride solution was added and thoroughly mixed before being combined with phosphate buffer solution to reach the desired volume. After being manufactured in an antiseptic environment, the ophthalmic solution was put into sterile containers [13]. The formula was created as indicated in the next. The following illustrates how the formula was made.:

- Nesiritide 0.005 mg/ml
- Nesiritide drug 0.005 g
- Benzalkonium chloride 1%(w/w)"1 ml"
- Phosphate buffer to 100 ml

Measurement parameters

The IOP was measured for both eyes with the aid of a Schiotz tonometer according to the instruction of manufacture. The other examined parameters were pupil diameter, light papillary reflex, corneal sensation reflex and conjunctival redness. These parameters were recorded before starting the experiment and after drug application [14].

Induction model for ocular hypertension

According to Melena (1998) and colleagues, who discovered that this model of induction is mimicking human chronic open angle glaucoma, optic hypertension was produced in the second portion of the investigation. This formulation offers a sub conjunctival injection of 0.7 ml of betamethasone suspension that includes betamethasone sodium phosphate (3 mg/ml) and betamethasone (acetate) fraction of betamethasone for an easily accessible and sustained release [15].

Experimental design in normotensive rabbit

In this part three groups were involved, each group consisting of six rabbits. All animals had been examined for the studied parameters on the day before the application of the tested agent. On the seven next days, the experiment had been done by the instillation of the tested agents into the right eye and distilled water instilled into left eye twice dialy at 10:00 a.m. and at 10:00 p.m., except for latanoprost, which was administered once daily. The tested parameters were recorded 30 minutes before instillation and 30, to 60 minutes after instillation. The parameters were also measured in the left eyes to detect the contralateral effects of the tested agent.

The studied groups were the negative control group (right eye received inactive ingredients while left eye received distilled water), latanoprost 0.005% group, nesiritide eye drop 0.005%.

Statistical analysis

Microsoft Excel 2010 and statistical package for social science (SPSS) version 26 software were used for data analysis. Numeric variables were expressed as mean±SD and all statistical comparisons were made by means of an independent t-test and a one-way analysis of variance (ANOVA) t-test with $P < 0.05$ was considered statistically significant. Categorical variables were expressed as numbers and analyzed; represented by tables and figures. The correlation was done between scores using the Pearson correlation test; the correlation coefficient is considered to be significant at P level < 0.05.

Results

Effects of tested drugs on mean IOP and clinical features among normotensive groups during a

week of treatment. There was no significant difference of mean IOP was found among control group during all days of treatment, P = 0.9. Latanoprost treated group, nesiritide 0.005% treated group were associated with significant higher decline in mean IOP during day 7 of treatment, P <0.001 (Figures 1-3).

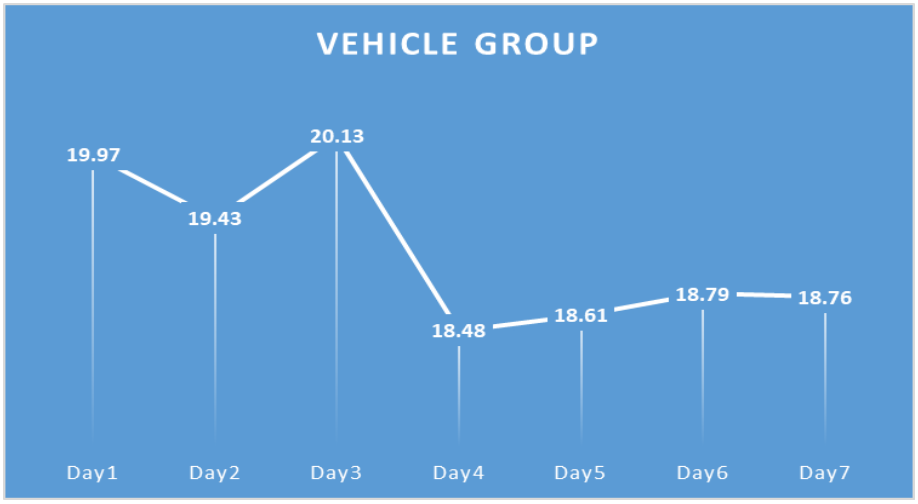

Figure 1. Effect of vehicle (phosphate-buffer saline) on mean IOP*of apparently healthy rabbits

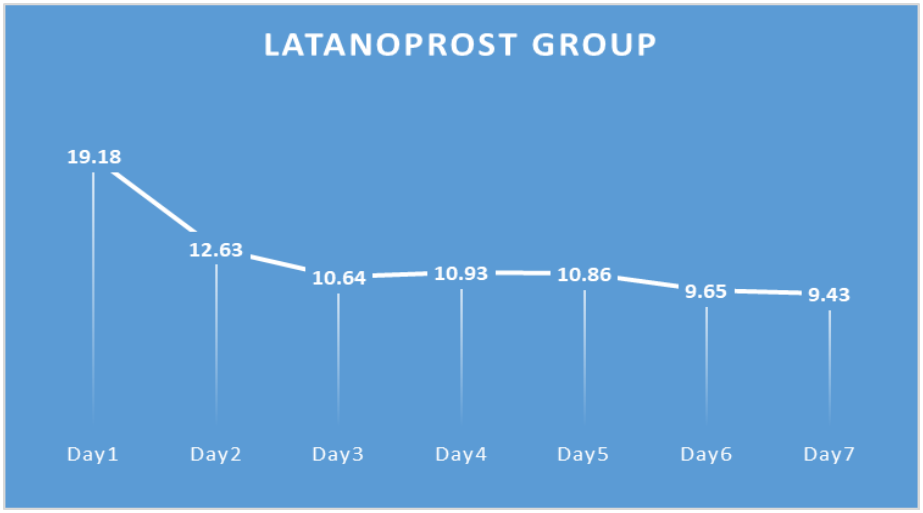

Figure 2. Comparison between mean IOP of latanoprost treated group and days of treatment

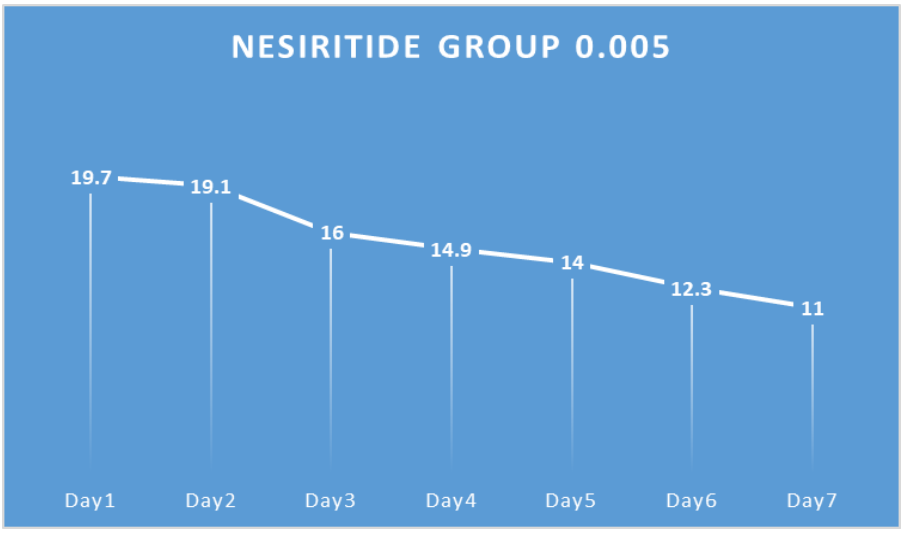

Figure 3. Effect of nesiritide 0.005% drops on mean IOP*of ocular normotensive rabbits

Effects of tested drugs on normotensive groups during a week of treatment according to the clinical features

All normotensive groups during all 7 days of treatment have positive corneal reflex. Pupillary diameter was significantly higher among control group in day 7, among latanoprost treated group in day 5 of treatment, and among nesiritide 0.005% group in day 7 of treatment, P <0.001. All Normotensive groups during all 7 days of treatment have constant pupillary light reflex.

No conjuctival redness was found among Normotensive groups during a week of treatment except that for latanoprost treated group, where it was significantly associated with conjuctival redness during days 3, 4, and 5 of treatment, P <0.001.

Effects of tested drugs on mean IOP among betamethasone induced hypertensive groups during a week of treatment

There was no significant difference of mean IOP was found among Vehicle group during all days of treatment, P = 0.9. Latanoprost treated group shows a significant higher decline in mean IOP in day 7 of treatment, (P <0.001). Similarly, Nesiritide 0.005% treated group shows decline in mean IOP during day 7 of treatment, (P <0.001) (Figures 6-8).

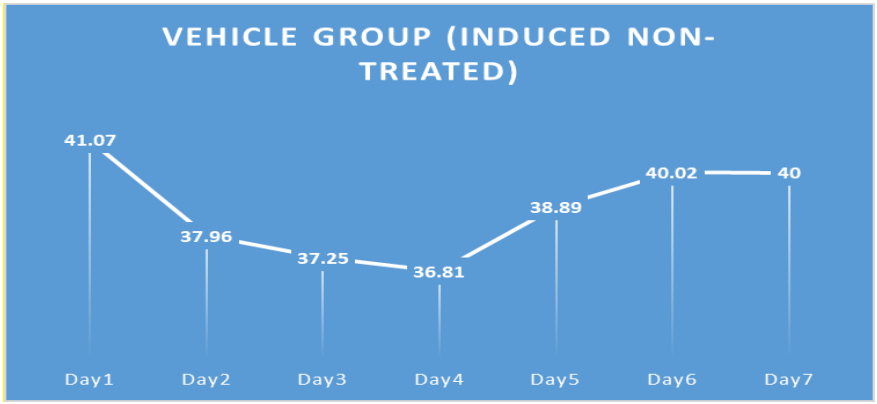

Figure 6: Effect of vehicle (phosphate-buffered saline) drops on mean IOP of betamethasone-induced ocular hypertensive rabbits

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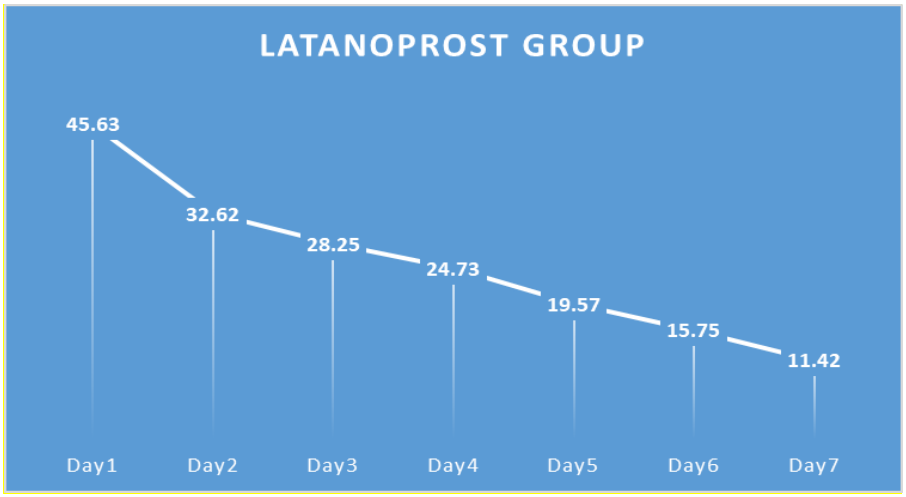

Figure 7. Effect of vehicle (latanoprost 0.005%) drops on mean IOP of betamethasone-induced ocular hypertensive rabbits

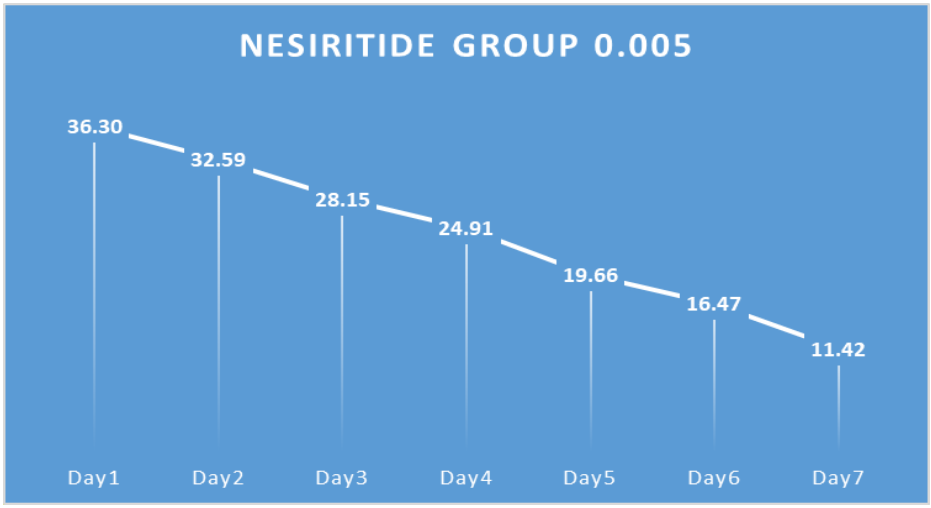

Figure 8. Effect of (Nesiritide 0.005%) drops on mean IOP of betamethasone-induced hypertensive rabbits

Comparison between normotensive groups according to mean IOP and days of treatment revealed that nesiritide 0.005% tested drugs were less potent in reducing mean IOP along the 7 days of treatment in comparison to Latanoprost group, P <0.001.

Effects of tested drugs on betamethasone induced hypertensive groups during the week of treatment according to the Clinical features

All betamethasone induced hypertensive groups have positive corneal reflex without corneal redness. Pupillary diameter was significantly higher among Vehicle group in day 2 of treatment; among Latanoprost treated group in day 1 of treatment, while among nesiritide 0.005% group it was significantly higher in day 7 of treatment, (P <0.001).

Discussion

The 32 amino acid homo sapien BNP, that is typically made by the ventricular cardiac muscle, is found in nesiritide (Natrecor), a recombinant version. Nesiritide stimulates cyclic guanosine monophosphate, which results in the relaxation of smooth muscle cells, and counter regulates the renin-angiotensin-aldosterone pathway to promote cardiovascular fluid balance [16].

Important causally reversible risk factor for glaucoma is increased IOP. IOP elevation is mostly caused by aqueous outflow obstruction, which can be treated by either boosting outflow or decreasing aqueous humor generation [17]. The current glaucoma treatment strategy aims to lower IOP by combining various types of topical hypotensive medications with surgical treatments. In most cases, the course of treatment is initiated in stages, beginning with nominal drug remedy, progressing to pharmacological combinations, and eventually, if imperative, including laser therapy and surgical interference [9].

Although the greatest cure selection for reducing the danger of advancement is currently topical hypotensive therapy, there are still several problems with relying on this approach, containing diurnal alterations in IOP, changes in optical blood derive, and neuro-preservation. Also, difficulties with stoic compliance as well as ineffective topical medication distribution methods make this therapy technique more challenging [12].

The CNP analog TAK-639, which has recently been demonstrated to have considerable IOP reducing efficacy, belongs to the class of natriuretic peptide analogs. The drug is currently undergoing Phase I clinical studies [10].

In the current research, nesiritide is the tested drug. The drug was formulated as eye drops to examine its topical effect in reduction of intraocular pressure when used as a twice dose daily. In the third day administration of the nesiritide, a significant decline in the ocular pressure was observed compared to the baseline reading and this reduction continued till the end of the experiment both in normotensive and in betamethasone-induced ocular hypertension. The positive thing in this study is the ability of nesiritide eye drops to decrease the IOP near and less potent than that of the reference drug, latanoprost eye drops.

In betamethasone-induced ocular hypertensive groups, the reduction in the IOP was significant on the third day and continued to reduce toward the normal level during the period of the study. Maximal IOP reduction was in the seventh day with a reduction of 69% to low IOP levels.

According to the statistical analysis, Latanoprost significantly decreased IOP during the course of the 7-day treatment by 75% as compared to baseline in hypertensive model. Furthermore, the reducing effect of Nesiritide groups was 69% after 7 days of treatment with (nesiritide 0.005%) eye drops, so the lowering effect of nesiritide 0.005% is less than that of latanoprost.

Regarding the incidence of conjunctival redness following topical administration of latanoprost, the examination revealed neither conjunctival redness that might be brought on by short-term therapy nor any indication of inflammation. Despite the fact that conjunctival hyperemia is one of the side effects of latanoprost [18], a group of researchers conducted a meta-diagnosis of disarranged impersonal experimentations and found that using latanoprost in the cure of glaucoma patients is connected beside a less frequency of conjunctival hyperemia from there on utilizing travoprost and bimatoprost [19].

Fortunately, no changes have been observed in the above ocular clinical features in rabbits managed by nesiritide eye drops neither in normotensive experiment nor in betamethasone-induced ocular hypertension experiment. The small number of rabbits is the main limit in addition to the wrong IOP measurment probably so there is a need for further studies in an attempt to elicit the incidence of side effects of this new topically-applied agent.

In conclusions, neseritide eye drops in 0.005% concentration have significant IOP-lowering effect. Reductions in the IOP by using of nesiritide eye drops 0.005% was less potent

than that obtained by reduction of IOP by using latanoprost 0.005% eye drops in both normotensive and steroid-induced hypertensive rabbit eye model. The present study proved the safety of nesiritide eye drops in 0.005% concentration without any detectable local side effects along the trial period.

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Author contribution

Both authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Abdul-Jabbar and Dr. Al-Zubaidy. The first draft of the manuscript was written by Abdul-Jabbar and both authors commented on previous versions of the manuscript. Both authors read and approved the final manuscript. Both authors declare that all data were generated in-house and that no paper mill was used.

Conflict of interest

The authors declare no competing interests.

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Correspondence to Maimona A. Abdul-Jabbar
E-mail: maimonaayad1986@gmail.com
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